FACULTY OF HEALTH SCIENCE; AARHUS UNIVERSITY

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

Research year report

Kristina Laugesen

Department of Clinical Epidemiology, Aarhus University Hospital

Supervisors

Henrik Toft Sørensen, MD, PhD, DMSc, professor (main supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital Denmark

Morten Olsen, MD, PhD (co-supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital Denmark

Ane Birgitte Telén Andersen, PhD-student, MPH (co-supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital Denmark

Preface

This study was carried out during my research year at Department of Clinical Epidemiology, Aarhus University Hospital, Denmark (February 2012 - January 2013).

I would like to express my gratefulness to my main supervisor Henrik Toft Sørensen and the Department of Clinical Epidemiology. This department contributes to research of high standard and I feel lucky to have been a part of the research environment here. From my point of view a research environment of high standard originates not only from bright and innovative people but also from the ability to work together, share knowledge and ideas and make use of people´s different skills, all qualities possessed by this department. Thank you for having introduced me to epidemiological research, I have definitely been encouraged to continue research in this field.

Also I would like to say thank you for giving me the possibility to go to Boston for three months during my research year. It has been an experience of great personal and intellectual gain. A special thanks to Elizabeth Hatch who have warmly welcomed us at the Department of Public Health, Boston University.

I would like to thank my co-supervisors, Morten Olsen and Ane Birgitte Telén Andersen, for their patience, supervision, and for learning me skills of epidemiology and writing. Their doors have always been open for me and I have been lucky to have you as guides during my first experience in research. It has been of great importance for me to feel welcome. Also, a special thanks to Trine Frøslev who have contributed to the statistical analyses and guidance in this project.

Finally, thank you to all colleagues. Especially Anna Byrjalsen with whom I have shared most of my experiences with this year and Mette Nørgaard, Reimar Wernich Thomsen and Rikke Bech Nielsen for having supervised me in another project.

I hope to be lucky to work with you all again in my future career.

Kristina Laugesen

Funding

This study was supported by grants from:

- Department of Clinical Epidemiology’s Research Foundation
- Max og Anna Friedmanns Legat til Sygdomsbekæmpelse
- Familien Hede Nielsens Fond

List of abbreviations

ADHD	Attention deficit hyperactivity disorder
ATC code	Anatomical therapeutic chemical code
BMI	Body mass index
CPR number	Civil Personal Registration Number
CI	Confidence interval
DNPR	Danish National Prescription Registry
DNRP	Danish National Registry of Patients
DMBR	Danish Medical Birth Registry
HR	Hazard ratio
ICD-8	International Classification of Diseases, 8th revision
ICD-10	International Classification of Diseases, 10th revision
OR	Odds ratio
PCRR	Danish Psychiatric Registry
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressive agents

Abstract

Background Use of selective serotonin reuptake inhibitors (SSRIs) is increasing also in pregnant women. Existing studies on in utero exposure to antidepressant drugs and long-term neurodevelopmental outcomes are sparse.

Objectives To investigate if in utero exposure to antidepressant drugs is associated with an increased risk of attention deficit hyperactivity disorder (ADHD).

Methods We conducted a nationwide cohort study. From the Danish Medical Birth Registry we identified a cohort of singletons born alive from 1996 to 2009 with follow-up through 2010. ADHD was defined as redemption of a prescription for ADHD medication or receipt of an ADHD hospital diagnosis identified in national registries. The unique personal civil registration number assigned to each Danish citizen permitted accurate linkage of the registries. We used Cox proportional-hazards regression to compute adjusted hazard ratios (aHR), comparing exposed children and children born by former users to unexposed children born by never users. To effectively control for confounding from family-related factors we also conducted a within-mother between-pregnancy analysis using conditional logistic regression.

Results We identified a cohort of 877,778 children. The aHR comparing children exposed to any antidepressant in utero with children born to never users of antidepressants was 1.2 (95% confidence interval (CI): 1.1–1.4). The aHR was 1.6 (95% CI: 1.5–1.8) when comparing children born to former users with children born to never users of antidepressants. In the within-mother between-pregnancy analysis (n=867) the adjusted odds ratio was 0.7 (95% CI: 0.4-1.4).

Conclusion Using a general population comparison cohort we only observed a marginally increased risk of ADHD for children exposed to antidepressants in utero. Analyses based on a former user design and sibling comparison, confirm that this study provide no evidence of an association between in utero exposure to antidepressants and risk of ADHD.

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Introduction

Up to 13% of pregnant women experience depression (1), which untreated is associated with unhealthy maternal behaviors such as poor diet, tobacco and alcohol use (2-4). In addition, studies have found increased risk of poor birth outcomes in women with untreated depression, including preterm birth and low birth weight (5). However, use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has also been associated with adverse birth outcomes (6,7) as well as teratogenic effects (8,9).

The serotonin transporter, which is blocked by SSRIs, is expressed transiently in many brain areas during fetal life and serotonin plays a key role in neural development and maturation (10). In animal studies early-life exposure to SSRIs or tricyclic antidepressive agents (TCAs) in rodents causes behavioral changes (11,12). Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by significant difficulties in impulsiveness, inattention and hyperactivity (13). Its current prevalence is about 5% in children and the incidence is increasing (14). Proposed risk factors include genetics, preterm birth, and prenatal exposure to smoking or maternal stress (15-19).

Data on risk of ADHD following in utero exposure to antidepressants are sparse and limited by short and incomplete follow up and lack of data on important potential confounders (20). Evidence of an association between use of antidepressants during pregnancy and ADHD in the child would have major public health implications. In this study we investigated if in utero exposure to antidepressant drugs is 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 60,000) 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 health care system is through general practitioners, who either treat patients themselves or refer them to hospitals or privately practicing specialists.

Study population and design

Using the Danish Medical Birth Registry (DMBR) we identified all singletons born alive from 1996 until the end of 2009. The DMBR contains computerized records of all deliveries in Denmark since 1973. Each record includes the civil registration number (CPR number), on the mother, father and newborn as well as multiple variables on the birth, newborn and the mother. Data are collected by the midwives or physicians overseeing the deliveries (21). The CPR number is a 10-digit number assigned to each Danish citizen at birth and to residents upon immigration; it enabled accurate and unambiguous linkage of all registries at the individual level (22).

Maternal antidepressant drug use

In utero exposure to antidepressants was defined as redemption of a prescription for an antidepressant by the mother 30 days prior to or during pregnancy. Pregnancy was defined as starting from the first day in the last menstrual period, detected in the DMBR. Maternal redemption of prescription for an antidepressant was identified from the Danish Nationwide Prescription Registry (DNPR) (23). Since January 1994 the registry has recorded the following information whenever a prescription is redeemed in Denmark: CPR number of the patient, the medication classification code (the anatomical therapeutic chemical (ATC) classification system, WHO), and the date of dispensing. All antidepressant drugs, as well as drugs for ADHD, are available by prescription only.

ADHD

Using the Danish Psychiatric Registry (PCRR) (24) and the Danish National Registry of Patients (DNRP) (25) we identified all patients in the study population with inpatient or outpatient diagnoses of ADHD. The PCRR contains computerized data on all admissions to psychiatric hospitals and psychiatric wards in general hospitals in Denmark. Information on psychiatric outpatient clinic visits was included in 1995. The DNRP 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 DNRP and PCRR include patients' CPR numbers, dates of admission and discharge, and up to 20 discharge diagnoses from each admission, classified according to the 8th revision of the Danish version of the *International Classification of Diseases* (ICD-8) until 1993, and the 10th revision thereafter (ICD-10).

Because of the long waiting lists in the public sector, diagnosing and treatment of ADHD is also handled by private practicing psychiatrists and general practitioners in cooperation. These diagnoses will not be present in the PCRR or DNRP. Therefore, we further defined ADHD as redemption of a prescription for ADHD medication. Information on prescription redemption was obtained from the DNPR (23).

Covariates

We identified potential risk factors for ADHD, which are potentially associated with use of antidepressants. From the PCRR we obtained information on maternal and paternal psychiatric diagnoses. From the DNRP and DNPR we obtained information on maternal epilepsy or infections as well as use of anxiolytics/hypnotics/sedatives during pregnancy. From the MBR 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 (BMI, only available from 2004 and onwards), and marital status. From the MBR we also got information on the child's gestational age, birth weight and 5. min Apgar score. The latter are possible intermediary steps in a potential causal pathway from in utero antidepressant exposure to ADHD. Because 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 on an ADHD prescription, receipt of an ADHD diagnosis, emigration, death, or the end of follow-up on December 31 2010, whichever came first. We compared children exposed to antidepressants in utero, and also children of maternal former users, to unexposed children of never users. We used Cox proportional-hazards regression to compute crude and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). BMI and marital status were adjusted for separately in sub analyses, as BMI was only available from 2004 and onwards and marital status was incomplete registered. The assumption of proportional hazards was graphically verified.

Further, we stratified by maternal history of depression to investigate if a history of depression could underlie a possible association between in utero exposure to antidepressant and ADHD. We also stratified by child's birth weight, 5 min. Apgar score, and gestational age and by trimester. First-trimester exposure was defined as redemption of a prescription by the mother 30 days prior to beginning of pregnancy up to 12 weeks after beginning of pregnancy ; second-trimester exposure as prescription redemption after 12 weeks until 28 weeks of pregnancy; and third-trimester exposure as prescription redemption during the remainder of the pregnancy. If the mother redeemed more than one prescription during pregnancy, the first redemption was used to determine trimester of exposure. We did separate analyses according to type of antidepressant, *i.e.*, SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), TCAs, other antidepressants, and combinations of antidepressants. For these subgroups we conducted analyses comparing exposed children to children born by never users.

Finally, to further control for family-related factors such as genetics or socioeconomic status, we conducted a within-mother between-pregnancy analysis. In this analysis we restricted to mothers of 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 (ORs) with 95% CIs for receiving an ADHD diagnosis or redeeming a prescription for ADHD medication. First we adjusted only for calendar time to be able to compare this sibling analysis to the cohort analysis, which is a time-to-event analysis. Second we made full adjustment. All statistical analyses were performed using SAS (version 9.2; SAS Institute Inc, Cary, NC). The 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 was SSRIs , 78.1%. Median follow-up time was 8 years.

Maternal and paternal characteristics

The birth giving age was higher among antidepressant users than non-users. Maternal antidepressant users were more frequently smoking during pregnancy, unmarried, had psychiatric diagnosis other than depression, epilepsy or infections during pregnancy and more often used anxiolytics/hypnotics/sedatives during pregnancy than non-users. Fathers of children born to maternal users of antidepressants were also more likely to have a psychiatric diagnosis than fathers to unexposed (Table 1).

Birth outcomes

Gender distribution was the same for exposed and unexposed children (51% male). Children exposed in utero to antidepressants had a higher prevalence of low birth weight (3.7% vs. 2.1%), low Apgar score (7 or under) at 5 min (2.6% vs. 1.2%), and were more often born prematurely (15.4% vs. 8.6%) than unexposed children born by never users (Table 1).

Risk estimates

The aHR comparing children exposed to any antidepressant in utero with children born to never users of antidepressants was 1.2 (95% CI: 1.1–1.4) (Table 3). The aHR was 1.6 (95% CI: 1.5–1.8) when comparing children born to former users with children born to never users of antidepressants. Adjusting for BMI and marital status in sub analyses did not change the estimates. In the within-mother between-pregnancy analysis (n=867) the full adjusted odds ratio was 0.7 (95% CI: 0.4-1.4) (Table 5).

Discussion

In our population based cohort analysis we found a marginally increased risk of ADHD among children exposed in utero to antidepressant medication. However, additional analyses indicate that factors other than antidepressant medications explains this increased risk.

Our results extend the findings of an American study of claims-based data from 38,074 families concluding that children exposed to SSRIs were not at increased risk of ADHD (OR: 0.91, p = 0.74) whereas those exposed to bupropion were at increased risk (OR: 3.63, p = 0.02), especially after second-trimester exposure (20). Children were followed until the age of five years, and as ADHD is often diagnosed in older children this study may have identified only the most severe cases of ADHD. The study is also limited by lack of data on important potential confounders and incomplete follow-up.

The strengths of our study include its large study population with long and virtually complete follow-up. Also 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 control for family-related factors as genetics and socioeconomic status as possible confounders. The genetics as a confounder can be explained by the high prevalence of co morbidity as depression in people with ADHD (26). It is therefore likely that antidepressant drug use is overrepresented in women with ADHD compared to women without ADHD. Further, the heritability of the disorder is estimated high (17), and maternal ADHD is therefore a risk factor for ADHD in the child.

Our study also has limitations. We do not have data on actual antidepressant intake by the mother or actual timing. Furthermore, ADHD is a difficult diagnosis to confirm. In Denmark the diagnosis is made by a specialist in psychiatry or a neuro-paediatrician, though still it is a clinical diagnosis based on subjective criteria and it has been debated if ADHD is over diagnosed. If misclassification of the exposure is present in our study, it would be expected to be non-differential leading us to underestimate an association. Misclassification of the outcome could on the other hand be differential if children of mothers with a psychiatric diagnosis where more prone to be enrolled in psychiatric regime leading us to overestimate the association.

The within-mother between-pregnancy analysis may also be limited by non-differential misclassification of exposure which could lead us to underestimate an association. Our former user analysis though cooperates no causal association.

Conclusion

Overall, we only observed a marginally increased risk of ADHD when exposed to antidepressants in utero, but results in additional analyses suggested that any weak association observed was likely caused by confounding. Thus, this large scale study with complete long term follow-up for ADHD provide no evidence of an association between in utero exposure to antidepressants and risk of ADHD.

Tables

Table 1. Descriptive data on maternal, paternal and infants baseline characteristics of 877,778 singleton births in Denmark during 1996–2009, according to maternal use of antidepressant drugs during pregnancy.

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)
Mothers age at birth				
24 years of age or under	2,206 (14.7)	5,340 (11.6)	114,203 (14.0)	121,749 (13.9)
25 – 29 years of age	4,449 (29.6)	14,146 (30.7)	286,404 (35.1)	304,999 (34.8)
30 – 34 years of age	5,048 (33.6)	16,318 (35.5)	287,344 (35.2)	308,710 (35.2)
35 - 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 over	574 (3.9)	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 more 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)	1,447 (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 annulled civil partnership	4,840 (3230)	14,280 (31.1)	295,762 (36.2)	314,882 (35.9)
Missing or dead	6,119 (40.8)	18,534 (40.3)	160,106 (19.6)	184,759 (21.1)

A history of 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 (12.2)	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				
Anxiolytics/hypnotives/sedatives	1,764 (11.8)	1,354 (2.9)	5,137 (0.6)	8,255 (0.9)
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)	537 (3.6)	1,788 (3.9)	15,082 (1.9)	17,407 (2.0)
Normal weight (BMI: 18.5-24.9)	5,217 (34.8)	17,452 (38.0)	190,466 (23.3)	213,135 (24.3)
Overweight (BMI: 25-29.9)	2,166 (14.4)	6,332 (13.8)	63,044 (7.7)	71,542 (8.2)
Obese (BMI ≥ 30)	1,635 (10.9)	4,244 (9.2)	34,052 (4.2)	39,931 (4.6)
< 15 or missing	772 (5.1)	2,414 (5.3)	24,865 (3.0)	28,051 (3.2)
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 time at 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 (35.2)	309,077 (35.2)
2006 - 2009	7,714 (51.4)	23,730 (51.6)	215,248 (26.4)	246,692 (28.1)
Birth weight of the child (gram)				
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 (weeks)				
Extreme premature or very premature, 19-31	150 (1.0)	388 (0.8)	5,193 (0.6)	5,731 (0.7)
Moderate premature, 32 - 37	2,303 (15.4)	5,140 (11.2)	70,517 (8.6)	77,960 (8.9)
Normal age at birth, 38 - 48	12,482 (83.2)	40,272 (87.6)	735,496 (90.1)	788,250 (89.8)
Too low or missing age at birth	73 (0.5)	178 (0.4)	5,586 (0.7)	5,837 (0.7)
Apgar score at 5 min.				
Apgar score 7 or under	385 (2.6)	610 (1.3)	10,135 (1.2)	11,130 (1.3)
Apgar score over 7	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. Overview of the exposed group of children according to class of antidepressant.

Class of antidepressant	Frequency	Frequency, percent	Cumulative frequency	Cumulative frequency, percent
SSRIs	11,721	78.1	11,721	78.1
SNRIs	763	5.08	12,484	83.18
TCAs	716	4.77	13,200	87.95
Other	604	4.02	13,804	91.98
Combined	1,204	8.02	15.008	100.00

SSRIs: Selective serotonin reuptake inhibitors. SNRIs: Serotonin-norepinephrine reuptake inhibitors. TCAs: Tricyclic antidepressive agents.

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.

Antidepressant drug exposure in utero	**Crude HR and (95% CI), comparing exposed children to unexposed children born to never users**	**Adjusted[*] HR and (95% CI), comparing exposed children to unexposed children born to never users**
Any	2.0 (1.7 - 2.3)	1.2 (1.1 – 1.4)
First trimester exposure	2.0 (1.7 – 2.4)	1.2 (1.0 – 1.4)
Second trimester exposure	2.6 (1.7 – 4.2)	1.5 (0.9 – 2.4)
Third trimester exposure	1.3 (0.6 – 3.2)	0.8 (0.3 – 2.0)
SSRI	2.1 (1.8 – 2.4)	1.2 (1.0 – 1.5)
SNRI	1.2 (0.5 – 3.3)	1.0 (0.4 – 2.5)
TCA	1.8 (1.1 – 3.0)	1.1 (0.6 – 2.0)
Others	2.4 (1.3 – 4.4)	1.6 (0.8 – 3.0)
Combined use	1.9 (1.1– 3.4)	0.8 (0.4 – 1.7)

SSRI: Selective serotonin reuptake inhibitor. SNRI: Serotonin-norepinephrine reuptake inhibitor. TCAs: Tricyclic antidepressive agent.

[*]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), maternal medication (anxiolytics/hypnotics/sedatives) use during pregnancy.

Table 4. Stratified crude and adjusted hazard ratios (HR) 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.

Stratification variable	Crude HR and (95% CI)	Adjusted* HR and (95% CI)
Prior maternal diagnosis of depression		
No	2.0 (1.7 - 2.4)	1.3 (1.1 – 1.5)
Yes	0.7 (0.5 – 1.1)	0.7 (0.4 – 1.1)
Birth weight		
1500-1999 g	1.3 (0.4 – 4.0)	0.6 (0.2 – 2.0)
2000-2499 g	1.9 (1.0 – 3.6)	0.8 (0.4 – 1.7)
2500-2999 g	2.1 (1.5 – 2.9)	1.2 (0.8 – 1.7)
3000-5500 g	2.0 (1.7 – 2.3)	1.3 (1.1 – 1.5)
Very low, very high or missing	2.2 (0.9 – 5.2)	1.3 (0.6 – 3.3)
Apgar score at 5 min.		
Under 7	1.2 (0.4 – 3.2)	0.5 (0.2 – 1.3)
7 or over	2.0 (1.8 – 2.4)	1.3 (1.1 – 1.5)
Missing	1.4 (0.3 – 5.5)	0.6 (0.1 – 2.5)
Gestational age (weeks)		
Extremely premature/very premature, 29-31 weeks	1.4 (0.4 – 4.4)	0.9 (0.3 – 3.0)
Moderate premature, 32 - 37	1.7 (1.2 – 2.4)	1.0 (0.7 – 1.4)
Normal gestation, 38 - 48	2.0 (1.7 – 2.4)	1.3 (1.1 – 1.5)
Too low or missing age at birth	1.1 (0.2 – 7.0)	0.5 (0.1 – 3.9)

*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 and epilepsy), maternal medicine (anxiolytics/hypnotics/sedatives) use during pregnancy.

Table 5. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for a within-mother between-pregnancy analysis on a subpopulation of N = 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 any antidepressant at any time in pregnancy are compared to unexposed children.

Adjusted[*] OR and (95% CI)	**Adjusted[*] [*]OR and (95% CI)**
0.8 (0.5 – 1.2)	0.7 (0.4 – 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), maternal medicine use (anxiolytics/hypnotics/sedatives) during pregnancy.

Appendices

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

Class of antidepressant	Antidepressants	ATC codes
All antidepressants		N06A
SSRIs	Zimeldine, fluoxetine, citalopram, paroxetine, sertraline, alaproclate, fluvoxamine, etoperidone, escitalopram	N06AB
SNRIs	Venlafaxine, milnacipran, duloxetine, desvenlafaxine	N06AX16 (N06AA22); 17 (N06AA24); 21; 23
TCAs	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

SSRIs: Selective serotonin reuptake inhibitors. SNRIs: Serotonin-norepinephrine reuptake inhibitors. TCAs: Tricyclic antidepressive agents.

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

Class of ADHD 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 codes (ICD-8 codes), their *International Classification of Diseases*, 10th revision (ICD-10 codes), or their anatomical therapeutic chemical classification codes (ATC codes).

Covariates	**Categories and ICD-8, -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 (BMI)	< 18.5; 18.5-24.9; 25-29,9; ≥30
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
Parvo virus during pregnancy	ICD-10 code: B976
Other infections during pregnancy or use of antibiotics	ICD-10 codes: A00-A99, B00- B99 (excluded B58; 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)

Appendix 4. Stratification variables. Their categories, their *International Classification of Diseases*, 8th revision codes (ICD-8 codes), and their *International Classification of Diseases*, 10th revision (ICD-10 codes).

Possible intermediary variables	**Categories and ICD-8 or -10 codes**
Birth weight	<2000g; 2000-2499g; 2500-3000g; > 3000g
Gestational age	Extremely premature <28 weeks/very premature [28-32 weeks], moderately premature [32-37 weeks], normal >37 weeks
Apgar score at 5 min.	Apgar ≤ 7, Apgar ≥ 7
Maternal history of depression	ICD-8 code: 29809; 29609; 29629 ICD-10 codes: F251; F32; F33

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