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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 HRs comparing children exposed in utero and children born to former antidepressant users with children born 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 8 years; selective serotonin reuptake inhibitors were the most commonly used class of antidepressant during pregnancy (78% of users). The adjusted HR comparing children exposed to any antidepressant in utero with children born to never users was 1.2 (95% CI 1.1 to 1.4), and 1.6 (95% CI 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 OR was 0.7 (95% CI 0.4 to 1.4).

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

ARTICLE SUMMARY

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 healthcare 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 towards the null hypothesis.
- Attention deficit hyperactivity disorder 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 behavioural 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 characterised 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 computerised 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 on 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 optimising 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 WHO) 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.[25] 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.

Attention deficit hyperactivity disorder

ADHD was detected either as a diagnosis of ADHD or redemption of a prescription for ADHD medication. Using the Danish Psychiatric Registry[26] and the Danish National Registry of Patients,[27] we identified children in the study population with inpatient and outpatient hospital diagnoses of ADHD. The Danish Psychiatric Registry contains computerised 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

Risk factors for ADHD that were potentially associated with maternal use of antidepressants were identified. We obtained information on maternal and paternal psychiatric diagnoses anytime before baseline from the Danish Psychiatric Registry. Information was also gathered 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 5-min 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 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 31 December 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 HRs (aHR) with 95% CIs as measures of relative risk. Patients with missing data were excluded from the analyses. The assumption of proportional hazards was graphically verified.

Sibling comparison cohort

To optimise 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 ORs (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 this way we were able to compare the sibling analysis with the time-to-event analysis used in the general population comparison cohort.[28] A stratified Cox proportional-hazards regression showed the same results as the conditional logistic regression model. The second model was fully adjusted. All statistical analyses were performed using SAS (V.9.2; SAS Institute Inc, Cary, North Carolina, 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 online supplementary appendices.

RESULTS

We identified 877 778 singletons, of whom 15 008 (1.7%) were exposed to antidepressants in utero (tables 1 and 2). The most commonly used class of antidepressant by the mothers was SSRIs (78%, table 3). The overall median follow-up time was 8 years. A total of 12 841 (1.5%) participants who developed ADHD (8100 (0.9%) were detected as a diagnosis of ADHD, and 4741 (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 1).

Birth outcomes

Gender distribution was the same for exposed and unexposed children. Children exposed in utero to antidepressants had a higher prevalence of low birthweight (3.7% vs 2.1%), low Apgar score (seven or under) at 5 min (2.6% vs 1.2%) and were born prematurely more often (15.4% vs 8.6%) than unexposed children born by never users (table 2).

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 4). 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

Table 1 Maternal and paternal characteristics of 877 778 singleton births in Denmark in 1996–2009, according to maternal use of antidepressants 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)
Mother's age at birth				
24 years of age or less	2206 (14.7)	5340 (11.6)	114 203 (14.0)	121 749 (13.9)
25–29 years of age	4449 (29.6)	14 146 (30.8)	286 404 (35.1)	304 999 (34.7)
30–34 years of age	5048 (33.6)	16 318 (35.5)	287 344 (35.2)	308 710 (35.2)
35–39 years of age	2731 (18.2)	8377 (18.2)	111 166 (13.6)	122 274 (14.0)
40 years of age or more	574 (3.8)	1797 (3.9)	17 675 (2.2)	20 046 (2.3)
Birth order				
First child	6417 (42.8)	18 745 (40.8)	351 959 (43.1)	377 121 (43.0)
Second or later child	8591 (57.2)	27 233 (59.2)	464 833 (57.0)	500 657 (57.0)
Smoking status				
Non-smoker	9424 (62.8)	31 797 (69.2)	637 561 (78.1)	678 782 (77.3)
Smoker	5033 (33.5)	12 707 (27.6)	148 094 (18.1)	165 834 (18.9)
Missing data	551 (3.7)	1474 (3.2)	31 137 (3.8)	33 162 (3.8)
Marital status				
Married, civil partnership	4049 (27.0)	13 164 (28.6)	360 924 (44.2)	378 137 (43.1)
Single, widow, divorced or not registered/ annulled civil partner ship	4840 (32.2)	14 280 (31.1)	295 762 (36.2)	314 882 (35.9)
Missing or partner dead	6119 (40.8)	18 534 (40.3)	160 106 (19.6)	184 759 (21.0)
Maternal diagnosis of depression	3987 (26.6)	5176 (11.3)	2064 (0.3)	11 227 (1.3)
Maternal psychiatric diagnoses other than depression	4136 (27.6)	8659 (18.8)	28 247 (3.5)	41 042 (4.7)
Paternal psychiatric diagnoses	1823 (12.1)	4700 (10.2)	45 471 (5.6)	51 994 (5.9)
Maternal diseases	6998 (46.6)	20 298 (44.2)	276 823 (33.9)	304 199 (34.7)
Epilepsy	315 (2.1)	909 (2.0)	8313 (1.0)	9537 (1.1)
Infections during pregnancy	6838 (45.6)	19 829 (43.1)	271 789 (33.3)	298 456 (34.0)
Maternal medication use during pregnancy anxiolytics/hypnotives/sedatives	1764 (11.8)	1354 (2.9)	5137 (0.6)	8255 (0.9)
Maternal body mass index (BMI)				
No BMI (before 2004)	4681 (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)	1788 (3.9)	15 082 (1.8)	17 407 (2.0)
Normal weight (BMI 18.5–24.9 kg/m^2)	5217 (34.8)	17 452 (38.0)	190 466 (23.3)	213 135 (24.3)
Overweight (BMI 25–29.9 kg/m^2)	2166 (14.4)	6332 (13.8)	63 044 (7.7)	71 542 (8.2)
Obese (BMI≥30 kg/m^2)	1635 (10.9)	4244 (9.2)	34 052 (4.2)	39 931 (4.6)
BMI<15 kg/m^2 or missing	772 (5.1)	2414 (5.3)	24 865 (3.0)	28 051 (3.2)

Never users are women who had never redeemed a prescription for antidepressants.

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 4). In the within-mother between-pregnancy analysis, the full aOR was 0.7 (95% CI 0.4 to 1.4; table 5).

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 the 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.

Table 2 Characteristics of 877 778 singleton births in Denmark in 1996–2009, according to maternal use of antidepressants 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 (%)
Gender of the child				
Female	7233 (48.2)	22 216 (48.3)	397 731 (48.7)	427 180 (48.7)
Male	7775 (51.8)	23 762 (51.7)	419 061 (51.3)	450 598 (51.3)
Calendar period of birth				
1996–2000	2000 (13.3)	5542 (12.1)	314 467 (38.5)	322 009 (36.7)
2001–2005	5294 (35.3)	16 706 (36.3)	287 077 (35.1)	309 077 (35.2)
2006–2009	7714 (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)	5629 (0.7)	6210 (0.7)
2000–2499	549 (3.7)	1259 (2.7)	17 444 (2.1)	19 252 (2.2)
2500–2999	2164 (14.4)	5511 (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)	5193 (0.6)	5731 (0.7)
Moderately premature, 32–37 weeks	2303 (15.3)	5140 (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)	5586 (0.7)	5837 (0.7)
Apgar score at 5 min				
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)	9736 (1.2)	10 326 (1.2)

Never users are women who had never redeemed a prescription for antidepressants.

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 healthcare 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.

Table 3 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	1204 (8)
Total	15 008 (100)

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 categorised 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 categorised as never users some may have used the drugs before 1994. Such misclassification of exposure may have biased our result towards 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

Table 4 Crude and adjusted HRs and 95% CIs for time to redeem 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.

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 6% to 9%[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.

Table 5 Adjusted ORs and 95% 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

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

Children exposed in utero are compared with unexposed children.
*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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Competing interests None.

Ethics 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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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