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In utero exposure to methylphenidate, amphetamines and atomoxetine and offspring neurodevelopmental disorders – a population-based cohort study and meta-analysis

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The use of Attention-Deficit/Hyperactivity Disorder (ADHD) medications during pregnancy is increasing, raising concerns about potential long-term effects on offspring. This study investigates in utero exposure to methylphenidate, amphetamines and atomoxetine and risk of offspring neurodevelopmental disorders (NDDs). The population-based cohort study identified from Swedish registers included 861,650 children born by 572,731 mothers from 2008–2017. We categorized exposure based on redeemed medication during pregnancy and compared exposed children to those whose mothers discontinued medication before conception. Main outcomes were any NDD, including ADHD and autism spectrum disorder (ASD). Cox proportional hazards regression estimated hazard ratios (HRs), adjusting for maternal psychiatric and sociodemographic factors. Sensitivity analyses included stratifications by medication type, timing, and duration of exposure, and sibling comparisons. We also performed a meta-analysis combining data from the present study with those from a previous Danish study. Results showed no increased risk for any NDD ($HR_{adjusted}$ 0.95, 95% CI 0.82–1.11), ADHD ($HR_{adjusted}$ 0.92, 95% CI 0.78–1.08), or ASD ($HR_{adjusted}$ 0.86, 95% CI 0.63–1.18). Sensitivity analyses showed consistent patterns of no increased risks across different exposure durations, medication types and between siblings. Meta-analyses further supported the findings (pooled HR for any NDD 1.00, 95% CI 0.83;1.20). Our study provides evidence that in utero exposure to ADHD medications does not increase the risk of long-term NDDs in offspring. This study replicates safety data for methylphenidate and extends it with new safety data on amphetamines and atomoxetine. These findings are crucial for informing clinical guidelines and helping healthcare providers and expectant mothers make informed decisions.

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INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most prevalent neurodevelopmental disorder (NDD), affecting individuals across their lifespan [1]. With the increasing prescription rate of ADHD medications among women of reproductive age [2], there has been a concurrent rise in the use of these medications during pregnancy. Estimates suggest that up to 0.8% of pregnant women in the Nordic countries and over 1% of pregnant women in the United States are currently prescribed ADHD medications, making these among the most commonly used medications during pregnancy [3, 4]. Despite their widespread use, there is still insufficient replicated empirical evidence concerning the long-term safety of in utero exposure to ADHD medications, leading many expectant mothers to discontinue use due to concerns about potential harm to the unborn child [5, 6].

Several studies have focused on short-term outcomes of in utero exposure to ADHD medications in offspring, including congenital malformations [7–15] and adverse outcomes related to labour and delivery [6, 11–13, 16–18]. However, long-term outcomes in the offspring have received less attention. A recent study from our group, conducted using Danish national registers, provided initial insights by investigating long-term

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neurodevelopmental and growth outcomes in children exposed to ADHD medication in utero [19]. The findings indicated no increased risk of neurodevelopmental disorders (NDDs) among exposed offspring, and this finding was later replicated in a large US study using data from publicly and commercially insured pregnant women [20]. The US study, however, included only stimulants, amphetamine/dexamfetamine and methylphenidate, whereas the Danish study also included non-stimulants (i.e., atomoxetine and clonidine), but unfortunately lacked the power to stratify the analyses by specific medication types [19]. This distinction between medication types is crucial, as the medications operate through different mechanisms of action, potentially leading to diverse effects on foetal neurodevelopment.

Currently, there are no specific guidelines for the use of any type of ADHD medication during pregnancy, largely due to insufficient evidence about their risks and benefits [21]. Only observational studies are feasible, but they come with significant limitations, especially confounding by indication, which underscores the urgent need for high-quality research. Employing triangulation approaches that combine various epidemiological designs under different assumptions can enhance the robustness of the findings. Importantly, replication studies are critical to validate previous research findings on the use of ADHD medications during pregnancy to ensure robustness of the joint evidence base. Given the increasing number of women of reproductive age using ADHD medications, there is an urgent need for evidence from multiple studies with large data sets that can inform clinical guidelines and help clinicians and patients consider if the benefits of continued ADHD medication use during pregnancy outweigh any potential teratogenic effects to the foetus [8, 22, 23]. Therefore, the present study was conducted to provide additional evidence on the association between in utero exposure to ADHD medications and offspring NDDs and to expand this knowledge by examining the associations by types of medications with data from the Swedish national registers. Importantly, this study adds to previous ones by presenting an analysis of the effects of methylphenidate, amphetamines and atomoxetine separately, in addition to examining their effects when pooled together. To increase the robustness of our results, we also performed meta-analyses of the results from the recent Danish [19] and the current Swedish study.

METHODS

Data sources and study population

In this register-based cohort study, we drew on data from the Swedish National Registers linked via the unique personal identifier assigned to all individuals in Sweden upon birth or immigration [24]. We used the Swedish Medical Birth Register (MBR) to identify livebirths and pregnancy and birth related variables, as well as to identify mothers and fathers in relation to each included pregnancy. The MBR covers births since 1973 and has a coverage above 97% in Sweden since 2000 [25]. Medical diagnoses were identified in the National Patient Register (NPR), which contains diagnoses based on the International Classification of Diseases (ICD) codes, 10th Revision (ICD-10; 1997-onwards) from inpatient care since 1969 and outpatient specialist care since 2001 [26]. ADHD medication dispensations were identified in the Swedish Prescribed Drug Register (PDR), which contains all medications dispensed at Swedish pharmacies since 2005 coded according to the Anatomical Therapeutic Chemical (ATC) classification [27]. We used the Swedish Total Population Register to identify migrations, which includes data on all individuals living in Sweden since 1968 [24], and the Longitudinal Integration Database for Health Insurance and Labour Studies (LISA) [28] to identify sociodemographic variables, which contains data on education and labour market from Swedish inhabitants from 1990. Linked data were available until 31st December 2020.

Throughout this paper, we refer to pregnant and birthing individuals as "female," "women," or "mothers" for fluency. However, we acknowledge that not all individuals in our study identify with these terms.

We identified all singletons born in Sweden between 2008 and 2017 ($N = 1{,}083{,}757$) in MBR, to allow for a two-year ascertainment period before pregnancy to identify exposure to ADHD medication and a minimum of three years follow-up for all included children to identify our outcomes (definitions below). Children with missing information on either parent, missing or unlikely gestational age (<154 or > 315 days), chromosomal abnormalities identified in the NPR [ICD-10 codes Q90–Q99), of mothers with missing data on date of ultrasound or last menstrual period, and of mothers who immigrated to Sweden < 2 years before conception were excluded. After exclusions, the final study population included 861,650 children born by 572,731 mothers (Fig. 1).

In utero exposure to ADHD medication

In utero exposure to ADHD medication was identified from dispensation in the PDR. We considered all ADHD medications approved in Sweden during the study period, including stimulant medications (N06BA04 "methylphenidate", N06BA01 "amphetamine", N06BA02 "dexamfetamine", N06BA12 "lisdexamfetamine") and the non-stimulant medication atomoxetine (N06BA09). As in our prior work [19], ADHD medication dispensations from two years before pregnancy up to the date of delivery were included. Start of pregnancy was defined using the information on gestational age in MBR, 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. Exposure was categorised as follows: 1) "Unexposed" children were defined as no maternal ADHD medication dispensation in the two years prior to pregnancy up until delivery; this group consisted of the background population, but also included a smaller subset of children of mothers with an ADHD diagnosis, 2) "Discontinuation" was defined as maternal ADHD medication dispensation in the two years prior to pregnancy, not necessarily consistently, but no dispensation during pregnancy, 3) "Continuation" was defined as ADHD medication dispensation in the two years prior and during pregnancy, and 4) "New user" was defined as initiation during pregnancy or one month prior to conception but no dispensation in the two years prior. Continuation and new users were categorized as "Exposed". We also estimated the duration of exposure to ADHD medication during pregnancy by multiplying the number of defined daily doses per package by the number of packages dispensed.

Offspring neurodevelopmental disorders

Our main outcome was a registered diagnosis in the NPR of any neurodevelopmental disorder [ICD-codes F70–79, F84, F90–98], or, in line with prior research [5], a dispensation for any ADHD medication after the age of three years. Secondly, we also considered ADHD [F90 or prescription for ADHD medication,] and autism spectrum disorder (ASD [F84]) after age three as separate outcomes. Date of the outcome was defined by the date of the first diagnosis or the first ADHD medication dispensation, whichever came first.

Potential confounders

We evaluated several potential confounders including: maternal age at delivery (<25, 25–34, > 34 years), primiparity (yes/no), calendar year of delivery (2008–2011, 2012–2014, or 2015–2017) and maternal self-reported smoking during pregnancy (yes/no) identified in the MBR; Any maternal and paternal psychiatric history at delivery (ICD-8 codes 290–315, ICD-9 codes 290–319 and ICD-10 codes F00–F99) and psychiatric in- or outpatient treatment two years prior to pregnancy and until delivery (yes/no) identified in the NPR; Dispensing of other psychotropic medications during pregnancy with the ATC codes N06A antidepressants, N05A antipsychotics, N03A antiseizure, or N05B anxiolytics (yes/no) identified in the PDR; Maternal highest education (mandatory schooling to 9th grade /above mandatory school), civil status at delivery (married or cohabiting / single, divorced or widowed) identified in LISA.

Statistical analyses

We followed each child from age 3 years until a diagnosis, death, emigration, or end of follow-up (December 31, 2020), whichever occurred first. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox proportional hazards regression with the child's attained age as the underlying time scale and cluster robust standard errors to account for the correlation between included siblings. Proportionality was evaluated by visually inspecting "log-log" plots. Children of mothers using ADHD medication during pregnancy (continuation and new users) were compared to children of mothers discontinuing ADHD medication prior

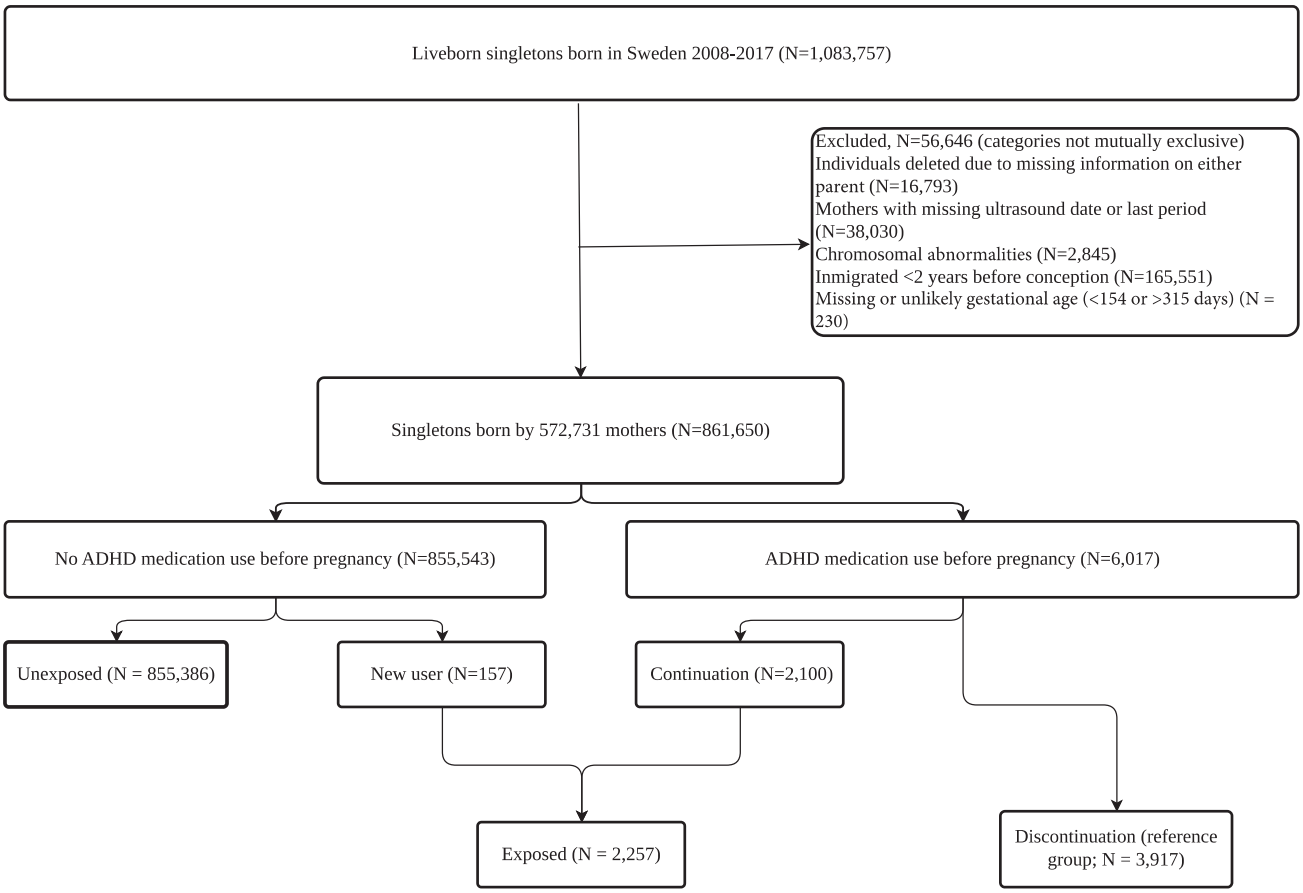


Fig. 1 Flowchart showing identification of study population.

to pregnancy to reduce unmeasured confounding related to maternal ADHD. We further stratified analyses in three ways. First, we stratified by medication type for methylphenidate, amphetamines (including lisdexamfetamine) and atomoxetine. Second, we stratified analyses by the timing of exposure start (first, second, and third trimester). Third, to determine if associations were modified by the duration of use, we stratified the duration of ADHD medication use during pregnancy into ≤ 90 days, 91–180 days, and ≥ 181 days. All analyses were adjusted for the maternal psychiatric and sociodemographic characteristics listed above.

Data management and statistical analyses were performed using SAS 9.4 and R version 4.3.2.

Meta-analysis

Meta-analysis was conducted using R version 4.3.2 with the "metafor" package [29]. Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were extracted from Bang Madsen et al. [19] and current analyses. Log-transformed hazard ratios (logHR) and their standard errors (SE) were calculated to standardize the effect sizes across the two studies. Meta-analytic pooling of the hazard ratios was performed using random-effects models assuming that the true effect sizes may differ across studies. The calculation of weights was based on the inverse variance of the effect estimates. Summary estimates from the meta-analyses were exponentiated to convert logHRs back to HRs for interpretability, and results were presented with 95% CIs. Forest plots were generated to visualise the individual and pooled study estimates, along with their respective confidence intervals.

Ethics

All methods were performed in accordance with the relevant guidelines and regulations. This study was approved by the Swedish Ethical Review Authority (reference number 2020-06540). Informed consent is not required for pseudo anonymised register-based research according to Swedish law.

Sensitivity analyses

We performed four sensitivity analyses to address unmeasured confounding factors and misclassification of the exposure:

1) **Fathers as negative controls**: We compared children of fathers who used or discontinued ADHD medication during the index pregnancy, hypothesizing that maternal use would more directly impact intrauterine exposure. Adjustments included maternal ADHD medication use during pregnancy, paternal age at delivery, and paternal psychiatric treatment during the two years before the index pregnancy, along with variables from the main analysis.
2) **Exclusion due to co-medication**: We excluded children of mothers prescribed other psychotropic medications during pregnancy to reduce confounding by other medications or polypharmacy.
3) **Sibling design**: We used a sibling comparison design, conducting stratified Cox regression analyses on family identifiers and comparing siblings discordant in their exposure status. Adjustments included maternal use of other psychotropic medications during pregnancy, birth order, and birth year.
4) **Exclusion based on number of prescriptions**: To minimize misclassification of ADHD medication exposure, we limited analyses to mothers who filled at least two prescriptions for ADHD medication during pregnancy, ensuring higher certainty of medication consumption during pregnancy.

RESULTS

Among the included 861,650 liveborn children, 2257 (0.3%) were exposed to ADHD medications during pregnancy, including 2100 children whose mothers continued using ADHD medication and 157 who initiated ADHD medication during pregnancy. In total, 3917 (0.5%) children were born to mothers who discontinued ADHD medications before pregnancy; these constituted the

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

Characteristics	Discontinuation *n* = 3917 n (%)	Exposed *n* = 2257 n (%)	Unexposed *n* = 855,386 n (%)
Sex of the child, female	1913 (49)	1104 (49)	415,457 (49)
Maternal age at delivery			
<25 years	1726 (44)	781 (35)	110,958 (13)
25–34 years	1784 (46)	1162 (51)	555,465 (65)
>34 years	407 (10)	314 (14)	188,963 (22)
Calendar year of delivery			
2008–2011	629 (16)	334 (15)	360,201 (42)
2012–2014	1291 (33)	736 (33)	253,585 (30)
2015–2017	1997 (51)	1187 (53)	241,600 (28)
Low birth weight (<2500 g)	160 (4.1)	119 (5.3)	24,728 (2.9)
Preterm birth (<37 weeks of gestation)	242 (6.2)	184 (8.2)	38,198 (4.5)
Primiparity	2334 (60)	1176 (52)	370,094 (43)
Any neurodevelopmental disorder	525 (13)	284 (13)	47,140 (5.5)
ADHD	473 (12)	245 (11)	40,130 (4.7)
ASD	124 (3.2)	63 (2.8)	11,485 (1.3)
ADHD medication type before or during pregnancy			
Amphetamine	34 (0.9)	21 (0.9)	NA
Dexamfetamine	80 (2.0)	62 (2.7)	
Lisdexamfetamine	218 (5.6)	234 (10)	
Methylphenidate	3069 (78)	1730 (77)	
Atomoxetine	516 (13)	209 (9.3)	
Duration of medication exposure during pregnancy	NA		NA
<= 90 days		227 (10)	
91–180 days		158 (7.0)	
>180 days		1872 (83)	
Timing of start of medication exposure	NA		NA
1st trimester		1509 (67)	
2nd trimester		263 (12)	
3rd trimester		485 (21)	
Maternal psychiatric history at delivery, yes	3479 (89)	2085 (92)	56,143 (6.6)
Outpatient psychiatric treatment 2 years before pregnancy to delivery, yes	3408 (87)	2056 (91)	50,185 (5.9)
Inpatient psychiatric treatment 2 years before pregnancy to delivery, yes	1156 (30)	803 (36)	16,266 (1.9)
Paternal psychiatric history at delivery, yes	764 (20)	547 (24)	27,890 (3.3)
Paternal outpatient psychiatric treatment 2 years before pregnancy to delivery, yes	707 (18)	516 (23)	25,635 (3.0)
Paternal inpatient psychiatric treatment 2 years before pregnancy to delivery, yes	230 (5.9)	178 (7.9)	6118 (0.7)
Maternal marital status at delivery (married or cohabiting)	2497 (64)	1362 (60)	769,296 (90)
Maternal highest education at delivery			
Elementary school	1699 (43)	971 (43)	74,260 (8.7)
Above elementary school	2218 (57)	1286 (57)	781,126 (91)
Smoking during pregnancy, yes	1116 (28)	822 (36)	61,408 (7.2)
Dispensing of other psychotropic prescriptions during pregnancy			
Any	971 (25)	1037 (46)	44,963 (5.3)
Antidepressant	670 (17)	567 (25)	33,967 (4.0)
Antipsychotics	61 (1.6)	107 (4.7)	1576 (0.2)
Antiseizure	76 (1.9)	85 (3.8)	3452 (0.4)
Anxiolytics	164 (4.2)	278 (12)	5968 (0.7)

ADHD attention deficit hyperactivity disorder, *ASD* autism spectrum disorder.

reference group (Fig. 1). Descriptive statistics by exposure status are presented in Table 1. More mothers in the discontinuation and exposed groups had children before age 25 (44 and 35%), compared to 13% in the unexposed group, and were more likely to have children born preterm (6 and 8%) and with low birthweight (4 and 5%) compared to the unexposed group (4.5 and 2.9%). The discontinuation and exposed groups also included a larger proportion of births in more recent calendar years, first time mothers, lower education level, and smoking during pregnancy, compared to the unexposed group. The type of ADHD medications dispensed was similar between mothers in the discontinuation group and the exposed group, with the most common being methylphenidate. The only exception was lisdexamfetamine, which was more frequently used in the exposed group (10%) than in the discontinuation group (5.6%). A higher proportion of mothers in the exposed group were dispensed other psychotropic prescriptions during pregnancy (46%) and reported smoking during pregnancy (46%) compared to the discontinuation group (25 and 28%, respectively). Differences between the discontinuation and the exposed group for other psychiatric and sociodemographic variables, such as education level, civil status, and broader psychiatric history, were limited.

In absolute numbers, there was no difference in the prevalence of NDDs in children of mothers in the discontinuation (13%) and exposed (13%) groups (Table 1). Mean follow-up time was 6.9 years (SD 2.3), 7.1 (2.3) and 7.2 (2.4) for NDDs overall, ADHD and ASD, respectively. Results from the Cox regressions are shown in Table 2. After adjusting for pregnancy, maternal psychiatric and sociodemographic characteristics, there was no increased hazard of any NDD (HR = 0.95, 95% 0.82;1.11), ADHD (HR = 0.92, 95% 0.78;1.08) or ASD (HR = 0.86, 95% 0.63;1.18) when comparing children in the exposed group with children in the discontinuation group. Similarly, stratified analyses by timing and duration of exposure did not show a statistically significant association between in-utero exposure to ADHD medication and any of the considered NDDs (Table 3). Stratified by medication type, results showed a consistent pattern with HRs for methylphenidate 0.94 (95% CI 0.79;1.11) and amphetamines 1.15 (95% CI 0.65;2.05) and for atomoxetine 1.03 (95% CI 0.64;1.65) for any NDD (Table 3).

Sensitivity analyses (Table 4) confirmed the robustness of the main analyses, showing no association between ADHD medication exposure and NDDs in the offspring.

Forest plots of the meta-analyses are shown in Fig. 2. With a total population of 3155 children exposed and 5187 in the discontinuation group, pooled HR estimates for any NDD, ADHD, and ASD were 1.00 (95% CI 0.83;1.20), 1.09 (95% CI 0.71;1.68), and 0.89 (95% CI 0.67;1.18), respectively.

DISCUSSION

In this large Swedish population-based cohort study, we replicate the previous findings of no association between in utero exposure to methylphenidate and amphetamines and risk of neurodevelopmental disorders in the offspring and extend the evidence by providing separate analyses for the non-stimulant ADHD medication atomoxetine, showing no increased risk either. Analyses stratified by timing and duration of exposure also showed no significant associations. Sensitivity analyses further adjusting for familial confounding through sibling analyses and using fathers as negative controls also confirmed these findings.

Our study leverages the comprehensive data available in Swedish national registers to replicate and extend the findings from previous studies [19, 20, 30], providing an important test of the initial conclusions that in utero exposure to ADHD medication does not increase the risk of NDDs in the offspring. Replication of findings in different contexts is crucial for validating the generalizability of research outcomes. Differences in healthcare systems, medication use patterns, and patient demographics can all influence study results. While there are similarities between the healthcare systems of Denmark and Sweden, several differences might influence the population of women who use ADHD medication during pregnancy. One notable difference is the accessibility and prevalence of ADHD medication use. In Sweden, the use of ADHD medication, both during pregnancy and in general, is significantly more common compared to Denmark [4, 31]. Also, in Sweden, the number of psychiatrists per capita is much higher [32] and citizens can self-refer for psychiatric assessment, bypassing primary care, whereas in Denmark, a referral from a primary care provider is required. This difference in healthcare pathways could lead to variations in the demographics and characteristics of women who use ADHD medication during pregnancy in these two countries, thereby creating a different confounder structure. Reassuringly, there are no indications that underlying variation in ADHD incidence and variability related to structural differences in the organization of health care seems to influence the results.

Through this rigorous scientific approach, we contribute to a clearer understanding of the safety of ADHD medication use during pregnancy, aiding healthcare providers and patients in making informed decisions about ADHD medication management in pregnancy. Our study also extends the findings from previous

Table 2. Results of the main analysis of the association between in utero exposure to ADHD medication and neurodevelopmental disorders in the offspring, including ADHD and ASD.

	Cases	Total number	Person years	Crude HR	Adjusted HR (95% CI)[a]
Any neurodevelopmental disorder					
ADHD medication discontinuation	525	3917	27,471	ref	ref
ADHD medication exposed	284	2257	15,660	0.97	0.95 (0.82–1.11)
ADHD					
ADHD medication discontinuation	473	3917	27,721	ref	ref
ADHD medication exposed	245	2257	15,813	0.93	0.92 (0.78–1.15)
ASD					
ADHD medication discontinuation	124	3917	28,204	ref	ref
ADHD medication exposed	63	2257	16,040	0.90	0.86 (0.63–1.18)

ADHD attention deficit hyperactivity disorder, *ASD* autism spectrum disorder, *HR* hazard ratio.
[a]Adjusted for maternal age at delivery, primiparity, calendar year of delivery, maternal self-reported smoking during pregnancy, any maternal and paternal psychiatric history at delivery, psychiatric in- or outpatient treatment two years prior to pregnancy and until delivery, dispensing of other psychotropic medications during pregnancy, maternal highest education, and civil status at delivery.

Table 3. Results of the main analysis stratified by duration of medication exposure, timing of start of medication exposure and medication types.

Stratification	Any neurodevelopmental disorder	Adjusted HR (95% CI)[a]
Duration	ADHD medication discontinuation	ref
	< = 90 days	0.88 (0.62–1.25)
	91–180 days	0.73 (0.44–1.22)
	>180 days	0.99 (0.84–1.16)
Timing of exposure	ADHD medication discontinuation	ref
	Exposure start 1st trimester	0.96 (0.81–1.14)
	Exposure start 2nd trimester	1.00 (0.71–1.40)
	Exposure start 3rd trimester	0.94 (0.71–1.26)
Medication type	ADHD medication discontinuation	ref
	Methylphenidate	0.94 (0.79–1.11)
	Amphetamines including dex- and lisdexamfetamine	1.15 (0.65–2.05)
	Atomoxetine	1.03 (0.64–1.65)
	ADHD	
Duration	ADHD medication discontinuation	ref
	Duration < = 90 days	0.80 (0.55–1.18)
	Duration 91–180 days	0.66 (0.38–1.17)
	Duration > 180 days	0.96 (0.81–1.15)
Timing of exposure	ADHD medication discontinuation	ref
	Exposure start 1st trimester	0.89 (0.74–1.07)
	Exposure start 2nd trimester	0.99 (0.69–1.41)
	Exposure start 3rd trimester	1.02 (0.75–1.39)
Medication type	ADHD medication discontinuation	ref
	Methylphenidate	0.89 (0.74–1.06)
	Amphetamines including dex- and lisdexamfetamine	1.05 (0.55–2.01)
	Atomoxetine	1.11 (0.68–1.82)
	ASD	
Duration	ADHD medication discontinuation	ref
	Duration < = 90 days	1.06 (0.54–2.07)
	Duration 91–180 days	0.75 (0.27–2.04)
	Duration > 180 days	0.84 (0.6–1.19)
Timing of exposure	ADHD medication discontinuation	Ref
	Exposure start 1st trimester	0.99 (0.7–1.39)
	Exposure start 2nd trimester	0.86 (0.4–1.84)
	Exposure start 3rd trimester	0.52 (0.26–1.03)
Medication type	ADHD medication discontinuation	ref
	Methylphenidate	0.82 (0.58–1.15)
	Amphetamines including dex- and lisdexamfetamine	1.82 (0.42–7.92)
	Atomoxetine	0.65 (0.16–2.76)

ADHD attention deficit hyperactivity disorder, *ASD* autism spectrum disorder, *HR* hazard ratio.
[a]Adjusted for maternal age at delivery, primiparity, calendar year of delivery, maternal self-reported smoking during pregnancy, any maternal and paternal psychiatric history at delivery, psychiatric in- or outpatient treatment two years prior to pregnancy and until delivery, dispensing of other psychotropic medications during pregnancy, maternal highest education, and civil status at delivery.

studies by providing results on the non-stimulant medication atomoxetine, showing no evidence of an increased risk of NDDs even for this compound.

As current guidelines do not include specific indications on the use of ADHD medication in pregnancy, our results are relevant as they can inform future guidelines on the treatment of ADHD.

Future research should focus on further elucidating the long-term safety of ADHD medications during pregnancy, including potential effects on other developmental domains not covered in this study. Studies with larger sample sizes and more detailed information on dosage and adherence could provide more granular insights. Additionally, research exploring the underlying mechanisms through which ADHD medications may or may not influence foetal development would be valuable.

Although our primary analysis focused on the risk of neurodevelopmental disorders in children exposed to ADHD medication in utero, descriptive analyses revealed a higher cumulative incidence of preterm birth and low birth weight among the exposed group. However, as these comparisons were not adjusted for potential confounders, the observed differences should be interpreted with caution. It is unclear whether these outcomes reflect a direct effect of ADHD medication exposure or

Table 4. Sensitivity analyses addressing different sources of biases with any neurodevelopmental disorder 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	525	3917	27,471	ref	ref
		Exposed	284	2257	15,660	0.97	0.95 (0.82–1.11)
Analysis using fathers as negative control[b]	Confounding by indication	Discontinuation	264	1989	14,285	ref	ref
		Exposed	655	5010	36,834	0.91	0.97 (0.84–1.12)
Analysis excluding those with use of other psychotropic medications[c]	Confounding	Discontinuation	515	3850	27,000	ref	ref
		Exposed	274	2154	14,943	0.99	0.97 (0.83–1.13)
Sibling control analysis[d]	Confounding by family context and genetics	Non-exposed	525	3917	27,471	ref	ref
		Exposed	284	2257	15,660	0.97	1.24 (0.72–2.13)
Analysis restricting to at least two prescription fills during pregnancy[a]	Misclassification of exposure	Discontinuation	452	3362	23,609	ref	ref
		Exposed	270	2171	14,999	0.97	0.96 (0.82–1.13)

[a]Adjusted for maternal age at delivery, primiparity, calendar year of delivery, maternal self-reported smoking during pregnancy, any maternal and paternal psychiatric history at delivery, psychiatric in- or outpatient treatment two years prior to pregnancy and until delivery, dispensing of other psychotropic medications during pregnancy, maternal highest education, and civil status at delivery.
[b]Same as above including maternal ADHD medication use during pregnancy, paternal age at delivery, paternal inpatient or outpatient psychiatric treatment from two years before pregnancy to delivery.
[c]Same as in main analyses except for use of other psychotropic medications.
[d]Adjusted for maternal use of other psychotropic medications during pregnancy, birth order, and birth year.

are driven by unmeasured confounders, such as maternal lifestyle factors (e.g., smoking, diet, and stress), co-existing psychiatric conditions, or broader health challenges.

Strengths and limitations

The main strength of our study lies in the use of comprehensive, high-quality data from the Swedish national registers, allowing for a detailed and robust analysis of a large cohort. The extensive follow-up period and the ability to control for a wide range of confounding factors, including maternal psychiatric history and sociodemographic characteristics, further strengthen our finding. An important strength is the analysis of the effects of stimulants and non-stimulants separately, which is informative for shared decision-making in clinical practice. Additionally, the replication of previous studies' results and the inclusion of meta-analyses enhance the reliability and generalizability of our conclusions.

Limitations must also be considered. Despite the nationwide nature of the study data and large sample size, statistical analyses were underpowered as indicated by the wide confidence intervals. Further, despite rigorous adjustments, residual confounding cannot be entirely ruled out, particularly regarding unmeasured genetic and environmental factors. Although the registers capture a range of important covariates, they do not include information on important factors related to maternal lifestyle during pregnancy such as alcohol and illegal drug use during pregnancy. However, diagnosed alcohol abuse was accounted for as a covariate if the woman had an in- or outpatient hospital contact related to substance use disorder during the two years before pregnancy up to delivery. Whilst we used sibling comparison to partly address this, this only accounts for ~50% of segregating genes and environmental factors that are shared by siblings.

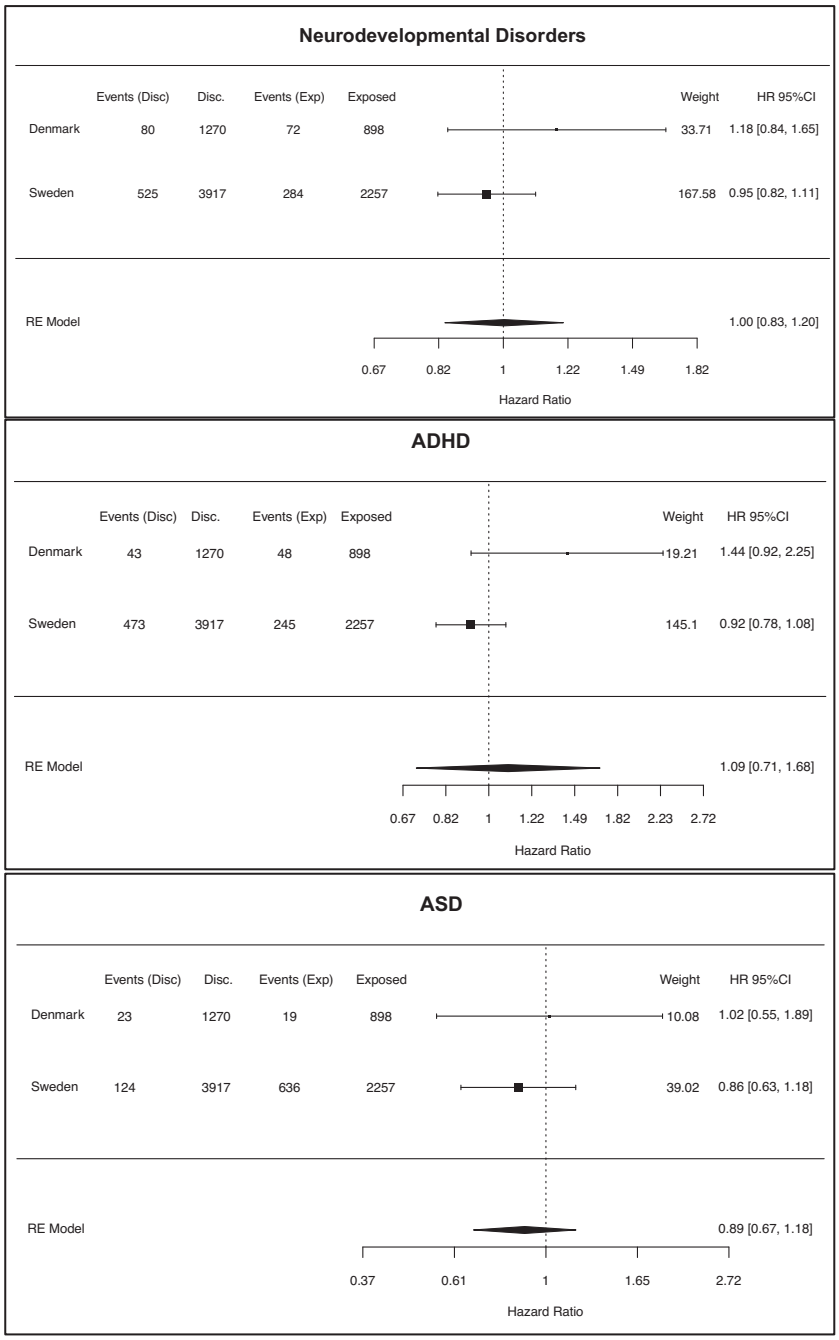
As with other pharmacoepidemiologic studies using register data, there is a risk of misclassification when defining exposure status based on redeemed prescriptions [33]. To address this, we conducted sensitivity analyses by (1) restricting the exposed group to those who redeemed at least two prescriptions during pregnancy and (2) stratifying by duration of ADHD medication exposure, with the longest duration being more than 180 days. Our findings remained robust across these analyses. However, the lack of clinical information about the doses of ADHD medication taken could have led to an underestimation of exposure time, as pregnant women might lower their dose during pregnancy or physicians might prescribe a lower dose.

CONCLUSIONS

Our study supports the safety of using ADHD medication during pregnancy in relation to neurodevelopmental disorders (NDDs) in offspring. These findings contribute to the growing evidence base needed to inform clinical guidelines and ensure that treatment decisions during pregnancy are based on robust and reliable data.

For new users, methylphenidate appears to be the 'safest' choice, given that it is the most thoroughly investigated ADHD medication. However, for patients who are already doing well on amphetamines or atomoxetine, there is currently no compelling reason to switch medications based on safety concerns regarding long-term outcomes. It is important to note that the sample sizes for these groups are relatively small, and more data on these medication classes are needed to confirm these findings.

Overall, our study provides reassuring evidence that continuing ADHD medication during pregnancy does not increase the risk of long-term NDDs in offspring. This information is crucial for healthcare providers and expectant mothers when making informed decisions about ADHD medication management during pregnancy. Future research should continue to explore the long-term safety of various ADHD medications during pregnancy, including further investigation into specific medication classes and their potential effects on other developmental domains.



Disc – Discontinuation
Exp - Exposed
ADHD – Attention Deficit Hyperactivity Disorder
ASD – Autism Spectrum Disorder
RE Model – Random Effects Model
HR – Hazard Ratio
95% CI – 95% Confidence Intervals

Fig. 2 Forest plots of the meta-analyses of the Danish and Swedish data.

DATA AVAILABILITY

Access to individual-level data from Sweden is governed by Swedish authorities. Each scientific project must be approved before initiation, and approval is granted to a specific Swedish research institution. Researchers at Swedish research institutions may obtain the relevant approval and data. International researchers may gain data access if governed by a Swedish research institution having needed approval and data access.

CODE AVAILABILITY

Code can be made accessible upon reasonable request.

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AUTHOR CONTRIBUTIONS

KBM, MGA and IB designed the study, and all authors contributed to the study conception and design. Data- management and analyses were performed by MGA. The first draft of the manuscript was written by KBM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript and agree to be accountable for the work.

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COMPETING INTERESTS

KBM has received speakers fee from MEDICE within the last 3 years. HL reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work. HL is editor-in-chief of JCPP Advances. CS is founder and owner of a private Swedish clinic for assessment and treatment of ADHD in children and adults (SMART Psykiatri) and the founder of a digital selfcare tool for female ADHD (Letterlife). CS has participated at advisory boards, served as invited speaker and received honorariums/travel expenses from Shire/Takeda, Nordic Drugs, UCB Pharma, DNE Pharma, Novartis, Evolan, Lundbeck A/S, Gideon Richter and Medice during 2017–2024, serve as PI for

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ADDITIONAL INFORMATION

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