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In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder: A nationwide Danish cohort study

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ABSTRACT

Objective To investigate whether in utero exposure to antidepressants is associated with increased risk of attention deficit hyperactivity disorder (ADHD).

Design Cohort study.

Setting Denmark.

Participants All Danish singletons born alive from 1996 to 2009 were included. Using national medical registries, we defined in utero exposure to antidepressants as redemption of an antidepressant prescription by the mother 30 days prior to or during pregnancy. We defined maternal former users of antidepressants as women, who had redeemed a prescription up to 30 days prior to pregnancy, and never users as women who had never redeemed a prescription.

Main outcome measures ADHD was defined as redemption of a prescription for ADHD medication or an ADHD hospital diagnosis. Children were followed through 2010, and we used proportional-hazards regression to compute adjusted hazard ratios comparing children exposed in utero and children born to former antidepressant users with children borne to never users. To adjust for confounding from family-related factors, we conducted a within-mother between-pregnancy analysis comparing exposed children with unexposed siblings using conditional logistic regression.

Results We identified a cohort of 877,778 children, of whom 1.7% were exposed in utero. The overall median follow-up time was eight years; selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of users). The adjusted hazard ratio comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% confidence interval: 1.1 to 1.4), and 1.6 (95% confidence interval: 1.5 to 1.8) comparing children born to former users to children born to never users of antidepressants. In the

within-mother between-pregnancy analysis (n=867), the adjusted odds ratio was 0.7 (95% confidence interval: 0.4 to 1.4).

Conclusion This study provides no evidence to support a causal association between in utero exposure to antidepressants and risk of ADHD.

ARTICLE SUMMARY

Article focus

- Use of selective serotonin reuptake inhibitors is increasing also in pregnant women. Existing studies on in utero exposure to antidepressants and long-term neurodevelopmental outcomes are sparse.
- In this study we investigated whether in utero exposure to antidepressants is associated with increased risk of attention deficit hyperactivity disorder (ADHD).

Key messages

- We identified a cohort of 877,778 children, of whom 1.7% were exposed to antidepressants in utero. Selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of maternal users).
- While our analyses based on a general population comparison cohort showed a weak association between in utero exposure to antidepressants and ADHD, a within-mother between-pregnancy analyses were not consistent with a causal association. This observation strongly indicates the presence of unmeasured confounding by family-related factors in our comparisons with the general population. Also a former user analysis in the general comparison cohort confirmed presence of unmeasured confounding factors.

- This study provides no evidence to support a causal association between in utero exposure to antidepressants and risk of ADHD.

Strengths and limitations of this study

- The study was based on a large study population with long and virtually complete follow-up. Our use of data from population-based databases in a setting of universal health care practically eliminates the risk of recall and selection bias.
- We were limited by our lack of data on actual antidepressant intake by the mother and on the actual timing of intake; we therefore used prescription redemption as a proxy for this information, which may have biased our result toward the null hypothesis.
- ADHD is a clinical diagnosis based on subjective criteria, and diagnoses may therefore vary among practitioners. Misclassification of the outcome could have led us to overestimate the association if children of mothers with a psychiatric diagnosis where more likely to obtain psychiatric treatment.

INTRODUCTION

Up to 13% of pregnant women experience depression,[1] but only approximately 2% are treated with antidepressants.[2] Untreated depression is associated with maternal tobacco and alcohol use, poor diet intake, and risk of poor birth outcomes, including preterm birth.[3-6] However, use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has also been associated with adverse birth outcomes [7,8] as well as teratogenic effects.[9,10]

Early-life exposure to SSRIs or tricyclic antidepressive agents may cause behavioral changes, as shown in rodents.[11,12] The serotonin transporter, which is blocked by SSRIs, is expressed transiently in many brain areas during fetal life; serotonin plays a key role in neural development and maturation.[13] Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by impulsiveness, inattention, and hyperactivity.[14] The incidence of ADHD is increasing, with a current prevalence of approximately 5% in children.[15] Proposed risk factors include genetics, preterm birth, and prenatal exposure to smoking or maternal stress.[16-20] However, evidence on the risk of ADHD following in utero exposure to antidepressants is sparse, and the existing study is limited by short and incomplete follow-up and lack of data on important potential confounders.[21]

Evidence of an association between the use of antidepressants during pregnancy and later ADHD in the child would have major public health implications. In this study, we investigated whether in utero exposure to antidepressants was associated with an increased risk of ADHD using nationwide Danish medical registries with virtually complete long-term follow-up.

METHODS

Setting

The Danish healthcare system (5.5 million inhabitants and a yearly birth rate of approximately 65,000) provides tax-supported health services to all residents guaranteeing access to primary and secondary care free of charge. Except for emergencies, initial contact with the healthcare system is through general practitioners, who either treat patients themselves or refer them to hospitals or private practice specialists.

Study population and design

Using the Danish Medical Birth Registry, we identified a cohort of all singletons born alive from 1996 until the end of 2009. The Danish Medical Birth Registry contains computerized records of all deliveries in Denmark since 1973. Each record includes the civil registration number of the mother, father, and newborn, as well as multiple variables regarding the delivery, the newborn, and the mother. Data are collected by midwives or physicians overseeing delivery.[22] The civil registration number is a 10-digit number assigned to each Danish citizen at birth and to residents upon immigration, enabling accurate and unambiguous linkage of relevant registries at the individual level.[23] Siblings born to the same mother were identified through the civil registration system.[23] Thus, in addition to a general population comparison cohort, it was possible to identify a sibling comparison cohort that was highly suitable for optimizing adjustment for important potential family-related and genetic confounders.

Maternal antidepressant use

In utero exposure to antidepressants was defined as maternal redemption of a prescription for an antidepressant 30 days prior to or during pregnancy, as identified through the Danish National Prescription Registry.[24] Since January 1994 the registry has recorded the following information whenever a prescription is redeemed in Denmark: the civil registration number of the patient, the medication classification code (the anatomical therapeutic chemical classification system of the World Health Organization), and the date of dispensing. All antidepressants, as well as drugs for ADHD, are available by prescription only. Pregnancy was defined as starting from the first day in the last menstrual period, according to the Danish Medical Birth Registry. First-trimester exposure was defined as redemption of a prescription by the mother 30 days prior to the beginning of pregnancy and up to 12 weeks after the beginning of pregnancy; second-trimester exposure was defined as prescription redemption between 12 weeks and 28 weeks of pregnancy, and third-trimester exposure was defined as prescription redemption during the remainder of the pregnancy.[27] If the mother redeemed more than one prescription during pregnancy, the first redemption was used to determine the trimester of exposure. We defined maternal former users of antidepressants as women, who had redeemed a prescription up to 30 days prior to pregnancy, and never users as women who had never redeemed a prescription.

ADHD

ADHD was detected either as a diagnosis of ADHD or redemption of a prescription for ADHD medication. Using the Danish Psychiatric Registry [25] and the Danish National Registry of Patients,[26] we identified children in the study population with inpatient and outpatient hospital diagnoses of ADHD. The Danish Psychiatric Registry contains computerized data on all

admissions to psychiatric hospitals and psychiatric wards in Denmark. The Danish National Registry of Patients has tracked all inpatients in Danish hospitals since 1977, and outpatient clinic and emergency room visits at all public hospitals since 1995. Data recorded in the Danish National Registry of Patients and the Danish Psychiatric Registry include civil registration number of the patient, dates of admission and discharge, and up to 20 discharge diagnoses from each admission, classified according to the 8th revision of the *International Classification of Diseases* until 1993, and the 10th revision thereafter.

Diagnosing and treating ADHD is also handled by private practice psychiatrists and general practitioners in cooperation, without hospital contact. These patients are not recorded in the Danish Psychiatric Registry or the Danish National Registry of Patients. Therefore, to ensure completeness, we defined ADHD as either a diagnosis of ADHD or a redemption of a prescription for ADHD medication. Information on prescription redemption was obtained from the Danish National Prescription Registry.[24]

Covariates

We identified risk factors for ADHD that were potentially associated with maternal use of antidepressants. We obtained information on maternal and paternal psychiatric diagnoses anytime before baseline from the Danish Psychiatric Registry. We gathered information on maternal epilepsy, infections, and use of anxiolytics/hypnotics/sedatives during pregnancy from the Danish National Registry of Patients and the Danish National Prescription Registry. From the Danish Medical Birth Registry we obtained information on maternal age at birth, gender of the child, the child's birth order, maternal smoking during pregnancy, maternal body mass index (only available from 2004 and onwards), and marital status. As body mass index was only available from 2004 and marital status was incompletely registered, body mass index and marital status were only

included as potential confounders in separate subanalyses. We also obtained information on the child's gestational age, birth weight, and five-minute Apgar score from the Danish Medical Birth Registry. These variables were investigated because they may play a role in a causal pathway linking in utero antidepressant exposure and ADHD. Since antidepressant use and ADHD prevalence both increased between 1996 and 2010, we also adjusted for calendar time.

Statistical analyses

The children were followed from date of birth until the date of redemption of an ADHD prescription, receipt of an ADHD diagnosis, emigration, death, or the end of follow-up on December 31 2010, whichever came first.

General population comparison cohort

We compared children exposed to antidepressants in utero and also children of maternal former users with the unexposed children of never users (women who never redeemed a prescription for antidepressants). We performed separate analyses according to type of antidepressant (SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressive agents, other antidepressants, and combinations of antidepressants). For these subgroups, we conducted analyses comparing exposed children to unexposed children of never users. With Cox proportional-hazards regression, we computed crude and adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) as measures of relative risk. Subjects with missing data were excluded from the analyses. The assumption of proportional hazards was graphically verified.

Sibling comparison cohort

To optimize control for family-related factors such as genetics and socioeconomic or medical status, we conducted a within-mother between-pregnancy cohort analysis by restricting the study population to children of mothers who had more than one child and at least one exposed and one unexposed pregnancy. We then compared exposed children to unexposed children using a conditional logistic regression model. We computed adjusted odds ratios (aOR) with 95% CIs for receiving an ADHD diagnosis or redeeming a prescription for ADHD medication. In the first model, we adjusted for calendar time at birth to account for differences in length of follow up. In that way we were able to compare this sibling analysis with the time-to-event analysis used in the general population comparison cohort.[28] We made full adjustment in the second model. All statistical analyses were performed using SAS (version 9.2; SAS Institute Inc, Cary, NC, USA). This study was approved by the Danish Data Protection Agency (Record no. 2011-41-6465). Codes used to define study variables are provided in the Appendices.

RESULTS

We identified 877,778 singletons, of whom 15,008 (1.7%) were exposed to antidepressants in utero (Table 1). The most commonly used class of antidepressant by the mothers was SSRIs (78%, Table 2). The overall median follow-up time was eight years. A total of 12,841 (1.5%) participants developed ADHD (8,100 (0.9%) were detected as a diagnosis of ADHD, and 4,741 (0.5%) were identified through redemption of a prescription for ADHD medication as a first-outcome measure).

Maternal and paternal characteristics

The birth-giving age was higher among antidepressant users than never users. Maternal antidepressant users more frequently smoked during pregnancy, were unmarried, had psychiatric diagnoses other than depression, epilepsy or infections during pregnancy. They also used anxiolytics/hypnotics/sedatives during pregnancy more often than never users. Fathers of children born to maternal users of antidepressants were also more likely to have a psychiatric diagnosis than fathers of children born to never users (Table 1a).

Birth outcomes

The gender distribution was the same for exposed and unexposed children. Children exposed in utero to antidepressants had a higher prevalence of low birth weight (3.7% vs. 2.1%), lower Apgar score (seven or under) at five minutes (2.6% vs. 1.2%), and were born prematurely more often (15.4% vs. 8.6%) than unexposed children borne by never users (Table 1b).

Risk estimates

The aHR comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% CI: 1.1 to 1.4; Table 3). The aHR was 1.6 (95% CI: 1.5 to 1.8) when comparing children born to former users of antidepressants with children born to never users. Adjusting for the mother's body mass index and marital status in subanalyses did not change the estimates (results not shown). When stratifying according to trimester and class of antidepressants, we detected a minor association between ADHD and exposure in utero to any kind of

antidepressant in the first and second trimesters, as well as exposure to SSRIs or the group "other antidepressants" (Table 3). In the within-mother between-pregnancy analysis (n=867), the full aOR was 0.7 (95% CI: 0.4 to 1.4; Table 4).

DISCUSSION

While our analyses based on a general population comparison cohort showed a weak association between in utero exposure to antidepressants and ADHD, the within-mother between-pregnancy analyses were not consistent with a causal association. This observation strongly indicates the presence of unmeasured confounding by family-related factors in our comparisons with the general population. Also the former user analysis in the general comparison cohort confirmed presence of unmeasured confounding factors.

Our results extend the findings of an American study of claims-based data from 38,074 families that concluded, in line with our findings, that children exposed to SSRIs were not at increased risk of ADHD (OR: 0.91, 95% CI: 0.51 to 1.60) while children exposed to bupropion were at increased risk (OR: 3.63, 95% CI: 1.20 to 11.04), especially after second-trimester exposure.[21] This previous study was limited by short and incomplete follow-up and lack of data on important potential confounders.

The strengths of our study include its large study population with long and virtually complete follow-up. Our use of data from population-based databases in a setting of universal health care practically eliminates the risk of recall and selection bias. Importantly, the within-mother between-pregnancy analysis allowed us to effectively adjust for family-related factors, such as genetics and socioeconomic and medical status.

We were limited by our lack of data on actual antidepressant intake by the mother and on the actual timing of intake; we therefore used prescription redemption as a proxy for this information, which may have biased our result toward the null hypothesis. Also, ADHD is a clinical diagnosis based on subjective criteria, and diagnoses may therefore vary among practitioners. Misclassification of the outcome could, on the other hand, have led us to overestimate the association if children of mothers with a psychiatric diagnosis where more likely to obtain psychiatric treatment. The within-mother between-pregnancy analysis may also be limited by misclassification of in utero exposure to antidepressants, which may have led us to underestimate an association in this analysis. [29] However, the strong association between former maternal antidepressant use and ADHD in offspring, compared with a lack of exposure to antidepressants in utero, further supports the importance of causative factors other than antidepressant use.

In conclusion, this large-scale study with complete long-term follow-up for ADHD provides no evidence to support an association between in utero exposure to antidepressants and risk of ADHD.

Footnotes

Acknowledgements: We thank all participants in this study.

Competing interests: None declared.

Contributors: KL, MO, ABTA, and HTS made primary contributions to writing the manuscript. All authors contributed to the study conception and study design. TF performed data collection and statistical analyses and commented on the manuscript. All authors contributed to the interpretation of results, all revised the manuscript critically, and all approved the final manuscript. HTS is guarantor for this study.

Ethical approval: Register studies do not require ethical approval in Denmark. This study was approved by the Danish Data Protection Agency (Record no. 2011-41-6465).

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Data sharing: No additional data available.

Table 1a. Maternal and paternal characteristics of 877,778 singleton births in Denmark in 1996-2009, according to maternal use of antidepressants during pregnancy. Never users are women who had never redeemed a prescription for antidepressants.

Characteristic	Exposed in utero N (%)	Not exposed in utero and born to former users N (%)	Not exposed in utero and born to never users N (%)	Total N (%)
All births	15,008 (100)	45,978 (100)	816,792 (100)	877,778 (100)
Mother's age at birth				
24 years of age or less	2,206 (14.7)	5,340 (11.6)	114,203 (14.0)	121,749 (13.9)
25 to 29 years of age	4,449 (29.6)	14,146 (30.8)	286,404 (35.1)	304,999 (34.7)
30 to 34 years of age	5,048 (33.6)	16,318 (35.5)	287,344 (35.2)	308,710 (35.2)
35 to 39 years of age	2,731 (18.2)	8,377 (18.2)	111,166 (13.6)	122,274 (14.0)
40 years of age or more	574 (3.8)	1,797 (3.9)	17,675 (2.2)	20,046 (2.3)
Birth order				
First child	6,417 (42.8)	18,745 (40.8)	351,959 (43.1)	377,121 (43.0)
Second or later child	8,591 (57.2)	27,233 (59.2)	464,833 (57.0)	500,657 (57.0)
Smoking status				
Non-smoker	9,424 (62.8)	31,797 (69.2)	637,561 (78.1)	678,782 (77.3)
Smoker	5,033 (33.5)	12,707 (27.6)	148,094 (18.1)	165,834 (18.9)
Missing data	551 (3.7)	1,474 (3.2)	31,137 (3.8)	33,162 (3.8)
Marital status				
Married, civil partnership	4,049 (27.0)	13,164 (28.6)	360,924 (44.2)	378,137 (43.1)
Single, widow, divorced, or not registered / annulled civil partner ship	4,840 (32.2)	14,280 (31.1)	295,762 (36.2)	314,882 (35.9)

Missing or partner dead	6,119 (40.8)	18,534 (40.3)	160,106 (19.6)	184,759 (21.0)
Maternal diagnosis of depression	3,987 (26.6)	5,176 (11.3)	2,064 (0.3)	11,227 (1.3)
Maternal psychiatric diagnoses other than depression	4,136 (27.6)	8,659 (18.8)	28,247 (3.5)	41,042 (4.7)
Paternal psychiatric diagnoses	1,823 (12.1)	4,700 (10.2)	45,471 (5.6)	51,994 (5.9)
Maternal diseases	6,998 (46.6)	20,298 (44.2)	276,823 (33.9)	304,199 (34.7)
Epilepsy	315 (2.1)	909 (2.0)	8,313 (1.0)	9,537 (1.1)
Infections during pregnancy	6,838 (45.6)	19,829 (43.1)	271,789 (33.3)	298,456 (34.0)
Maternal medication use during pregnancy	1,764 (11.8)	1,354 (2.9)	5,137 (0.6)	8,255 (0.9)
Anxiolytics/hypnotives/sedatives				
Maternal body mass index (BMI)				
No BMI (before 2004)	4,681 (31.2)	13,748 (29.9)	489,283 (60.0)	507,712 (57.8)
Underweight (BMI 15-18.4 kg/m^2)	537 (3.6)	1,788 (3.9)	15,082 (1.8)	17,407 (2.0)
Normal weight (BMI 18.5-24.9 kg/m^2)	5,217 (34.8)	17,452 (38.0)	190,466 (23.3)	213,135 (24.3)
Overweight (BMI 25-29.9 kg/m^2)	2,166 (14.4)	6,332 (13.8)	63,044 (7.7)	71,542 (8.2)
Obese (BMI $\geq$ 30 kg/m^2)	1,635 (10.9)	4,244 (9.2)	34,052 (4.2)	39,931 (4.6)
BMI < 15 kg/m^2 or missing	772 (5.1)	2,414 (5.3)	24,865 (3.0)	28,051 (3.2)

Table 1b. Characteristics of 877,778 singleton births in Denmark in 1996-2009, according to maternal use of antidepressants during pregnancy. Never users are women who had never redeemed a prescription for antidepressants.

Characteristic	Exposed in utero N (%)	Not exposed in utero and born to former users N (%)	Not exposed in utero and born to never users N (%)	Total N (%)
Gender of the child				
Female	7,233 (48.2)	22,216 (48.3)	397,731 (48.7)	427,180 (48.7)
Male	7,775 (51.8)	23,762 (51.7)	419,061 (51.3)	450,598 (51.3)
Calendar period of birth				
1996-2000	2,000 (13.3)	5,542 (12.1)	314,467 (38.5)	322,009 (36.7)
2001-2005	5,294 (35.3)	16,706 (36.3)	287,077 (35.1)	309,077 (35.2)
2006-2009	7,714 (51.4)	23,730 (51.6)	215,248 (26.4)	246,692 (28.1)
Birth weight in grams				
1500-1999	163 (1.1)	418 (0.9)	5,629 (0.7)	6,210 (0.7)
2000-2499	549 (3.7)	1,259 (2.7)	17,444 (2.1)	19,252 (2.2)
2500-2999	2,164 (14.4)	5,511 (12.0)	81,730 (10.0)	89,405 (10.2)
3000-5500	11,924 (79.5)	38,189 (83.1)	700,553 (85.8)	750,666 (85.5)
Very low, very high, or missing	208 (1.4)	601 (1.3)	11,436 (1.4)	12,245 (1.4)
Gestational age				
Extremely premature or very premature, 19-31 weeks	150 (1.0)	388 (0.8)	5,193 (0.6)	5,731 (0.7)

Moderately premature, 32-37 weeks	2,303 (15.3)	5,140 (11.2)	70,517 (8.6)	77,960 (8.9)
Normal gestational age at birth, 38-48 weeks	12,482 (83.2)	40,272 (87.6)	735,496 (90.0)	788,250 (89.8)
Too low or missing gestational age at birth	73 (0.5)	178 (0.4)	5,586 (0.7)	5,837 (0.7)
Apgar score at five minutes				
Apgar score seven or under	385 (2.6)	610 (1.3)	10,135 (1.2)	11,130 (1.3)
Apgar score over seven	14,463 (96.4)	44,938 (97.7)	796,921 (97.6)	856,322 (97.6)
Missing	160 (1.1)	430 (0.9)	9,736 (1.2)	10,326 (1.2)

Table 2. Distribution of 15,008 maternal antidepressants users according to classes of antidepressants.

Class of antidepressant	Maternal users (%)
Selective serotonin reuptake inhibitors	11,721 (78)
Serotonin-norepinephrine reuptake inhibitors	763 (5)
Tricyclic antidepressive agents	716 (5)
Other	604 (4)
Combined	1,204 (8)
Total	15,008 (100)

Table 3. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for time to redeeming a prescription for attention deficit hyperactivity disorder (ADHD) medication or receiving the diagnosis of ADHD, comparing exposed children to unexposed children born to never users (women who had never redeemed a prescription on antidepressants).

Antidepressant drug exposure in utero	Crude HR and (95% CI)	Adjusted* HR and (95% CI)
Any	2.0 (1.7 to 2.3)	1.2 (1.1 to 1.4)
First trimester exposure	2.0 (1.7 to 2.3)	1.2 (1.0 to 1.4)
Second trimester exposure	2.6 (1.7 to 4.2)	1.5 (0.9 to 2.4)
Third trimester exposure	1.3 (0.6 to 3.2)	0.8 (0.3 to 2.0)
Selective serotonin reuptake inhibitor	2.1 (1.8 to 2.4)	1.2 (1.0 to 1.5)
Serotonin-norepinephrine reuptake inhibitor	1.2 (0.5 to 3.3)	1.0 (0.4 to 2.5)
Tricyclic antidepressive agent	1.8 (1.1 to 3.0)	1.1 (0.6 to 2.0)
Others	2.4 (1.3 to 4.4)	1.6 (0.8 to 3.0)
Combined use	1.9 (1.1 to 3.4)	0.8 (0.4 to 1.7)

*Adjusted for gender of the child, calendar time at birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections, epilepsy), and maternal medication (anxiolytics/hypnotics/sedatives) use during pregnancy.

Table 4. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for a within-mother between-pregnancy analysis on a subpopulation of 867 children, restricted to mothers who had more than one child, with at least one exposed and at least one unexposed pregnancy. Children exposed in utero to are compared to unexposed children.

Adjusted* OR (95% CI)	Adjusted** OR (95% CI)
0.8 (0.5 to 1.2)	0.7 (0.4 to 1.4)

*Adjusted for calendar time at birth.

**Adjusted for calendar time at birth, gender of the child, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections and epilepsy), and maternal medicine use (anxiolytics/hypnotics/sedatives) during pregnancy.

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Appendix 1. Anatomical therapeutic chemical (ATC) classification codes for antidepressants.

Class of antidepressant	Antidepressants	ATC codes
All antidepressants		N06A
Selective serotonin reuptake inhibitors	Zimeldine, fluoxetine, citalopram, paroxetine, sertraline, alaproclate, fluvoxamine, etoperidone, escitalopram	N06AB
Serotonin-norepinephrine reuptake inhibitors	Venlafaxine, milnacipran, duloxetine, desvenlafaxine	N06AX16 (N06AA22); 17 (N06AA24); 21; 23
Tricyclic antidepressive agents	Desipramine, imipramine, imipramine oxide, clomipramine, opipramol, trimipramine, lofepramine, dibenzepin, amitriptyline, nortriptyline, protriptyline, doxepin, iprindole, melitracene, butriptyline, dosulepin (dothiepin), amoxapine, dimetacrine, amineptin, maprotiline, quinupramine	N06AA
Other	Isocarboxazid, nialamide, phenelzine, tranylcypromine, iproniazid, iproclozide, moclobemide, toloxatone, oxitriptan, tryptophan, mianserin, nomifensine, trazodone, nefazodone, minaprine, bifemelane, viloxazine, oxaflozane, mirtazapine, bupropion, medifoxamine, tianeptine, pivagabine, reboxetine, gepirone, agomelatine, vilazodone, pericon	N06AF; N06AG N06AX01-12 (or N07BA02); 13-15; 18-19; 22; 24-25

Appendix 2. Anatomical therapeutic chemical (ATC) codes for attention deficit hyperactivity disorder medications.

Class of medication		ATC codes
All medication		N06B
Central effect sympathomimetics	Amphetamine, dextroamphetamine, methamphetamine, methylphenidate, pemoline, fencamfamine, modafinil, fenozolone, atomoxetine, fenethylline	N06BA (or N06BB01-03)
Xanthin derivates	Coffein, propentofylline	N06BC

Appendix 3. Covariates listed with their categories, their *International Classification of Diseases*, 8th revision (ICD-8) codes, their *International Classification of Diseases*, 10th revision (ICD-10), or their anatomical therapeutic chemical (ATC) classification codes.

Covariates	Categories, ICD-8, ICD-10, or ATC codes
Mother's age at birth	≤ 24; 25-29; 30-34; 35-39; ≥ 40 years of age
Birth order	1; ≥ 2
Maternal smoking	Non-smoking, smoking
Marital status	Married/civil partnership, single/widow/divorced/ annulled civil partnership
Maternal body mass index	< 18.5; 18.5-24.9; 25-29,9; ≥ 30 kg/m^2
Maternal psychiatric diagnoses	
Schizophrenia and related disorders	ICD-8: 295; 297; 298 (excluded 29809); 299 ICD-10: F20-F29 (excluded F251)
Alcohol-related disorders	ICD-8: 291; 303; 98009 ICD-10: F10
Drug-related disorders	ICD-8: 29430; 29438; 29439; 304 ICD-10: F11-F16; F18-19
Affective disorders (depression not included)	ICD-8: 29619; 29639; 29689; 29699 ICD-10 codes: F30; F31; F34; F38; F39
Others (diagnoses for which antidepressant drug treatment is indicated are not included)	ICD-8 codes: 290; 292-294 (excluded 29430; 29438; 29439) 300-302 (excluded 30009; 30039; 30049); 305-309 (excluded 30650) ICD-10 codes: F00-F09; F49; F51-F99

Paternal psychiatric diagnoses	
Schizophrenia and related disorders	ICD-8: 295; 297; 298; 299 ICD-10: F20-F29
Alcohol-related disorders	ICD-8: 291; 303; 98009 ICD-10: F10
Drug-related disorders	ICD-8: 29430; 29438; 29439; 304 ICD-10: F11-F16; F18-19
Affective disorders	ICD-8: 296 ICD-10 codes: F30- F39
Others	ICD-8 codes: 290; 292-294 (excluded 29430; 29438; 29439); 300-302; 305-309 ICD-10 codes: F00-F09; F40-F99
Maternal diseases	
Epilepsy or use of antiepileptics	ICD-8 code: 345 ICD-10 code: G40 ATC code: N03
Urinary tract infections or pelvic inflammatory disease during pregnancy	ICD-10 code: O23
Rubella during pregnancy	ICD-10 code: B06
Parvovirus infection during pregnancy	ICD-10 code: B976
Other infections during pregnancy	ICD-10 codes: A00-A99, B00- B99 (excluded B58;

or use of antibiotics	B06; B976) ATC codes: J01 (or G04AB01-06; G04AC; J01DA01-19; 21-27; 30-42; 63)
Maternal medicine use during pregnancy	
Anxiolytics/hypnotics/ sedatives	ATC codes: N05B; N05C (or R06AE08; N05CG01; N05CM17)
Birth weight	< 2000; 2000-2499; 2500-3000; > 3000 g
Gestational age	Extremely premature (< 28 weeks); very premature (28-32 weeks); moderately premature (32-37 weeks); normal (>37 weeks)
Apgar score at five minutes	Apgar ≤ 7; Apgar ≥ 7
Maternal history of depression	ICD-8 code: 29809; 29609; 29629 ICD-10 codes: F251; F32; F33

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7,8,9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,8,9
Bias	9	Describe any efforts to address potential sources of bias	8,9,10
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9,15,16,17,18
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10
		(*b*) Describe any methods used to examine subgroups and interactions	9,10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,15,16,17,18
		(b) Indicate number of participants with missing data for each variable of interest	15,16,17,18
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11,12,20,21
		(*b*) Report category boundaries when continuous variables were categorized	15,16,17,18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20,21
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder: A nationwide Danish cohort study

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In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder: A nationwide Danish cohort study

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Keywords: Antidepressive agents, prenatal, attention deficit hyperactivity disorder

ABSTRACT

Objective To investigate whether in utero exposure to antidepressants is associated with increased risk of attention deficit hyperactivity disorder (ADHD).

Design Cohort study.

Setting Denmark.

Participants All Danish singletons born alive from 1996 to 2009 were included. Using national medical registries, we defined in utero exposure to antidepressants as redemption of an antidepressant prescription by the mother 30 days prior to or during pregnancy. We defined maternal former users of antidepressants as women, who had redeemed a prescription up to 30 days prior to pregnancy, and never users as women who had never redeemed a prescription.

Main outcome measures ADHD was defined as redemption of a prescription for ADHD medication or an ADHD hospital diagnosis. Children were followed through 2010, and we used proportional-hazards regression to compute adjusted hazard ratios comparing children exposed in utero and children born to former antidepressant users with children borne to never users. To adjust for confounding from family-related factors, we conducted a within-mother between-pregnancy analysis comparing exposed children with unexposed siblings using conditional logistic regression.

Results We identified a cohort of 877,778 children, of whom 1.7% were exposed in utero. The overall median follow-up time was eight years; selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of users). The adjusted hazard ratio comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% confidence interval: 1.1 to 1.4), and 1.6 (95% confidence interval: 1.5 to 1.8) comparing children born to former users to children born to never users of antidepressants. In the

within-mother between-pregnancy analysis (n=867), the adjusted odds ratio was 0.7 (95% confidence interval: 0.4 to 1.4).

Conclusion This study provides no evidence to support a causal association between in utero exposure to antidepressants and risk of ADHD.

ARTICLE SUMMARY

Article focus

- Use of selective serotonin reuptake inhibitors is increasing in pregnant women. Existing studies on in utero exposure to antidepressants and long-term neurodevelopmental outcomes are sparse.
- In this study we investigated whether in utero exposure to antidepressants is associated with increased risk of attention deficit hyperactivity disorder (ADHD).

Key messages

- We identified a cohort of 877,778 children, of whom 1.7% were exposed to antidepressants in utero. Selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of maternal users).
- While our analyses based on a general population comparison cohort showed a weak association between in utero exposure to antidepressants and ADHD, a within-mother between-pregnancy analysis was not consistent with a causal association. This observation strongly indicates the presence of unmeasured confounding by family-related factors in our comparisons with the general population. Also a former user analysis in the general comparison cohort confirmed presence of unmeasured confounding factors.

- This study provides no evidence to support a causal association between in utero exposure to antidepressants and risk of ADHD.

Strengths and limitations of this study

- The study was based on a large study population with long and virtually complete follow-up. Our use of data from population-based databases in a setting of universal health care practically eliminates the risk of recall and selection biases.
- We were limited by our lack of data on actual antidepressant intake by the mother and on the actual timing of intake; we used prescription redemption as a proxy for this information, which may have biased our results toward the null hypothesis.
- ADHD is a clinical diagnosis based on subjective criteria, and diagnoses therefore may vary among practitioners. Misclassification of the outcome could have led us to overestimate the association if children of mothers with a psychiatric diagnosis were more likely to obtain psychiatric treatment.

INTRODUCTION

Up to 13% of pregnant women experience depression,[1] but only approximately 2% are treated with antidepressants.[2] Untreated depression is associated with maternal tobacco and alcohol use, poor dietary intake, and risk of poor birth outcomes, including preterm birth.[3-6] However, use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has also been associated with adverse birth outcomes [7,8] as well as teratogenic effects.[9,10]

Early-life exposure to SSRIs or tricyclic antidepressive agents may cause behavioral changes, as observed in rodents.[11,12] The serotonin transporter, which is blocked by SSRIs, is expressed transiently in many brain areas during fetal life; serotonin plays a key role in neural development and maturation.[13] Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by impulsiveness, inattention, and hyperactivity.[14] The incidence of ADHD is increasing, with a current prevalence of approximately 5% in children.[15] Proposed risk factors include genetics, preterm birth, and prenatal exposure to smoking or maternal stress.[16-20] However, evidence about risk of ADHD following in utero exposure to antidepressants is limited to one study, which found no evidence for an association between in utero exposure to SSRIs and ADHD (OR: 0.91, 95% CI: 0.51 to 1.60) .[21]

Evidence of an association between antidepressant use during pregnancy and later ADHD in the offspring would have major public health implications. In this study, we investigated whether in utero exposure to antidepressants was associated with an increased risk of ADHD using nationwide Danish medical registries with virtually complete long-term follow-up.

METHODS

Setting

The Danish healthcare system (5.5 million inhabitants and a yearly birth rate of approximately 65,000) provides tax-supported health services to all residents guaranteeing access to primary and secondary care free of charge. Except for emergencies, initial contact with the healthcare system is through general practitioners, who either treat patients themselves or refer them to hospitals or to private practice specialists.

Study population and design

Using the Danish Medical Birth Registry, we identified a cohort of all singletons born alive from 1996 until the end of 2009. The Danish Medical Birth Registry contains computerized records of all deliveries in Denmark since 1973. Each record includes the civil registration number of the mother, father, and newborn, as well as multiple variables regarding the delivery, the newborn, and the mother. Data are collected by midwives or physicians overseeing delivery.[22] The civil registration number is a 10-digit number assigned to each Danish citizen at birth and to residents upon immigration, enabling accurate and unambiguous linkage of relevant registries at the individual level.[23] Siblings born to the same mother were identified through the civil registration system.[23] Thus, in addition to a general population comparison cohort, it was possible to identify a sibling comparison cohort that was highly suitable for optimizing adjustment for important potential family-related and genetic confounders.

Maternal antidepressant use

In utero exposure to antidepressants was defined as maternal redemption of a prescription for an antidepressant 30 days prior to or during pregnancy, as identified through the Danish National Prescription Registry.[24] Since January 1994 the registry has recorded the following information whenever a prescription is redeemed in Denmark: the civil registration number of the patient, the medication classification code (the anatomical therapeutic chemical classification system of the World Health Organization), and the date of dispensing. All antidepressants, as well as drugs for ADHD, are available by prescription only in Denmark. Pregnancy was defined as starting from the first day in the last menstrual period, according to the Danish Medical Birth Registry. First-trimester exposure was defined as redemption of a prescription by the mother 30 days prior to the beginning of pregnancy and up to 12 weeks after the beginning of pregnancy; second-trimester exposure was defined as prescription redemption between 12 weeks and 28 weeks of pregnancy, and third-trimester exposure was defined as prescription redemption during the remainder of the pregnancy.[27] If the mother redeemed more than one prescription during pregnancy, the first redemption was used to determine the trimester of exposure. We defined maternal former users of antidepressants as women, who had redeemed a prescription up to 30 days prior to pregnancy, and never users as women who had never redeemed a prescription.

ADHD

ADHD was detected either as a diagnosis of ADHD or redemption of a prescription for ADHD medication. Using the Danish Psychiatric Registry [25] and the Danish National Registry of Patients,[26] we identified children in the study population with inpatient and outpatient hospital diagnoses of ADHD. The Danish Psychiatric Registry contains computerized data on all admissions to psychiatric hospitals and psychiatric wards in Denmark. The Danish National

Registry of Patients has tracked all inpatient stays in Danish hospitals since 1977, and outpatient clinic and emergency room visits at all public hospitals since 1995. Data recorded in the Danish National Registry of Patients and the Danish Psychiatric Registry include civil registration number of the patient, dates of admission and discharge, and up to 20 discharge diagnoses from each admission, classified according to the 8th revision of the *International Classification of Diseases* until 1993, and the 10th revision thereafter.

Diagnosing and treating ADHD is also handled by private practice psychiatrists and general practitioners in cooperation, without hospital contact. These patients are not recorded in the Danish Psychiatric Registry or the Danish National Registry of Patients. Therefore, to ensure completeness, we defined ADHD as either a diagnosis of ADHD or a redemption of a prescription for ADHD medication. Information on prescription redemption was obtained from the Danish National Prescription Registry.[24]

Covariates

We identified risk factors for ADHD that were potentially associated with maternal use of antidepressants. We obtained information on maternal and paternal psychiatric diagnoses anytime before baseline from the Danish Psychiatric Registry. We gathered information on maternal epilepsy, infections, and use of anxiolytics/hypnotics/sedatives during pregnancy from the Danish National Registry of Patients and the Danish National Prescription Registry. From the Danish Medical Birth Registry we obtained information on maternal age at birth, gender of the child, the child's birth order, maternal smoking during pregnancy, maternal body mass index , and marital status. As body mass index was only available starting in 2004 and marital status was incompletely registered, body mass index and marital status were only included as potential confounders in separate subanalyses. We also obtained information on the child's gestational age,

birth weight, and five-minute Apgar score from the Danish Medical Birth Registry. These variables were investigated because they may play a role in a causal pathway linking in utero antidepressant exposure and ADHD. Since antidepressant use and ADHD prevalence both increased between 1996 and 2010, we also adjusted for calendar time.

Statistical analyses

The children were followed from date of birth until the date of redemption of an ADHD prescription, receipt of an ADHD diagnosis, emigration, death, or the end of follow-up on December 31 2010, whichever came first.

General population comparison cohort

We compared children exposed to antidepressants in utero and also children of maternal former users with the unexposed children of never users (women who never redeemed a prescription for antidepressants). We performed separate analyses according to type of antidepressant (SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressive agents, other antidepressants, and combinations of antidepressants). For these subgroups, we conducted analyses comparing exposed children to unexposed children of never users. With Cox proportional-hazards regression, we computed crude and adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) as measures of relative risk. Subjects with missing data were excluded from the analyses. The assumption of proportional hazards was graphically verified.

Sibling comparison cohort

To optimize control for family-related factors such as genetics and socioeconomic or medical status, we conducted a within-mother between-pregnancy cohort analysis by restricting the study population to children of mothers who had more than one child and at least one exposed and one unexposed pregnancy. We then compared exposed children to unexposed children using a conditional logistic regression model. We computed adjusted odds ratios (aOR) with 95% CIs for receiving an ADHD diagnosis or redeeming a prescription for ADHD medication. In the first model, we adjusted for calendar time at birth to account for differences in length of follow up. In that way we were able to compare the sibling analysis with the time-to-event analysis used in the general population comparison cohort.[28] The second model was fully adjusted. All statistical analyses were performed using SAS (version 9.2; SAS Institute Inc, Cary, NC, USA). This study was approved by the Danish Data Protection Agency (Record no. 2013-41-1790). Codes used to define study variables are provided in the Appendices.

RESULTS

We identified 877,778 singletons, of whom 15,008 (1.7%) were exposed to antidepressants in utero (Table 1). The most commonly used class of antidepressant by the mothers was SSRIs (78%, Table 2). The overall median follow-up time was eight years. A total of 12,841 (1.5%) participants developed ADHD (8,100 (0.9%) were detected as a diagnosis of ADHD, and 4,741 (0.5%) were identified through redemption of a prescription for ADHD medication as a first-outcome measure). In the within-mother between-pregnancy analysis we identified 867 children (330 groups of siblings) of whom 348 (40%) were exposed to antidepressants in utero. Of the 348 exposed children, 79 (23%) developed ADHD. Of the 519 unexposed children, 270 (52%)

developed ADHD. Of 330 groups of siblings 311 groups contained one child with ADHD and 19 pairs contained two children with ADHD.

Maternal and paternal characteristics

Age at delivery was higher among antidepressant users than never users. Maternal antidepressant users more frequently smoked during pregnancy, were unmarried, had psychiatric diagnoses other than depression, epilepsy or infections during pregnancy. They also used anxiolytics/hypnotics/sedatives during pregnancy more often than never users. Fathers of children born to maternal users of antidepressants were also more likely to have a psychiatric diagnosis than fathers of children born to never users (Table 1a).

Birth outcomes

Gender distribution was the same for exposed and unexposed children. Children exposed in utero to antidepressants had a higher prevalence of low birth weight (3.7% vs. 2.1%), low Apgar score (seven or under) at five minutes (2.6% vs. 1.2%), and were born prematurely more often (15.4% vs. 8.6%) than unexposed children borne by never users (Table 1b).

Risk estimates

The aHR comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% CI: 1.1 to 1.4; Table 3). The aHR was 1.6 (95% CI: 1.5 to 1.8) when comparing children born to former users of antidepressants with children born to never users. Adjusting for the mother's body mass index and marital status in subanalyses did not change the

estimates (results not shown). When stratifying according to trimester and class of antidepressants, we detected a minor association between ADHD and exposure in utero to any kind of antidepressant in the first and second trimesters, as well as exposure to SSRIs or the group "other antidepressants" (Table 3). In the within-mother between-pregnancy analysis, the full aOR was 0.7 (95% CI: 0.4 to 1.4; Table 4).

DISCUSSION

While our analyses based on a general population comparison cohort showed a weak association between in utero exposure to antidepressants and ADHD, the within-mother between-pregnancy analyses were not consistent with a causal association. This observation strongly indicates the presence of unmeasured confounding by family-related factors in our comparisons with the general population. The former user analysis in the general comparison cohort also confirmed presence of unmeasured confounding factors.

Our results extend the findings of an American study of claims-based data from 38,074 families that concluded, in line with our findings, that children exposed to SSRIs were not at increased risk of ADHD (OR: 0.91, 95% CI: 0.51 to 1.60) while children exposed to bupropion were at increased risk (OR: 3.63, 95% CI: 1.20 to 11.04), especially after second-trimester exposure.[21] The study was limited by maternal smoking during pregnancy as a potential confounder, especially in the results for exposure to bupropion as this antidepressant is used for smoking cessation. Bupropion (which in Denmark is used for smoking cessation only) was contained in the group "other" antidepressants in our study. The number of children exposed to this drug in utero was only 135 and due to sparse data we did not perform separate regression analyses.

The strengths of our study include its large study population with long and virtually complete follow-up. Our use of data from population-based databases in a setting of universal health care practically eliminates the risk of recall and selection biases. Importantly, the within-mother between-pregnancy analysis allowed us to effectively adjust for family-related factors, such as genetics and socioeconomic and medical status.

We were limited by our lack of data on actual antidepressant intake by the mother and on the actual timing of intake. We used prescription redemption as a proxy for this information which could lead to misclassification of exposure status. Regarding children classified as exposed in utero, we cannot be sure that women who redeemed a prescription 30 days before or during pregnancy actually used the drugs during pregnancy. Also, drugs redeemed earlier in life could have been stored for later use. Therefore women categorized as former users might have been using antidepressants during pregnancy. Furthermore, the Danish National Prescription Registry [24] has only recorded information since 1994. Among women who were categorized as never users some may have used the drugs before 1994. Such misclassification of exposure may have biased our result toward the null. Also, ADHD is a clinical diagnosis based on subjective criteria, and diagnoses may vary among practitioners. Misclassification could have led us to overestimate the association if children of mothers with a psychiatric diagnosis were more likely to obtain psychiatric treatment. At the same time, children with ADHD were identified based on hospital diagnoses and drug prescriptions. Thus, patients with ADHD diagnosed by private psychiatrists or general practitioners and not prescribed drug treatment would be misclassified as not having ADHD. This could lead to an underestimation of the association. The within-mother between-pregnancy analysis also may be limited by misclassification of exposure status and outcome. Such misclassification may have led us to underestimate an association in this analysis.[29] However, the strong association between former maternal antidepressant use and ADHD in offspring, compared

with a lack of exposure to antidepressants in utero, further supports the importance of causative factors other than antidepressant use. Comorbid ADHD in mothers using antidepressants would potentially conceal a causal association between in utero exposure to antidepressants and ADHD, given the strong ADHD risk conveyed by parental ADHD. However, given the reported prevalence of ADHD among adults with major depression, ranging from 9%-16% [30] we do not believe parental ADHD can explain the null association.

In conclusion, this large-scale study with complete long-term follow-up for ADHD provides no evidence to support an association between in utero exposure to antidepressants and risk of ADHD.

Footnotes

Acknowledgements: We thank all participants in this study.

Competing interests: None declared.

Contributors: KL, MO, ABTA, and HTS made primary contributions to writing the manuscript. All authors contributed to the study conception and study design. TF performed data collection and statistical analyses and commented on the manuscript. All authors contributed to the interpretation of results, all revised the manuscript critically, and all approved the final manuscript. HTS is guarantor for this study.

Ethical approval: Register studies do not require ethical approval in Denmark. This study was approved by the Danish Data Protection Agency (Record no. 2013-41-1790).

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Data sharing: No additional data available.

Table 1a. Maternal and paternal characteristics of 877,778 singleton births in Denmark in 1996-2009, according to maternal use of antidepressants during pregnancy. Never users are women who had never redeemed a prescription for antidepressants.

Characteristic	Exposed in utero N (%)	Not exposed in utero and born to former users N (%)	Not exposed in utero and born to never users N (%)	Total N (%)
All births	15,008 (100)	45,978 (100)	816,792 (100)	877,778 (100)
Mother's age at birth				
24 years of age or less	2,206 (14.7)	5,340 (11.6)	114,203 (14.0)	121,749 (13.9)
25 to 29 years of age	4,449 (29.6)	14,146 (30.8)	286,404 (35.1)	304,999 (34.7)
30 to 34 years of age	5,048 (33.6)	16,318 (35.5)	287,344 (35.2)	308,710 (35.2)
35 to 39 years of age	2,731 (18.2)	8,377 (18.2)	111,166 (13.6)	122,274 (14.0)
40 years of age or more	574 (3.8)	1,797 (3.9)	17,675 (2.2)	20,046 (2.3)
Birth order				
First child	6,417 (42.8)	18,745 (40.8)	351,959 (43.1)	377,121 (43.0)
Second or later child	8,591 (57.2)	27,233 (59.2)	464,833 (57.0)	500,657 (57.0)
Smoking status				
Non-smoker	9,424 (62.8)	31,797 (69.2)	637,561 (78.1)	678,782 (77.3)
Smoker	5,033 (33.5)	12,707 (27.6)	148,094 (18.1)	165,834 (18.9)
Missing data	551 (3.7)	1,474 (3.2)	31,137 (3.8)	33,162 (3.8)
Marital status				
Married, civil partnership	4,049 (27.0)	13,164 (28.6)	360,924 (44.2)	378,137 (43.1)
Single, widow, divorced, or not registered / annulled civil partner ship	4,840 (32.2)	14,280 (31.1)	295,762 (36.2)	314,882 (35.9)

Missing or partner dead	6,119 (40.8)	18,534 (40.3)	160,106 (19.6)	184,759 (21.0)
Maternal diagnosis of depression	3,987 (26.6)	5,176 (11.3)	2,064 (0.3)	11,227 (1.3)
Maternal psychiatric diagnoses other than depression	4,136 (27.6)	8,659 (18.8)	28,247 (3.5)	41,042 (4.7)
Paternal psychiatric diagnoses	1,823 (12.1)	4,700 (10.2)	45,471 (5.6)	51,994 (5.9)
Maternal diseases	6,998 (46.6)	20,298 (44.2)	276,823 (33.9)	304,199 (34.7)
Epilepsy	315 (2.1)	909 (2.0)	8,313 (1.0)	9,537 (1.1)
Infections during pregnancy	6,838 (45.6)	19,829 (43.1)	271,789 (33.3)	298,456 (34.0)
Maternal medication use during pregnancy	1,764 (11.8)	1,354 (2.9)	5,137 (0.6)	8,255 (0.9)
Anxiolytics/hypnotives/sedatives				
Maternal body mass index (BMI)				
No BMI (before 2004)	4,681 (31.2)	13,748 (29.9)	489,283 (60.0)	507,712 (57.8)
Underweight (BMI 15-18.4 kg/m^2)	537 (3.6)	1,788 (3.9)	15,082 (1.8)	17,407 (2.0)
Normal weight (BMI 18.5-24.9 kg/m^2)	5,217 (34.8)	17,452 (38.0)	190,466 (23.3)	213,135 (24.3)
Overweight (BMI 25-29.9 kg/m^2)	2,166 (14.4)	6,332 (13.8)	63,044 (7.7)	71,542 (8.2)
Obese (BMI $\geq$ 30 kg/m^2)	1,635 (10.9)	4,244 (9.2)	34,052 (4.2)	39,931 (4.6)
BMI < 15 kg/m^2 or missing	772 (5.1)	2,414 (5.3)	24,865 (3.0)	28,051 (3.2)

Table 1b. Characteristics of 877,778 singleton births in Denmark in 1996-2009, according to maternal use of antidepressants during pregnancy. Never users are women who had never redeemed a prescription for antidepressants.

Characteristic	Exposed in utero N (%)	Not exposed in utero and born to former users N (%)	Not exposed in utero and born to never users N (%)	Total N (%)
Gender of the child				
Female	7,233 (48.2)	22,216 (48.3)	397,731 (48.7)	427,180 (48.7)
Male	7,775 (51.8)	23,762 (51.7)	419,061 (51.3)	450,598 (51.3)
Calendar period of birth				
1996-2000	2,000 (13.3)	5,542 (12.1)	314,467 (38.5)	322,009 (36.7)
2001-2005	5,294 (35.3)	16,706 (36.3)	287,077 (35.1)	309,077 (35.2)
2006-2009	7,714 (51.4)	23,730 (51.6)	215,248 (26.4)	246,692 (28.1)
Birth weight in grams				
1500-1999	163 (1.1)	418 (0.9)	5,629 (0.7)	6,210 (0.7)
2000-2499	549 (3.7)	1,259 (2.7)	17,444 (2.1)	19,252 (2.2)
2500-2999	2,164 (14.4)	5,511 (12.0)	81,730 (10.0)	89,405 (10.2)
3000-5500	11,924 (79.5)	38,189 (83.1)	700,553 (85.8)	750,666 (85.5)
Very low, very high, or missing	208 (1.4)	601 (1.3)	11,436 (1.4)	12,245 (1.4)
Gestational age				
Extremely premature or very premature, 19-31 weeks	150 (1.0)	388 (0.8)	5,193 (0.6)	5,731 (0.7)

Moderately premature, 32-37 weeks	2,303 (15.3)	5,140 (11.2)	70,517 (8.6)	77,960 (8.9)
Normal gestational age at birth, 38-48 weeks	12,482 (83.2)	40,272 (87.6)	735,496 (90.0)	788,250 (89.8)
Too low or missing gestational age at birth	73 (0.5)	178 (0.4)	5,586 (0.7)	5,837 (0.7)
Apgar score at five minutes				
Apgar score seven or under	385 (2.6)	610 (1.3)	10,135 (1.2)	11,130 (1.3)
Apgar score over seven	14,463 (96.4)	44,938 (97.7)	796,921 (97.6)	856,322 (97.6)
Missing	160 (1.1)	430 (0.9)	9,736 (1.2)	10,326 (1.2)

Table 2. Distribution of 15,008 maternal antidepressants users according to classes of antidepressants.

Class of antidepressant	Maternal users (%)
Selective serotonin reuptake inhibitors	11,721 (78)
Serotonin-norepinephrine reuptake inhibitors	763 (5)
Tricyclic antidepressive agents	716 (5)
Other	604 (4)
Combined	1,204 (8)
Total	15,008 (100)

Table 3. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for time to redeeming a prescription for attention deficit hyperactivity disorder (ADHD) medication or receiving the diagnosis of ADHD, comparing exposed children to unexposed children born to never users (women who had never redeemed a prescription on antidepressants).

Antidepressant drug exposure in utero	Crude HR and (95% CI)	Adjusted* HR and (95% CI)
Any	2.0 (1.7 to 2.3)	1.2 (1.1 to 1.4)
First trimester exposure	2.0 (1.7 to 2.3)	1.2 (1.0 to 1.4)
Second trimester exposure	2.6 (1.7 to 4.2)	1.5 (0.9 to 2.4)
Third trimester exposure	1.3 (0.6 to 3.2)	0.8 (0.3 to 2.0)
Selective serotonin reuptake inhibitor	2.1 (1.8 to 2.4)	1.2 (1.0 to 1.5)
Serotonin-norepinephrine reuptake inhibitor	1.2 (0.5 to 3.3)	1.0 (0.4 to 2.5)
Tricyclic antidepressive agent	1.8 (1.1 to 3.0)	1.1 (0.6 to 2.0)
Others	2.4 (1.3 to 4.4)	1.6 (0.8 to 3.0)
Combined use	1.9 (1.1 to 3.4)	0.8 (0.4 to 1.7)

*Adjusted for gender of the child, calendar time at birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections, epilepsy), and maternal medication (anxiolytics/hypnotics/sedatives) use during pregnancy.

Table 4. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for a within-mother between-pregnancy analysis on a subpopulation of 867 children, restricted to mothers who had more than one child, with at least one exposed and at least one unexposed pregnancy. Children exposed in utero are compared to unexposed children.

Adjusted* OR (95% CI)	Adjusted** OR (95% CI)
0.8 (0.5 to 1.2)	0.7 (0.4 to 1.4)

*Adjusted for calendar time at birth.

**Adjusted for calendar time at birth, gender of the child, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections and epilepsy), and maternal medicine use (anxiolytics/hypnotics/sedatives) during pregnancy.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7,8,9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,8,9
Bias	9	Describe any efforts to address potential sources of bias	8,9,10
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9,15,16,17,18
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10
		(*b*) Describe any methods used to examine subgroups and interactions	9,10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,15,16,17,18
		(b) Indicate number of participants with missing data for each variable of interest	15,16,17,18
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11,12,20,21
		(*b*) Report category boundaries when continuous variables were categorized	15,16,17,18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20,21
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder: A nationwide Danish cohort study

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Keywords: Antidepressive agents, prenatal, a~~A~~ttention deficit hyperactivity disorder

ABSTRACT

Objective To investigate whether in utero exposure to antidepressants is associated with increased risk of attention deficit hyperactivity disorder (ADHD).

Design Cohort study.

Setting Denmark.

Participants All Danish singletons born alive from 1996 to 2009 were included. Using national medical registries, we defined in utero exposure to antidepressants as redemption of an antidepressant prescription by the mother 30 days prior to or during pregnancy. We defined maternal former users of antidepressants as women, who had redeemed a prescription up to 30 days prior to pregnancy, and never users as women who had never redeemed a prescription.

Main outcome measures ADHD was defined as redemption of a prescription for ADHD medication or an ADHD hospital diagnosis. Children were followed through 2010, and we used proportional-hazards regression to compute adjusted hazard ratios comparing children exposed in utero and children born to former antidepressant users with children borne to never users. To adjust for confounding from family-related factors, we conducted a within-mother between-pregnancy analysis comparing exposed children with unexposed siblings using conditional logistic regression.

Results We identified a cohort of 877,778 children, of whom 1.7% were exposed in utero. The overall median follow-up time was eight years; selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of users). The adjusted hazard ratio comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% confidence interval: 1.1 to 1.4), and 1.6 (95% confidence interval: 1.5 to 1.8) comparing children born to former users to children born to never users of antidepressants. In the

within-mother between-pregnancy analysis (n=867), the adjusted odds ratio was 0.7 (95% confidence interval: 0.4 to 1.4).

Conclusion This study provides no evidence to support a causal association between in utero exposure to antidepressants and risk of ADHD.

ARTICLE SUMMARY

Article focus

- Use of selective serotonin reuptake inhibitors is increasing ~~also~~ in pregnant women. Existing studies on in utero exposure to antidepressants and long-term neurodevelopmental outcomes are sparse.
- In this study we investigated whether in utero exposure to antidepressants is associated with increased risk of attention deficit hyperactivity disorder (ADHD).

Key messages

- We identified a cohort of 877,778 children, of whom 1.7% were exposed to antidepressants in utero. Selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of maternal users).
- While our analyses based on a general population comparison cohort showed a weak association between in utero exposure to antidepressants and ADHD, a within-mother between-pregnancy ~~analyses were~~ analysis was not consistent with a causal association. This observation strongly indicates the presence of unmeasured confounding by family-related factors in our comparisons with the general population. Also a former user analysis in the general comparison cohort confirmed presence of unmeasured confounding factors.

- This study provides no evidence to support a causal association between in utero exposure to antidepressants and risk of ADHD.

Strengths and limitations of this study

- The study was based on a large study population with long and virtually complete follow-up. Our use of data from population-based databases in a setting of universal health care practically eliminates the risk of recall and selection ~~bias~~biases.
- We were limited by our lack of data on actual antidepressant intake by the mother and on the actual timing of intake; we ~~therefore~~ used prescription redemption as a proxy for this information, which may have biased our results toward the null hypothesis.
- ADHD is a clinical diagnosis based on subjective criteria, and diagnoses ~~may~~ therefore may vary among practitioners. Misclassification of the outcome could have led us to overestimate the association if children of mothers with a psychiatric diagnosis were ~~where~~ more likely to obtain psychiatric treatment.

INTRODUCTION

Up to 13% of pregnant women experience depression,[1] but only approximately 2% are treated with antidepressants.[2] Untreated depression is associated with maternal tobacco and alcohol use, poor dietary ~~diet~~ intake, and risk of poor birth outcomes, including preterm birth.[3-6] However, use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has also been associated with adverse birth outcomes [7,8] as well as teratogenic effects.[9,10]

Early-life exposure to SSRIs or tricyclic antidepressive agents may cause behavioral changes, as observed~~shown~~ in rodents.[11,12] The serotonin transporter, which is blocked by SSRIs, is expressed transiently in many brain areas during fetal life; serotonin plays a key role in neural development and maturation.[13] Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by impulsiveness, inattention, and hyperactivity.[14] The incidence of ADHD is increasing, with a current prevalence of approximately 5% in children.[15] Proposed risk factors include genetics, preterm birth, and prenatal exposure to smoking or maternal stress.[16-20] However, evidence about ~~on the~~ risk of ADHD following in utero exposure to antidepressants is limited to one study, which found no evidence for an association between in utero exposure to SSRIs and ADHD (OR: 0.91, 95% CI: 0.51 to 1.60) ~~sparse, and the existing study is limited by short and incomplete follow-up and lack of data on important potential confounders~~.[21]

Evidence of an association between ~~the use of~~ antidepressant~~s~~ use during pregnancy and later ADHD in the offspring~~child~~ would have major public health implications. In this study, we investigated whether in utero exposure to antidepressants was associated with an increased risk of ADHD using nationwide Danish medical registries with virtually complete long-term follow-up.

METHODS

Setting

The Danish healthcare system (5.5 million inhabitants and a yearly birth rate of approximately 65,000) provides tax-supported health services to all residents guaranteeing access to primary and secondary care free of charge. Except for emergencies, initial contact with the healthcare system is through general practitioners, who either treat patients themselves or refer them to hospitals or to private practice specialists.

Study population and design

Using the Danish Medical Birth Registry, we identified a cohort of all singletons born alive from 1996 until the end of 2009. The Danish Medical Birth Registry contains computerized records of all deliveries in Denmark since 1973. Each record includes the civil registration number of the mother, father, and newborn, as well as multiple variables regarding the delivery, the newborn, and the mother. Data are collected by midwives or physicians overseeing delivery.[22] The civil registration number is a 10-digit number assigned to each Danish citizen at birth and to residents upon immigration, enabling accurate and unambiguous linkage of relevant registries at the individual level.[23] Siblings born to the same mother were identified through the civil registration system.[23] Thus, in addition to a general population comparison cohort, it was possible to identify a sibling comparison cohort that was highly suitable for optimizing adjustment for important potential family-related and genetic confounders.

Maternal antidepressant use

In utero exposure to antidepressants was defined as maternal redemption of a prescription for an antidepressant 30 days prior to or during pregnancy, as identified through the Danish National Prescription Registry.[24] Since January 1994 the registry has recorded the following information whenever a prescription is redeemed in Denmark: the civil registration number of the patient, the medication classification code (the anatomical therapeutic chemical classification system of the World Health Organization), and the date of dispensing. All antidepressants, as well as drugs for ADHD, are available by prescription only in Denmark. Pregnancy was defined as starting from the first day in the last menstrual period, according to the Danish Medical Birth Registry. First-trimester exposure was defined as redemption of a prescription by the mother 30 days prior to the beginning of pregnancy and up to 12 weeks after the beginning of pregnancy; second-trimester exposure was defined as prescription redemption between 12 weeks and 28 weeks of pregnancy, and third-trimester exposure was defined as prescription redemption during the remainder of the pregnancy.[27] If the mother redeemed more than one prescription during pregnancy, the first redemption was used to determine the trimester of exposure. We defined maternal former users of antidepressants as women, who had redeemed a prescription up to 30 days prior to pregnancy, and never users as women who had never redeemed a prescription.

ADHD

ADHD was detected either as a diagnosis of ADHD or redemption of a prescription for ADHD medication. Using the Danish Psychiatric Registry [25] and the Danish National Registry of Patients,[26] we identified children in the study population with inpatient and outpatient hospital diagnoses of ADHD. The Danish Psychiatric Registry contains computerized data on all

admissions to psychiatric hospitals and psychiatric wards in Denmark. The Danish National Registry of Patients has tracked all inpatients stays in Danish hospitals since 1977, and outpatient clinic and emergency room visits at all public hospitals since 1995. Data recorded in the Danish National Registry of Patients and the Danish Psychiatric Registry include civil registration number of the patient, dates of admission and discharge, and up to 20 discharge diagnoses from each admission, classified according to the 8th revision of the *International Classification of Diseases* until 1993, and the 10th revision thereafter.

Diagnosing and treating ADHD is also handled by private practice psychiatrists and general practitioners in cooperation, without hospital contact. These patients are not recorded in the Danish Psychiatric Registry or the Danish National Registry of Patients. Therefore, to ensure completeness, we defined ADHD as either a diagnosis of ADHD or a redemption of a prescription for ADHD medication. Information on prescription redemption was obtained from the Danish National Prescription Registry.[24]

Covariates

We identified risk factors for ADHD that were potentially associated with maternal use of antidepressants. We obtained information on maternal and paternal psychiatric diagnoses anytime before baseline from the Danish Psychiatric Registry. We gathered information on maternal epilepsy, infections, and use of anxiolytics/hypnotics/sedatives during pregnancy from the Danish National Registry of Patients and the Danish National Prescription Registry. From the Danish Medical Birth Registry we obtained information on maternal age at birth, gender of the child, the child's birth order, maternal smoking during pregnancy, maternal body mass index ~~(only available from 2004 and onwards)~~, and marital status. As body mass index was only available starting in~~from~~ 2004 and marital status was incompletely registered, body mass index and marital

status were only included as potential confounders in separate subanalyses. We also obtained information on the child's gestational age, birth weight, and five-minute Apgar score from the Danish Medical Birth Registry. These variables were investigated because they may play a role in a causal pathway linking in utero antidepressant exposure and ADHD. Since antidepressant use and ADHD prevalence both increased between 1996 and 2010, we also adjusted for calendar time.

Statistical analyses

The children were followed from date of birth until the date of redemption of an ADHD prescription, receipt of an ADHD diagnosis, emigration, death, or the end of follow-up on December 31 2010, whichever came first.

General population comparison cohort

We compared children exposed to antidepressants in utero and also children of maternal former users with the unexposed children of never users (women who never redeemed a prescription for antidepressants). We performed separate analyses according to type of antidepressant (SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressive agents, other antidepressants, and combinations of antidepressants). For these subgroups, we conducted analyses comparing exposed children to unexposed children of never users. With Cox proportional-hazards regression, we computed crude and adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) as measures of relative risk. Subjects with missing data were excluded from the analyses. The assumption of proportional hazards was graphically verified.

Sibling comparison cohort

To optimize control for family-related factors such as genetics and socioeconomic or medical status, we conducted a within-mother between-pregnancy cohort analysis by restricting the study population to children of mothers who had more than one child and at least one exposed and one unexposed pregnancy. We then compared exposed children to unexposed children using a conditional logistic regression model. We computed adjusted odds ratios (aOR) with 95% CIs for receiving an ADHD diagnosis or redeeming a prescription for ADHD medication. In the first model, we adjusted for calendar time at birth to account for differences in length of follow up. In that way we were able to compare the ~~this~~ sibling analysis with the time-to-event analysis used in the general population comparison cohort.[28] ~~We made full adjustment in the~~The second model was fully adjusted. All statistical analyses were performed using SAS (version 9.2; SAS Institute Inc, Cary, NC, USA). This study was approved by the Danish Data Protection Agency (Record no. 2013-41-1790 ~~2011-41-6465~~). Codes used to define study variables are provided in the Appendices.

RESULTS

We identified 877,778 singletons, of whom 15,008 (1.7%) were exposed to antidepressants in utero (Table 1). The most commonly used class of antidepressant by the mothers was SSRIs (78%, Table 2). The overall median follow-up time was eight years. A total of 12,841 (1.5%) participants developed ADHD (8,100 (0.9%) were detected as a diagnosis of ADHD, and 4,741 (0.5%) were identified through redemption of a prescription for ADHD medication as a first-outcome measure). In the within-mother between-pregnancy analysis we identified 867 children (330 groups of siblings) of whom 348 (40%) were exposed to antidepressants in utero. Of the 348 exposed children, 79 (23%) developed ADHD. Of the 519 unexposed children, 270 (52%)

developed ADHD. Of 330 groups of siblings 311 groups contained one child with ADHD and 19 pairs contained two children with ADHD.

Maternal and paternal characteristics

~~The birth giving age~~Age at delivery was higher among antidepressant users than never users. Maternal antidepressant users more frequently smoked during pregnancy, were unmarried, had psychiatric diagnoses other than depression, epilepsy or infections during pregnancy. They also used anxiolytics/hypnotics/sedatives during pregnancy more often than never users. Fathers of children born to maternal users of antidepressants were also more likely to have a psychiatric diagnosis than fathers of children born to never users (Table 1a).

Birth outcomes

~~The g~~Gender distribution was the same for exposed and unexposed children. Children exposed in utero to antidepressants had a higher prevalence of low birth weight (3.7% vs. 2.1%), low~~er~~ Apgar score (seven or under) at five minutes (2.6% vs. 1.2%), and were born prematurely more often (15.4% vs. 8.6%) than unexposed children borne by never users (Table 1b).

Risk estimates

The aHR comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% CI: 1.1 to 1.4; Table 3). The aHR was 1.6 (95% CI: 1.5 to 1.8) when comparing children born to former users of antidepressants with children born to never users. Adjusting for the mother's body mass index and marital status in subanalyses did not change the

estimates (results not shown). When stratifying according to trimester and class of antidepressants, we detected a minor association between ADHD and exposure in utero to any kind of antidepressant in the first and second trimesters, as well as exposure to SSRIs or the group "other antidepressants" (Table 3). In the within-mother between-pregnancy analysis ~~(n=867)~~, the full aOR was 0.7 (95% CI: 0.4 to 1.4; Table 4).

DISCUSSION

While our analyses based on a general population comparison cohort showed a weak association between in utero exposure to antidepressants and ADHD, the within-mother between-pregnancy analyses were not consistent with a causal association. This observation strongly indicates the presence of unmeasured confounding by family-related factors in our comparisons with the general population. ~~Also the~~The former user analysis in the general comparison cohort also confirmed presence of unmeasured confounding factors.

Our results extend the findings of an American study of claims-based data from 38,074 families that concluded, in line with our findings, that children exposed to SSRIs were not at increased risk of ADHD (OR: 0.91, 95% CI: 0.51 to 1.60) while children exposed to bupropion were at increased risk (OR: 3.63, 95% CI: 1.20 to 11.04), especially after second-trimester exposure.[21] The study was limited by maternal smoking during pregnancy as a potential confounder, especially in the results for exposure to bupropion as this antidepressant is used for smoking cessation. Bupropion (which in Denmark is used for smoking cessation only) was contained in the group "other" antidepressants in our study. The number of children exposed to this drug in utero was only 135 and due to sparse data we did not perform separate regression analyses.

~~This previous study was limited by short and incomplete follow-up and lack of data on important potential confounders.~~

The strengths of our study include its large study population with long and virtually complete follow-up. Our use of data from population-based databases in a setting of universal health care practically eliminates the risk of recall and selection ~~bias~~biases. Importantly, the within-mother between-pregnancy analysis allowed us to effectively adjust for family-related factors, such as genetics and socioeconomic and medical status.

We were limited by our lack of data on actual antidepressant intake by the mother and on the actual timing of intake. We used prescription redemption as a proxy for this information which could lead to misclassification of exposure status. Regarding children classified as exposed in utero, we cannot be sure that women who redeemed a prescription 30 days before or during pregnancy actually used the drugs during pregnancy. Also, drugs redeemed earlier in life could have been stored for later use. Therefore women categorized as former users might have been using antidepressants during pregnancy. Furthermore, the Danish National Prescription Registry [24] has only recorded information since 1994. Among women who were categorized as never users some may have used the drugs before 1994. Such misclassification of exposure~~which~~ may have biased our result toward the null ~~hypothesis~~. Also, ADHD is a clinical diagnosis based on subjective criteria, and diagnoses may ~~therefore~~ vary among practitioners. Misclassification ~~of the outcome~~ could~~, on the other hand,~~ have led us to overestimate the association if children of mothers with a psychiatric diagnosis w~~h~~ere more likely to obtain psychiatric treatment. At the same time, children with ADHD were identified based on hospital diagnoses and drug prescriptions. Thus, patients with ADHD diagnosed by private psychiatrists or general practitioners and not prescribed drug treatment would be misclassified as not having ADHD. This could lead to an underestimation of the association. The within-mother between-pregnancy analysis ~~may~~ also may be limited by

misclassification of ~~in utero~~ exposure status and outcome. Such misclassification may have led us to underestimate an association in this analysis.[29] However, the strong association between former maternal antidepressant use and ADHD in offspring, compared with a lack of exposure to antidepressants in utero, further supports the importance of causative factors other than antidepressant use. Comorbid ADHD in mothers using antidepressants would potentially conceal a causal association between in utero exposure to antidepressants and ADHD, given the strong ADHD risk conveyed by parental ADHD. However, given the reported prevalence of ADHD among adults with major depression, ranging from 9%-16% [30] we do not believe parental ADHD can explain the null association.

In conclusion, this large-scale study with complete long-term follow-up for ADHD provides no evidence to support an association between in utero exposure to antidepressants and risk of ADHD.

Footnotes

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Competing interests: None declared.

Contributors: KL, MO, ABTA, and HTS made primary contributions to writing the manuscript. All authors contributed to the study conception and study design. TF performed data collection and statistical analyses and commented on the manuscript. All authors contributed to the interpretation of results, all revised the manuscript critically, and all approved the final manuscript. HTS is guarantor for this study.

Ethical approval: Register studies do not require ethical approval in Denmark. This study was approved by the Danish Data Protection Agency (Record no. ~~2011-41-6465~~ 2013-41-1790).

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Data sharing: No additional data available.

Table 1a. Maternal and paternal characteristics of 877,778 singleton births in Denmark in 1996-2009, according to maternal use of antidepressants during pregnancy. Never users are women who had never redeemed a prescription for antidepressants.

Characteristic	Exposed in utero N (%)	Not exposed in utero and born to former users N (%)	Not exposed in utero and born to never users N (%)	Total N (%)
All births	15,008 (100)	45,978 (100)	816,792 (100)	877,778 (100)
Mother's age at birth				
24 years of age or less	2,206 (14.7)	5,340 (11.6)	114,203 (14.0)	121,749 (13.9)
25 to 29 years of age	4,449 (29.6)	14,146 (30.8)	286,404 (35.1)	304,999 (34.7)
30 to 34 years of age	5,048 (33.6)	16,318 (35.5)	287,344 (35.2)	308,710 (35.2)
35 to 39 years of age	2,731 (18.2)	8,377 (18.2)	111,166 (13.6)	122,274 (14.0)
40 years of age or more	574 (3.8)	1,797 (3.9)	17,675 (2.2)	20,046 (2.3)
Birth order				
First child	6,417 (42.8)	18,745 (40.8)	351,959 (43.1)	377,121 (43.0)
Second or later child	8,591 (57.2)	27,233 (59.2)	464,833 (57.0)	500,657 (57.0)
Smoking status				
Non-smoker	9,424 (62.8)	31,797 (69.2)	637,561 (78.1)	678,782 (77.3)
Smoker	5,033 (33.5)	12,707 (27.6)	148,094 (18.1)	165,834 (18.9)
Missing data	551 (3.7)	1,474 (3.2)	31,137 (3.8)	33,162 (3.8)
Marital status				
Married, civil partnership	4,049 (27.0)	13,164 (28.6)	360,924 (44.2)	378,137 (43.1)
Single, widow, divorced, or not registered / annulled civil partner ship	4,840 (32.2)	14,280 (31.1)	295,762 (36.2)	314,882 (35.9)

Missing or partner dead	6,119 (40.8)	18,534 (40.3)	160,106 (19.6)	184,759 (21.0)
Maternal diagnosis of depression	3,987 (26.6)	5,176 (11.3)	2,064 (0.3)	11,227 (1.3)
Maternal psychiatric diagnoses other than depression	4,136 (27.6)	8,659 (18.8)	28,247 (3.5)	41,042 (4.7)
Paternal psychiatric diagnoses	1,823 (12.1)	4,700 (10.2)	45,471 (5.6)	51,994 (5.9)
Maternal diseases	6,998 (46.6)	20,298 (44.2)	276,823 (33.9)	304,199 (34.7)
Epilepsy	315 (2.1)	909 (2.0)	8,313 (1.0)	9,537 (1.1)
Infections during pregnancy	6,838 (45.6)	19,829 (43.1)	271,789 (33.3)	298,456 (34.0)
Maternal medication use during pregnancy	1,764 (11.8)	1,354 (2.9)	5,137 (0.6)	8,255 (0.9)
Anxiolytics/hypnotives/sedatives				
Maternal body mass index (BMI)				
No BMI (before 2004)	4,681 (31.2)	13,748 (29.9)	489,283 (60.0)	507,712 (57.8)
Underweight (BMI 15-18.4 kg/m^2)	537 (3.6)	1,788 (3.9)	15,082 (1.8)	17,407 (2.0)
Normal weight (BMI 18.5-24.9 kg/m^2)	5,217 (34.8)	17,452 (38.0)	190,466 (23.3)	213,135 (24.3)
Overweight (BMI 25-29.9 kg/m^2)	2,166 (14.4)	6,332 (13.8)	63,044 (7.7)	71,542 (8.2)
Obese (BMI $\geq$ 30 kg/m^2)	1,635 (10.9)	4,244 (9.2)	34,052 (4.2)	39,931 (4.6)
BMI < 15 kg/m^2 or missing	772 (5.1)	2,414 (5.3)	24,865 (3.0)	28,051 (3.2)

Table 1b. Characteristics of 877,778 singleton births in Denmark in 1996-2009, according to maternal use of antidepressants during pregnancy. Never users are women who had never redeemed a prescription for antidepressants.

Characteristic	Exposed in utero N (%)	Not exposed in utero and born to former users N (%)	Not exposed in utero and born to never users N (%)	Total N (%)
Gender of the child				
Female	7,233 (48.2)	22,216 (48.3)	397,731 (48.7)	427,180 (48.7)
Male	7,775 (51.8)	23,762 (51.7)	419,061 (51.3)	450,598 (51.3)
Calendar period of birth				
1996-2000	2,000 (13.3)	5,542 (12.1)	314,467 (38.5)	322,009 (36.7)
2001-2005	5,294 (35.3)	16,706 (36.3)	287,077 (35.1)	309,077 (35.2)
2006-2009	7,714 (51.4)	23,730 (51.6)	215,248 (26.4)	246,692 (28.1)
Birth weight in grams				
1500-1999	163 (1.1)	418 (0.9)	5,629 (0.7)	6,210 (0.7)
2000-2499	549 (3.7)	1,259 (2.7)	17,444 (2.1)	19,252 (2.2)
2500-2999	2,164 (14.4)	5,511 (12.0)	81,730 (10.0)	89,405 (10.2)
3000-5500	11,924 (79.5)	38,189 (83.1)	700,553 (85.8)	750,666 (85.5)
Very low, very high, or missing	208 (1.4)	601 (1.3)	11,436 (1.4)	12,245 (1.4)
Gestational age				
Extremely premature or very premature, 19-31 weeks	150 (1.0)	388 (0.8)	5,193 (0.6)	5,731 (0.7)

Moderately premature, 32-37 weeks	2,303 (15.3)	5,140 (11.2)	70,517 (8.6)	77,960 (8.9)
Normal gestational age at birth, 38-48 weeks	12,482 (83.2)	40,272 (87.6)	735,496 (90.0)	788,250 (89.8)
Too low or missing gestational age at birth	73 (0.5)	178 (0.4)	5,586 (0.7)	5,837 (0.7)
Apgar score at five minutes				
Apgar score seven or under	385 (2.6)	610 (1.3)	10,135 (1.2)	11,130 (1.3)
Apgar score over seven	14,463 (96.4)	44,938 (97.7)	796,921 (97.6)	856,322 (97.6)
Missing	160 (1.1)	430 (0.9)	9,736 (1.2)	10,326 (1.2)

Table 2. Distribution of 15,008 maternal antidepressants users according to classes of antidepressants.

Class of antidepressant	Maternal users (%)
Selective serotonin reuptake inhibitors	11,721 (78)
Serotonin-norepinephrine reuptake inhibitors	763 (5)
Tricyclic antidepressive agents	716 (5)
Other	604 (4)
Combined	1,204 (8)
Total	15,008 (100)

Table 3. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for time to redeeming a prescription for attention deficit hyperactivity disorder (ADHD) medication or receiving the diagnosis of ADHD, comparing exposed children to unexposed children born to never users (women who had never redeemed a prescription on antidepressants).

Antidepressant drug exposure in utero	Crude HR and (95% CI)	Adjusted* HR and (95% CI)
Any	2.0 (1.7 to 2.3)	1.2 (1.1 to 1.4)
First trimester exposure	2.0 (1.7 to 2.3)	1.2 (1.0 to 1.4)
Second trimester exposure	2.6 (1.7 to 4.2)	1.5 (0.9 to 2.4)
Third trimester exposure	1.3 (0.6 to 3.2)	0.8 (0.3 to 2.0)
Selective serotonin reuptake inhibitor	2.1 (1.8 to 2.4)	1.2 (1.0 to 1.5)
Serotonin-norepinephrine reuptake inhibitor	1.2 (0.5 to 3.3)	1.0 (0.4 to 2.5)
Tricyclic antidepressive agent	1.8 (1.1 to 3.0)	1.1 (0.6 to 2.0)
Others	2.4 (1.3 to 4.4)	1.6 (0.8 to 3.0)
Combined use	1.9 (1.1 to 3.4)	0.8 (0.4 to 1.7)

*Adjusted for gender of the child, calendar time at birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections, epilepsy), and maternal medication (anxiolytics/hypnotics/sedatives) use during pregnancy.

Table 4. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for a within-mother between-pregnancy analysis on a subpopulation of 867 children, restricted to mothers who had more than one child, with at least one exposed and at least one unexposed pregnancy. Children exposed in utero ~~to~~ are compared to unexposed children.

Adjusted* OR (95% CI)	Adjusted** OR (95% CI)
0.8 (0.5 to 1.2)	0.7 (0.4 to 1.4)

*Adjusted for calendar time at birth.

**Adjusted for calendar time at birth, gender of the child, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections and epilepsy), and maternal medicine use (anxiolytics/hypnotics/sedatives) during pregnancy.

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