ARTICLE

In utero exposure to ADHD medication and long-term offspring outcomes

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Attention Deficit Hyperactivity Disorder (ADHD) medication is increasingly being used during pregnancy. Concerns have been raised as to whether ADHD medication has long-term adverse effects on the offspring. The authors investigated whether in utero exposure to ADHD medication was associated with adverse long-term neurodevelopmental and growth outcomes in offspring. The population-based cohort study in the Danish national registers included 1,068,073 liveborn singletons from 1998 to 2015 followed until any developmental diagnosis, death, emigration, or December 31, 2018. Children of mothers who continued ADHD medication (methylphenidate, amphetamine, dexamphetamine, lisdexamphetamine, modafinil, atomoxetine, clonidine) during pregnancy and children of mothers who discontinued ADHD medication before pregnancy were compared using Cox regression. Main outcomes were neurodevelopmental psychiatric disorders, impairments in vision or hearing, epilepsy, seizures, or growth impairment during childhood or adolescence. In total, 898 children were exposed to ADHD medication during pregnancy compared to 1270 children whose mothers discontinued ADHD medication before pregnancy. After adjustment for demographic and psychiatric characteristics of the mother, no increased risk of any offspring developmental disorders was found combined (aHR 0.97, 95% CI 0.81 to 1.17) or for separate subcategories. Similarly, no increased risk was found for any sub-categories of outcomes in the negative control or sibling controlled analyses. Neurodevelopment and growth in offspring do not differ based on antenatal exposure to ADHD medication. These findings provide reassurance for women with ADHD who depend on ADHD medication for daily functioning and who consider continuing medication in pregnancy.

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder affecting individuals across the lifespan [1]. In parallel to the increasing number of women of reproductive age using ADHD medication [2, 3], a steep increase in ADHD medication use during pregnancy has been observed [4, 5]. With treatment prevalence recently estimated above 1% of pregnant women, ADHD medications now rank among the most commonly prescribed medications during pregnancy [5, 6]. Meanwhile, no specific guidelines exist for using ADHD medication during pregnancy due to the lack of empirical evidence for the safety and consequences of in utero exposure to these medications [7]. Thus, out of concern for the unborn child, most women currently choose to discontinue their use of ADHD medication around conception [8]. While the consequences of discontinuation are limited in daily life for some women; others struggle to maintain employment and are at higher risk for serious health outcomes, including motor vehicle crashes, accidents, injuries, and suicidality [9, 10].

Studies have assessed short-term offspring outcomes associated with prenatal exposure to ADHD medication, including congenital malformations [4, 11–18], and outcomes related to labor and delivery [14–16, 19, 20] with conflicting findings. Recent systematic reviews suggested no convincing evidence to indicate that in utero exposure to ADHD medication results in teratogenic effects [21–23]. Potential effects on cardiac malformations (Modafinil exposure), gestational age and weight cannot be ruled out, but the risk differences appears small [22, 23]. It should be noted that due to the observational nature of existing studies, the possibility of drawing causal inferences is limited. In particular, confounding by indication is challenging in observational treatment studies [24] due to the high heritability of ADHD [25] and

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because patients in medical treatment for ADHD are likely to be more severely affected by their disorder and other comorbid conditions than those who are not [23].

The medications most commonly used to treat ADHD are stimulants, which act by increasing the release of catecholamines into the synaptic cleft. Catecholamine synthesis begins mid-gestation, and catecholamine signaling activity is required for the completion of normal fetal development [26, 27]. Thus, it is possible that chronic alterations in catecholamine signaling in the fetus could result in alterations in neural development and growth later in life. Moreover, given that growth restriction is one of the major clinical concerns when ADHD medication is prescribed in children and adolescents, there is a need to study in utero exposure to these medications [28].

In this population-based register study, we examined whether in utero exposure to ADHD medication was associated with adverse long-term neurodevelopmental outcomes and/or growth impairment. We used multiple rigorous study designs to address different potential sources of biases, including confounding by indication.

METHODS

Study design and population

We conducted a population-based cohort study using the Danish nationwide registers. All liveborn singletons born from 1998 to 2015 were identified from the Danish Medical Birth Registry [29] ($N = 1{,}092{,}668$). In all, 24,595 children were excluded due to missing or unlikely gestational age (<154 or >315 days), chromosomal abnormalities (ICD-10 [International Classification of Diseases, 10th revision] codes Q90-Q99) identified from the Danish National Patient Register [30], and missing paternal links, resulting in a population of 1,068,073 singletons born by 628,478 mothers (Fig. 1). Note, throughout this paper, we, for fluency, refer to pregnant and birthing individuals as "female", "women" or "mothers" while acknowledging that not all individuals included in our study choose this label.

In utero exposure to ADHD medication

ADHD medication use during pregnancy was defined as filling one or more prescriptions for ADHD medication from 30 days before pregnancy until delivery. We obtained the information from the Danish National Prescription Registry [31] using the following Anatomical Therapeutic Chemical (ATC) classification codes for stimulant treatment: N06BA04 "Methylphenidate", N06BA01 "Amphetamine", N06BA02 "Dexamphetamine", N06BA12 "Lisdexamphetamine", and other treatment: N06BA07 "Modafinil", N06BA09 "Atomoxetine", C02AC01 "Clonidine". Timing of ADHD medication use was indicated by the date of dispensing the prescription.

Start of pregnancy was defined using the information on gestational age registered in the Danish Medical Birth Register, based on the first- or second-trimester ultrasound scan or, when ultrasound data were unavailable, the first day of the mother's last menstrual period (29). ADHD medication prescriptions redeemed by the mother from two years before pregnancy to delivery were included, and we categorized children in exposure groups according to the timing/dates of dispensing: 1) "Unexposed": no maternal ADHD medication use two years before pregnancy or during pregnancy, 2) "Discontinuation": maternal ADHD medication use in the two years prior to pregnancy but not during pregnancy, 3) "Continuation": use both before and during pregnancy, 4) "New user": initiation during pregnancy or one month prior to conception but no use within the previous 2 years. Exposure groups 3 and 4 were categorized as "Exposed".

Duration of ADHD medication use during pregnancy was calculated by multiplying the number of defined daily doses per package by number of packages dispensed.

Offspring developmental outcomes

We reported results for three developmental outcomes, combined and separate, with onset during childhood: neurodevelopmental psychiatric disorders, other neurodevelopmental impairments, and growth impairments (detailed ICD-10 diagnostic codes are shown in Supplementary Table 1).

We defined neurodevelopmental psychiatric diagnoses as either a hospital diagnosis for psychiatric disorders with ICD-10 codes F70–98 or at least one prescription for ADHD medication after age 3 years. Information on hospital contacts was obtained from the Danish Psychiatric Central Research Register [32] and ADHD medication from the Danish National Prescription Register [31]. Occurrence of the outcome was defined as the date of the first hospital contact for the selected psychiatric disorder or the date of the first ADHD prescription, whichever occurred first. Secondly, we investigated subcategories of psychiatric disorders; autism spectrum disorder (F84.0, F84.1, F84.5, F84.8, or F84.9) and ADHD (F90, F98.8 or prescription for ADHD medication, both after the age of 3 years).

Other neurodevelopmental impairments (impairment in vision, hearing, epilepsy, seizures) and growth impairment were identified from the Danish National Patient Register [30]. Vision and hearing impairments included ICD-10 codes H47.6, H50, H54, H55, H90, H91.0, H91.8, H91.9, H93.2, and Z03.7A. Epilepsy and other seizures included ICD-10 codes G40, G41, P90, and R56.8. Febrile seizure cases (R56.0) were only included if the children had been hospitalized or received outpatient care between the ages of 3 months to 5 years and had no prior diagnosis of epilepsy, cerebral palsy, intracranial tumors, severe head trauma, or intracranial infections. Growth impairment included ICD-10 codes R62.8, R62.9, E34.3 and E30.0.

Potential confounders

Potential confounders were chosen a priori based on directed acyclic graphs and included: maternal age at delivery (<25, 25–34, >34 years), primiparity (yes/no), maternal and paternal psychiatric history at delivery (ICD-8 codes 290-315 and ICD-10 codes F00-99), psychiatric in- or outpatient treatment two years prior to pregnancy and until delivery (yes/no), dispensing of other psychotropic medication prescriptions during pregnancy with the ATC codes N06A antidepressants, N05A antipsychotics, N03A antiseizure, or N05B anxiolytics (yes/no), number of hospital visits not related to psychiatry during pregnancy (0–1, 2–3, or ≥4), maternal highest education (mandatory schooling to 9th grade /above mandatory school); calendar year of delivery (1998–2003, 2004–09, or 2010–15), maternal self-reported smoking during pregnancy (yes/no), marital status at delivery (married or cohabiting/single, divorced or widowed). Data on the covariates were retrieved from the Danish National Patient Register, the Danish Psychiatric Central Research Register, the Danish Medical Birth Register, the Danish National Prescription Registry and Statistics Denmark's registers on socioeconomic status [33].

Statistical analyses

Each child was followed from birth until a diagnosis, death, emigration, or December 31, 2018, whichever occurred first. We conducted the analyses using Cox proportional hazards regression models with the child's age as the underlying time scale. The proportional hazards assumption was assessed by visual inspection of Kaplan-Meier curves and log(−log) plots. Estimates were presented as hazard ratios (HRs) with 95% confidence intervals (CI). We used robust estimation for correction of standard errors to account for dependence between siblings and the estimates were adjusted for the above-mentioned covariates.

We compared children of mothers using ADHD medication during pregnancy (continuation and new users) with children of mothers discontinuing ADHD medication prior to pregnancy to control for unmeasured confounding related to maternal ADHD. To determine if associations were modified by duration of use, we divided the duration of ADHD medication use during pregnancy into ≤90 days, 91–180 days, and ≥181 days.

Due to about 4% missing values for the covariates smoking and education in the total cohort, we applied 20 imputations using the Markov Chain Monte Carlo procedures for imputing missing values [34].

Ethics

The Danish Data Protection Agency and the Danish Health Data Authority approved this study. According to Danish law, informed consent is not required for register-based studies. All data were de-identified and not recognizable at an individual level.

Sensitivity analyses

We applied a triangulation approach to test the robustness of the findings with four different pre-planned sensitivity analyses to address different sources of potential bias [35]. First, we repeated the analyses comparing children of fathers who used ADHD medication during the index

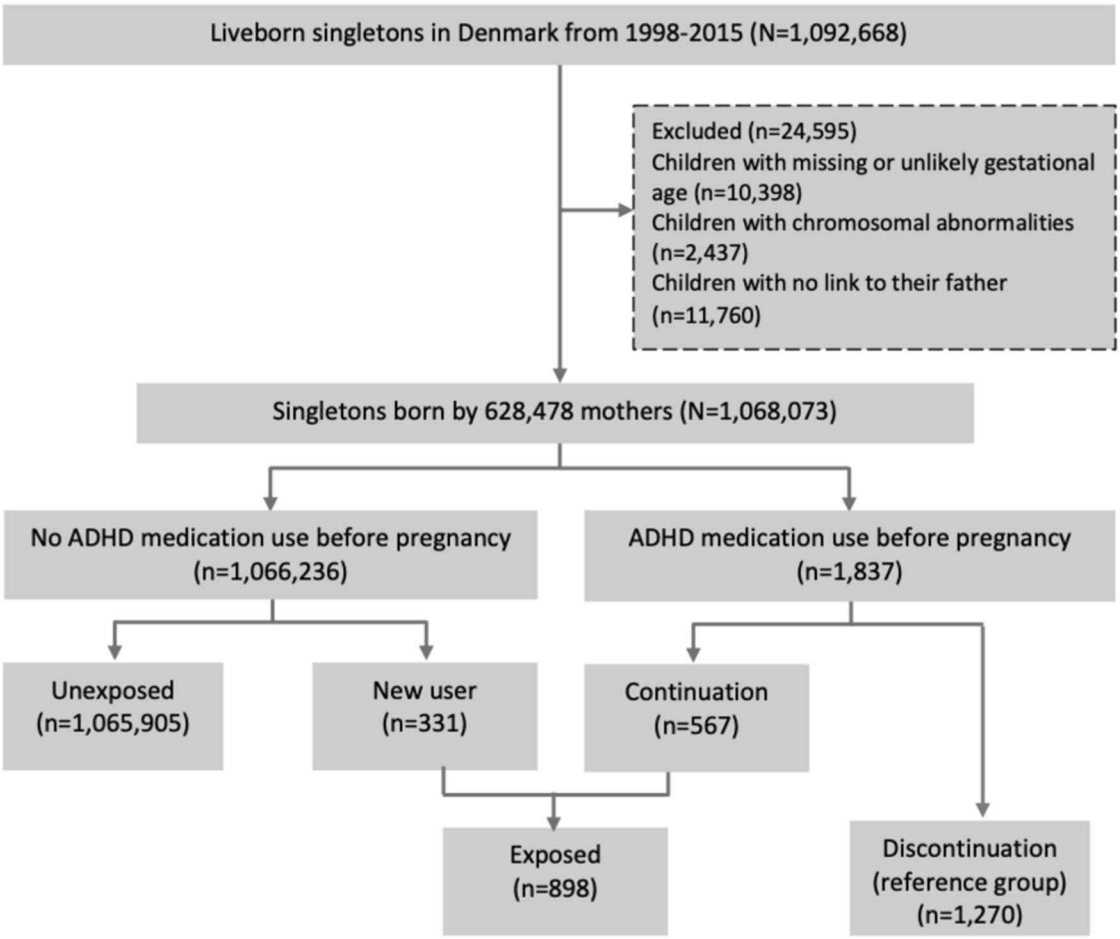

Fig. 1 Flowchart of the identification of the exposed group and comparison group (discontinuers) from all liveborn singletons in Denmark from 1998–2015.

pregnancy with those of fathers who discontinued prior to the index pregnancy to examine whether associations were confounded by shared environmental or genetic factors. Our hypothesis was that if any potential effect is due to intrauterine exposure, maternal ADHD medication use during pregnancy should have a greater influence than paternal ADHD medication use in the same period [23]. When applying paternal ADHD medication use as a negative control exposure, we also adjusted for maternal ADHD medication use during pregnancy, paternal age at delivery (continuous variable), and paternal inpatient or outpatient psychiatric treatment from two years before index pregnancy to delivery (yes/no). Second, we excluded women who dispensed prescriptions for other psychotropic medications during pregnancy to reduce potential confounding by other psychotropic medications or polypharmacy. Third, we applied a sibling comparison design conducting stratified Cox regression analyses by family identifiers comparing only siblings discordant on exposure status (exposed or unexposed to in utero ADHD medication) to account for confounding by factors shared by siblings (e.g., genetics, socioeconomic status, or postnatal environment) [36]. In the sibling analysis, we adjusted for maternal use of other psychotropic medications during pregnancy, birth order and birth year. Finally, to reduce misclassification of ADHD medication exposure, we restricted analyses to mothers who filled at least two prescriptions for ADHD medication during pregnancy, excluding mothers with only one prescription filled. This aimed to enhance certainty that the medication was taken during pregnancy.

RESULTS

Among 1,068,073 liveborn children, we identified 1837 (0.2%) children of mothers who used ADHD medication before pregnancy, of which 1270 discontinued and 567 continued medication use. Of those whose mothers did not use ADHD medication before pregnancy (1,066,236 children), 331 started ADHD medication one month before conception or during pregnancy, resulting in 898 exposed children (Fig. 1). The two exposed groups (new users and continuers) did not meaningfully differ in examined variables (Supplementary Table 2). In the discontinuation and exposed groups, a larger proportion of mothers were below age 25 years at delivery (40.9% and 33.6%) versus 12.8% in the unexposed group, and a larger proportion of children were born preterm (8.0% and 9.1%) and had low birthweight (6.2% and 6.5%) compared to the unexposed group (5.7% and 3.6%). The discontinuation and exposed groups had lower proportions of mothers with schooling past 9th grade (41% and 39.8%, respectively) compared to the unexposed group (82.2%) and higher proportions of smokers during pregnancy (41.2% and 42.9%) compared to the unexposed group (15.4%). Compared to the discontinuation group, mothers in the exposed group were more likely to have had outpatient psychiatric treatment between two years preconception and delivery (40.9% vs 37.6%) and to be dispensed other psychotropic prescriptions during pregnancy (36.9% vs 21.9%) (Table 1). Offspring developmental outcomes were more prevalent in the discontinuation (22.1%) and exposed (22.5%) groups compared with the unexposed (17.3%) (Table 2). Mean follow-up time was five years in both the discontinuation and exposed groups (median 5 years, maximum 20 years).

Comparisons between ADHD medication discontinuation and exposed groups

After adjustment for demographic and psychiatric characteristics of the mother, no increased risk of any offspring neurodevelopmental

Table 1. Characteristics of the study population according to maternal ADHD medication use before and during pregnancy.

Characteristics	Unexposed ($n = 1{,}065{,}905$) *n* (%)	ADHD medication discontinuation ($n = 1270$) *n* (%)	ADHD medication exposed during pregnancy ($n = 898$) *n* (%)
Maternal age at delivery			
<25 years	136,450 (12.8)	519 (40.9)	302 (33.6)
25–34 years	736,118 (69.2)	612 (48.2)	490 (54.6)
>34	192,337 (18.0)	139 (10.9)	106 (11.8)
Primiparity	473,356 (44.4)	795 (62.6)	502 (55.9)
Calendar year of delivery			
1998–2006	556,238 (52.2)	49 (3.9)	19 (2.1)
2007–2015	509,667 (47.8)	1,221 (96.1)	879 (97.8)
Sex of child, female	518,812 (48.7)	619 (48.7)	446 (49.7)
Preterm birth (<37 weeks of gestation)	60,301 (5.7)	102 (8.0)	82 (9.1)
Low birth weight (<2500 g)	38,388 (3.6)	79 (6.2)	58 (6.5)
Maternal highest education at delivery			
Elementary school (9th grade)	189,845 (17.8)	749 (59.0)	541 (60.2)
Above elementary school	827,737 (77.7)	498 (39.2)	343 (38.2)
Missing	48,323 (4.5)	23 (1.8)	14 (1.4)
Outpatient psychiatric treatment 2 years before pregnancy to delivery	24,571 (2.3)	477 (37.6)	367 (40.9)
Inpatient psychiatric treatment 2 years before pregnancy to delivery	5329 (0.5)	91 (7.2)	77 (8.6)
No of non-psychiatric hospital visits during pregnancy			
0–1	330,422 (31.0)	185 (14.6)	125 (13.9)
2–3	500,463 (46.9)	547 (43.1)	378 (42.1)
>=4	235,020 (22.1)	538 (42.3)	395 (43.9)
ADHD medication during pregnancy			
Stimulant (Methylphenidate, Amphetamines)	NA	NA	723 (80.5)
Methylphenidate			703
Amphetamines			20
Other (Atomoxetine, Clonidine, Modafinil)	NA	NA	175 (19.5)
Atomoxetine			125
Clonidine, Modafinil			50
Dispensing of other psychotropic prescriptions during pregnancy			
Any	35,333 (3.3)	279 (21.9)	332 (36.9)
Antidepressants	25,786 (2.4)	205 (16.1)	263 (29.3)
Antipsychotics	2852 (0.3)	57 (4.5)	92 (10.2)
Antiseizure	5214 (0.5)	47 (3.7)	51 (5.7)
Anxiolytics	6217 (0.6)	31 (2.4)	41 (4.7)
Maternal self-reported smoking during pregnancy			
Yes	164,270 (15.4)	523 (41.2)	385 (42.9)
No	855,029 (80.2)	714 (56.2)	491 (54.7)
Missing	46,606 (4.4)	33 (2.6)	22 (2.5)
Maternal marital status at delivery			
Married or cohabiting	929,599 (87.2)	817 (64.3)	548 (61.0)
Paternal psychiatric history at delivery, yes	45,894 (4.3)	239 (18.8)	193 (21.5)

or growth impairment was found (aHR 0.97, 95% CI 0.81–1.17). Point estimates showed no association for first-trimester exposure only (aHR 1.04, 95% CI 0.83 to 1.29) nor when stratified by number of days exposed (aHR <91 days 1.05, 95% CI 0.85–1.30; aHR 91–180 days 0.90, 95% CI 0.64–1.27; aHR >180 days 0.84, 95% CI 0.61–1.17). Similarly, while point estimates were slightly higher for neurodevelopmental psychiatric disorders in the offspring (aHR 1.18, 95% CI 0.84–1.65), especially for ADHD (aHR 1.44, 95% CI 0.92–2.25), none of the estimates reached statistical significance. For cerebral visual (aHR 0.68, 95% CI 0.35–1.32) and hearing (aHR 1.04, 95% CI 0.67–1.62) impairment or febrile seizures (aHR1.02, 95% CI 0.69 to 1.50), results did not suggest an increased risk for the

Table 2. Absolute number and percentage of offspring developmental specific and combined outcomes according to exposure group.

Offspring outcomes	Unexposed ($n = 1{,}065{,}297$) *n* (%)	ADHD medication discontinuation ($n = 1270$) *n* (%)	ADHD medication during pregnancy ($n = 898$) *n* (%)
Any developmental impairment	184,469 (17.3)	281 (22.1)	202 (22.5)
Neurodevelopmental psychiatric disorders	59,340 (5.6)	80 (6.3)	72 (8.0)
Autism	19,742 (1.9)	23 (1.8)	19 (2.1)
ADHD	33,194 (3.1)	43 (3.4)	48 (5.4)
Other neurodevelopmental impairments	104,197 (9.8)	169 (13.3)	107 (11.9)
Cerebral visual impairment	12,821 (1.2)	26 (2.1)	13 (1.5)
Hearing impairment	32,430 (3.0)	45 (3.5)	35 (3.9)
Epilepsy	27,096 (2.5)	49 (3.9)	21 (2.3)
Febrile seizures	41,443 (3.9)	69 (5.4)	46 (5.1)
Growth impairment	41,574 (3.9)	78 (6.1)	55 (6.1)

exposed group, while risk of epilepsy was decreased (aHR 0.58, 95% CI 0.34–0.98) (Table 3).

Sensitivity analyses

In the sensitivity analyses, we addressed confounding by shared environmental or genetic factors and indication for treatment and bias due to ADHD medication exposure misclassification (summarized in Table 4). None of the analyses showed statistically significantly increased risks of "any developmental impairments". When we examined subcategories of neurodevelopmental disorders, the risk of offspring ADHD was increased for the exposed group in the analyses, where mothers who had dispensed prescriptions for other psychotropic medications during pregnancy were excluded (aHR 1.85, 95% CI 1.04–3.27) and for mothers dispensing at least two prescriptions for ADHD medication during pregnancy (aHR 1.69, 95% CI 1.04–.75) (Supplementary Tables 3 and 4). In the analysis using paternal ADHD medication use as negative control exposure, a slightly higher risk of ADHD in the exposed group was found, although not statistically significant (aHR 1.23 95% CI 0.88–1.73) (Supplementary Table 5). No increased risk was found for the exposed group versus unexposed group for any subcategories of outcomes in the sibling control analysis (Supplementary Table 6).

DISCUSSION

Summary of findings

In this large population-based study, we demonstrated no differences in rates of ADHD, ASD, cerebral visual or auditory impairments, seizure disorders, or restriction in growth when comparing children who were antenatally exposed to ADHD medication with children whose mothers discontinued ADHD medication prior to pregnancy.

Only one study has examined the long-term effect of ADHD medication exposure during pregnancy; the Quebec Pregnancy/Child Cohort, in which 133 children had been exposed in utero to ADHD medication [37]. In the sub-cohort of women with ADHD and the sibling comparison analysis, there was no association between in utero exposure and ADHD diagnosis in the child [37]. While that study is potentially reassuring for women who wish to continue ADHD medication during pregnancy; the findings needed to be confirmed in a larger dataset and extended to other important and clinically relevant developmental disorders besides ADHD.

We speculated before undertaking this study that subtle changes in catecholamine signaling could result in neurodevelopmental alterations in offspring exposed to stimulants in utero. However, in the main and sibling control analyses, we did not find increased risks for common childhood neurodevelopmental outcomes, such as ADHD and autism spectrum disorders. Sensitivity analyses excluding mothers who had dispensed prescriptions for other psychotropic medications during pregnancy and mothers dispensing at least two prescriptions for ADHD medication during pregnancy showed an increased risk of offspring ADHD only. As the risk was only increased for ADHD, we speculate that the association may be driven by severity of maternal ADHD potentially via two different mechanisms; a) offspring of mothers with severe ADHD have a higher disease liability for ADHD, and b) through referral bias, that is, offspring of mothers with severe ADHD are assessed more carefully for ADHD.

Common side effects of stimulant ADHD medication include appetite suppression, insomnia, and growth impairment in children [28]. During pregnancy, exposure to stimulant medication could affect birth weight due to preterm birth or being small for gestational age [14], but growth trajectories in infancy have not been investigated. Thus, one crucial objective of our study was to determine whether antenatal exposure to ADHD medication could have long-term adverse effects related to restricted growth. Reassuringly, our results do not suggest that this is a concern.

Lastly, seizures are a known risk of amphetamine toxicity [38], and while this does not usually occur at clinically effective doses, it is possible that the developing brain could be more susceptible. Our finding of no difference in childhood febrile seizures between the exposed and discontinuation groups is reassuring. We found a decreased risk of epilepsy in offspring exposed to ADHD medication; however, this finding was not supported by the sensitivity analyses examining siblings discordant for exposure, nor when dispensed prescriptions were restricted to at least two fills.

In accordance with international studies, we found that compared with the background population, mothers with ADHD were younger at childbirth, were more likely to be smoking during pregnancy and to have children born preterm or with low birthweight irrespective of ADHD medication use during pregnancy [22, 39].

Limitations

Our study has limitations. First, although our study to date has the largest sample size, the number of exposed children is still relatively small, and the sample size was insufficient to evaluate associations with, for instance, the different types of ADHD medications. Future research would benefit from larger sample sizes to replicate findings and conduct stratified analyses on the different medication types. Second, it should also be noted that the use of registry data requires our defined outcomes to be formal diagnoses entered into the medical record, and our work

Table 3. Primary analysis comparing children of mothers discontinuing ADHD medication prior to pregnancy with children of mothers using ADHD medication during pregnancy on combined and specific developmental impairments, including stratification on timing, duration, and type of ADHD medication exposure.

	Cases	Total number	Person years	Crude HR	Adjusted HR (95% CI)[a]
Any developmental impairment					
ADHD medication discontinuation	281	1270	6537	ref	Ref
ADHD medication exposed	202	898	4743	0.99	0.97 (0.81–1.17)
Timing of ADHD medication exposure					
First trimester only	116	491	2616	1.04	1.04 (0.83–1.29)
2nd/3rd trimester or more than one trimester	86	407	2126	0.94	0.90 (0.71–1.15)
Duration of ADHD medication exposure					
<91 days	124	515	2754	1.06	1.05 (0.85–1.30)
91–180 days	37	185	924	0.92	0.90 (0.64–1.27)
>180 days	41	198	1065	0.90	0.84 (0.61–1.17)
Type of ADHD medication					
Stimulant	164	723	3806	1.01	0.98 (0.81–1.19)
Other	38	175	937	0.94	0.94 (0.67–1.33)
Neurodevelopmental psychiatric disorders					
ADHD medication discontinuation	80	1270	7611	Ref	Ref
ADHD medication exposed	72	898	5400	1.24	1.18 (0.84–1.65)
Autism					
ADHD medication discontinuation	23	1270	7792	Ref	Ref
ADHD medication exposed	19	898	5522	1.16	1.02 (0.55–1.89)
ADHD					
ADHD medication discontinuation	43	1270	7724	Ref	Ref
ADHD medication exposed	48	898	5475	1.56	1.44 (0.92–2.25)
Other neurodevelopmental impairments					
ADHD medication discontinuation	169	1270	7027	Ref	Ref
ADHD medication exposed	107	898	5072	0.89	0.89 (0.69–1.14)
Cerebral visual impairment					
ADHD medication discontinuation	26	1270	7717	Ref	Ref
ADHD medication exposed	13	898	5531	0.69	0.68 (0.35–1.32)
Hearing impairment					
ADHD medication discontinuation	45	1270	7611	Ref	Ref
ADHD medication exposed	35	898	5396	1.09	1.04 (0.67–1.62)
Epilepsy					
ADHD medication discontinuation	49	1270	7602	Ref	Ref
ADHD medication exposed	21	898	5492	0.61	0.58 (0.34–0.98)
Febrile seizures					
ADHD medication discontinuation	69	1270	7544	Ref	Ref
ADHD medication exposed	46	898	5344	0.94	1.02 (0.69–1.50)
Growth impairment					
ADHD medication discontinuation	78	1270	7452	Ref	Ref
ADHD medication exposed	55	898	5317	0.99	0.92 (0.65–1.31)

[a]Adjusted for maternal age, parity, maternal psychiatric history, in- or outpatient admission to psychiatric ward within 2 years prior to pregnancy and until delivery, use of other psychotropic medications during pregnancy, number of hospitalizations during pregnancy not related to psychiatry, smoking during pregnancy, living alone, education, birthyear, psychiatric history of the father.

cannot rule out subtler, subclinical changes in growth or behavior that would not be so severe as to result in a medical diagnosis. Also, while the registers include information on various important covariates, other covariates including alcohol and illegal drug use are not collected. However, diagnosed alcohol abuse was included as a covariate if the woman had an in- or outpatient hospital contact from two years before pregnancy to delivery because of this. Third, there is a risk of misclassification, like in other pharmacoepidemiologic studies using register data when using redeemed prescriptions to define exposure status. To accommodate this, we conducted sensitivity analyses (1) restricting the exposed group to those who redeemed at least two prescriptions during pregnancy and (2) stratified on duration of ADHD medication exposure with the largest being more than 180

Table 4. Sensitivity analyses addressing different sources of potential biases with the overall category 'any developmental impairment' as the outcome.

Analysis	Potential source of bias addressed	Exposure status	Cases	Total number	Person years	Crude HR	Adjusted HR (95% CI)
Primary analysis[a]	Confounding by indication	Discontinuation	281	1270	6537	Ref	Ref
		Exposed	202	898	4743	0.99	0.97 (0.81–1.17)
Analysis using fathers as negative control[b]	Confounding by indication	Discontinuation	247	1253	6918	Ref	Ref
		Exposed	602	2639	15493	1.11	1.11 (0.96–1.29)
Analysis excluding those with use of other psychotropic medications[c]	Confounding	Discontinuation	211	991	5110	Ref	Ref
		Exposed	121	566	2980	0.98	0.99 (0.79–1.23)
Sibling control analysis[d]	Confounding by family context and genetics	Non-exposed	205	552	4892	Ref	Ref
		Exposed	86	395	2236	0.85	0.71 (0.46–1.08)
Analysis restricting to at least two prescription fills during pregnancy[a]	Misclassification of exposure	Discontinuation	281	1270	6537	Ref	Ref
		Exposed	142	615	3227	1.03	0.99 (0.81–1.22)

[a]Adjusted for maternal age, parity, maternal psychiatric history, in- or outpatient admission to psychiatric ward within 2 years prior to pregnancy and until delivery, use of other psychotropic medications during pregnancy, number of hospitalizations during pregnancy not related to psychiatry, smoking during pregnancy, living alone, education, birthyear, psychiatric history of the father.
[b]Same as above including maternal ADHD medication use during pregnancy, paternal age at delivery (continuous variable), and paternal inpatient or outpatient psychiatric treatment from two years before pregnancy to delivery (yes/no).
[c]Adjusted for maternal age, parity, maternal psychiatric history, in- or outpatient admission to psychiatric ward within 2 years prior to pregnancy and until delivery, number of hospitalizations during pregnancy not related to psychiatry, smoking during pregnancy, living alone, education, birthyear, psychiatric history of the father.
[d]Adjusted for maternal use of other psychotropic medications during pregnancy, birth order, and birth year.

exposed days. Still, our findings remained robust. However, lack of clinical information about doses of ADHD medication taken could have resulted in an underestimation of exposure time, given that the pregnant woman may decide to lower her dose, or the physician could prescribe a lower dose.

CONCLUSIONS

Our results are important because stimulant medications are critical for many adults, including women of childbearing age, to perform their essential functions at work, home, and school [10]. Pregnant women who depend on stimulants for daily functioning must weigh the potential of exposing their fetus to unknown developmental risks against potential medical, financial, and other consequences to both mother and child that are associated with exacerbation of ADHD symptoms when stopping the medication, such as inability to maintain employment and unsafe driving. The present study provides reassurance that several essential categories of child outcomes that could reasonably be suspected to be affected by stimulants, including body growth, neurodevelopment, and seizure risk, do not differ based on antenatal stimulant exposure. Future studies would benefit from larger sample sizes making it possible to conduct stratified analyses on ADHD medication type. Further investigation in other health care systems and of other types of outcomes, such as psychiatric diagnoses in older age groups, would also be of interest. The addition of other types of studies, such as clinical cohort studies, could be used to investigate subtler neurodevelopmental outcomes not accessible in the registers.

CODE AVAILABILITY

Statistical analyses were performed in Stata 15.1 (StataCorp, College Station, TX, USA) and code to perform analyses can be made available by request.

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AUTHOR CONTRIBUTIONS

KBM, TKR, XL, NM, TMO, and VB designed the study. KBM, NM, and XL conducted the analysis and KBM wrote the first draft of the manuscript. TKR, XL, NM, HL, JWD, HK, JBG, JHN, PHT, TMO, and VB made significant contributions to the interpretation of the analysis and writing of the study. All authors have revised the article critically and all share responsibility for the content of the manuscript. All authors have approved the manuscript.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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