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ORIGINAL RESEARCH

Antipsychotic use in pregnancy and risk of attention/deficit-hyperactivity disorder and autism spectrum disorder: a Nordic cohort study

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ABSTRACT

Background Antipsychotics are increasingly used among women of childbearing age and during pregnancy.

Objective To determine whether children exposed to antipsychotics *in utero* are at increased risk of attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD), accounting for maternal diagnoses of bipolar, psychotic and other psychiatric disorders.

Design
Population-based cohort study, including a sibling analysis.

Setting
Nationwide data on all pregnant women and their live-born singletons in Denmark (1997-2017), Finland (1996-2016), Iceland (2004-2017), Norway (2004-2017), and Sweden (2006-2016).

Participants
4 324 086 children were eligible for inclusion to the study cohort.

Intervention
Antipsychotic exposure *in utero*, assessed by pregnancy trimester, type of antipsychotic, and varying patterns of use.

Main outcome measures
Non-mutually exclusive diagnoses of ADHD and ASD. We used Cox proportional hazard models to calculate hazard ratios (HRs) controlling for maternal psychiatric disorders and other potential confounding factors.

Findings Among 4 324 086 singleton births, 15 466 (0.4%) were exposed to antipsychotics *in utero*. During a median follow-up of 10 years, we identified 72 257 children with ADHD and 38 674 children with ASD. Unadjusted HRs were raised for both outcomes but shifted substantially towards the null after adjustment; 1.10 (95%CI 1.00 to 1.27) for ADHD and 1.12 (0.97 to 1.29) for ASD. Adjusted HRs remained consistent by trimester of exposure and type of antipsychotic. Comparing *in utero* exposure with pre-pregnancy use yielded HRs of 0.74 (0.62 to 0.87) for ADHD and 0.88 (0.70 to 1.10) for ASD. Sibling analyses yielded HRs of 1.14 (0.79 to 1.64) for ADHD and 1.34 (0.75 to 2.39) for ASD.

Discussion Our findings suggest little or no increased risk of child ADHD or ASD after *in utero* exposure to antipsychotics.

Clinical implications Results regarding child neurodevelopment are reassuring for women who need antipsychotics during pregnancy.

What is already known on this topic

- Indications for antipsychotic use have expanded in recent years with frequent off-label use.
- Antipsychotics are increasingly used among women of reproductive age and during pregnancy.
- Long-term safety data are sparse and little is known about the consequences of exposure to antipsychotics *in utero* for child neurodevelopment.

What are the new findings?

- The findings of this multinational cohort study of over 4 million births, suggest little or no increased risk of attention-deficit/hyperactivity disorder or autism spectrum disorder among children exposed to antipsychotics *in utero* when accounting for maternal psychotic or bipolar disorder and other psychiatric disorders.
- Our results do not support a recommendation to discontinue treatment for women who need antipsychotics during pregnancy.

INTRODUCTION

Although the primary indications for antipsychotic medications are schizophrenia and bipolar disorder, these medications are also used to treat other conditions such as anxiety, depression, insomnia, substance abuse, pain and nausea.[1–4] In a multinational study covering 10 countries, we recently

demonstrated increasing use of newer (atypical) antipsychotics in pregnancy,[5] which may have fewer adverse effects and be less likely to affect fertility than older (typical) antipsychotics.[6]

The risks of congenital anomalies and short-term neonatal complications associated with antipsychotic exposure *in utero* have been evaluated in epidemiologic studies,[7–9] however, data on the risk of neurodevelopmental disorders during childhood are sparse.[10–13] This is despite potential neurotoxic effects of some antipsychotics in vitro and in vivo,[14] and evidence that these substances cross the placenta.[15] Two recent systematic reviews[11 12] concluded that there was no clear evidence of long-term effects after exposure to antipsychotics *in utero*. Some evidence suggested an effect on short-term developmental delay in childhood, but this was based on limited data and larger studies with long-term follow-up are needed.[1 10 12]

Given the paucity of safety evidence, we aimed to examine the risk of adverse neurodevelopmental outcomes in children who were exposed to antipsychotics *in utero*. We leveraged nationwide register data from five Nordic countries covering more than four million births to evaluate associations between exposure to antipsychotics *in utero* and subsequent risks of attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) in children. We conducted analyses stratified by maternal psychiatric disorders, for which antipsychotics are indicated, to account for confounding by indication as well as sibling analyses to account for shared genetic and environmental factors.

METHODS

Study design and data sources

We conducted a population-based cohort study based on nationwide population data and health registers from the five Nordic countries. Personal identification numbers, assigned to each resident at birth or immigration, enabled individual-level data linkage across prospectively collected data on prescription fills, health conditions, sociodemographic characteristics, pregnancy characteristics and birth outcomes. Reporting to the Nordic registers is mandatory and regulated by national laws.[16]

Study population

According to data availability in each country, the study population included all live-born singletons in the Medical Birth Registers of Denmark 1997–2017, Finland 1996–2016, Iceland 2004–2017, Norway 2004–2017 and Sweden 2006–2016. We also identified siblings born to the same mother during these periods. We excluded children with missing or invalid data on gestational age and those with a chromosomal anomaly or fetal alcohol-spectrum disorder diagnosed in the first year of life (online supplemental figure 1).

Antipsychotic exposure

We determined medication exposure through the nationwide prescription registers[17] and identified antipsychotics according to the Anatomical Therapeutic Chemical (ATC)[18] classification group N05A. We divided substances into typical and atypical antipsychotics (online supplemental table 1). Lithium (N05AN01) has a different mechanism of action and was not considered as an antipsychotic in this study. Prochlorperazine (N05AB04) is almost exclusively used as an antiemetic in pregnancy,[5] and children who were exposed to this substance and no other antipsychotic *in utero* were excluded (online supplemental figure 1). In general, antipsychotics are dispensed for a maximum of 3 months' use in the Nordic countries.

The start of pregnancy and gestational age were based on estimation of the last menstrual period (LMP) using prenatal ultrasound. We defined children as exposed *in utero* if mothers filled at least one antipsychotic prescription during pregnancy, that is, from LMP to birth. This was examined as the primary exposure window. We also assessed antipsychotic exposure by trimester of pregnancy: first (LMP to 97 days after LMP), second (98 days after LMP to 202 days after LMP) and third (203 days after LMP to birth). Children whose mothers did not fill a prescription for an antipsychotic drug from 90 days before LMP to birth were considered unexposed, and, thus, comprised the primary comparison group.

Outcome ascertainment

For child neurodevelopmental outcomes, we identified all (non-mutually exclusive) diagnoses of ADHD and ASD through records in the Nordic health registers, which cover inpatient hospital care, outpatient specialist visits and prescription fills. Children were considered to have ADHD at age 3 or older once they had: two recorded diagnoses of F90.0, F90.1 or F90.2 according to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) or one recorded diagnosis and two prescription fills for centrally acting sympathomimetics (N06BA, excluding modafinil) or guanfacine (C02AC02). For ASD, children were considered to have the outcome if at age 1 or older they had a recorded ICD-10 diagnosis of F84.0, F84.1 or F84.5. Previous studies suggest a high specificity of these diagnoses in the Nordic registers, with positive predictive values over 90%, and that prescription fills are a valid indicator of ADHD diagnosis.[19–22] By requiring two recorded ADHD diagnoses or one diagnosis and two prescription fills, we further enhanced the specificity of the outcome.

Covariates

We considered several demographic and clinical factors in our analyses. As covariates, we included country, birth year, maternal birth country, education, age, cohabitation, smoking status and body mass index (BMI) in early pregnancy, parity and sex of child (eTable 2). Maternal BMI was not available in the Danish data set. We identified maternal comorbidities recorded from 12 months before LMP to birth and use of other medication, including teratogenic substances, from 90 days before LMP to birth. As indications for antipsychotic use, we considered recorded maternal diagnoses of (1) psychotic or bipolar disorder, (2) other psychiatric disorder, (3) no recorded psychiatric condition. Online supplemental table 2 lists all data sources, ICD-10 and ATC codes, variable categories and assessment windows we used to define covariates.

Data analysis

We used Cox proportional hazard regression models in all analyses, with children's age as the underlying timescale, to estimate both crude and adjusted HRs and 95% CIs for the association between ADHD and ASD and antipsychotic exposure *in utero*. The two distinct outcomes were analysed separately. Follow-up started at the date of birth and ended at the date when the outcome definition was met, emigration, death or end of the study period, whichever came first.

In the primary analysis, we compared risks of ADHD and ASD among children exposed and unexposed to antipsychotics *in utero*. We performed multivariable analyses with two levels of adjustments: (1) country, birth year, sex of child, maternal age and parity and (2) all measured confounding variables (table 1,

Table 1 Maternal and child characteristics by exposure to antipsychotics during pregnancy and maternal diagnosis of psychotic or bipolar disorder

	Full study population		Maternal psychotic or bipolar disorders	
	Exposed (n=15 466)	Unexposed (n=4 308 620)	Exposed (n=4385)	Unexposed (n=8356)
Maternal characteristics	n (%)	n (%)	n (%)	n (%)
Age at delivery, years				
<20	446 (2.9)	76 196 (1.8)	92 (2.1)	190 (2.3)
20–24	2564 (16.6)	580 868 (13.5)	655 (14.9)	1493 (17.9)
25–29	4285 (27.7)	1 367 998 (31.8)	1141 (26.0)	2562 (30.7)
30–34	4448 (28.8)	1 447 387 (33.6)	1283 (29.3)	2413 (28.9)
35–39	2822 (18.2)	692 412 (16.1)	903 (20.6)	1351 (16.2)
≥40	901 (5.8)	143 759 (3.3)	311 (7.1)	347 (4.2)
Education				
Compulsory	3732 (24.1)	477 050 (11.1)	1000 (22.8)	2227 (26.7)
Secondary	3760 (24.3)	1 305 399 (30.3)	1053 (24.0)	2886 (34.5)
Postsecondary	2024 (13.1)	1 010 008 (23.4)	469 (10.7)	1490 (17.8)
Postgraduate	359 (2.3)	263 335 (6.1)	92 (2.1)	276 (3.3)
Missing	5591 (36.2)	1 252 828 (29.1)	1771 (40.4)	1477 (17.7)
Cohabiting				
Yes	11 133 (72.0)	3 508 251 (81.4)	3039 (69.3)	5963 (71.4)
No	4249 (27.5)	783 164 (18.2)	1325 (30.2)	2365 (28.3)
Missing	84 (0.5)	17 205 (0.4)	21 (0.5)	28 (0.3)
Mother born within source country				
Yes	12 170 (78.7)	3 478 423 (80.7)	3473 (79.2)	7016 (84.0)
No	2574 (16.6)	701 117 (16.3)	675 (15.4)	1135 (13.6)
Missing	722 (4.7)	129 080 (3.0)	237 (5.4)	205 (2.5)
BMI*, early pregnancy				
<18.5	418 (2.7)	99 837 (2.3)	94 (2.1)	261 (3.1)
18.5–24	5097 (33.0)	1 735 832 (40.3)	1364 (31.1)	3337 (39.9)
25–29	3038 (19.6)	682 603 (15.8)	1043 (23.8)	1743 (20.9)
30–34	1525 (9.9)	246 832 (5.7)	562 (12.8)	819 (9.8)
≥35	922 (6.0)	117 031 (2.7)	387 (8.8)	476 (5.7)
Missing	4466 (28.9)	1 426 485 (33.1)	935 (21.3)	1720 (20.6)
Smoking, early pregnancy				
Yes	4600 (29.7)	475 860 (11.0)	1515 (34.5)	2031 (24.3)
No	9310 (60.2)	3 499 645 (81.2)	2570 (58.6)	5782 (69.2)
Missing	1556 (10.1)	333 115 (7.7)	300 (6.8)	543 (6.5)
Parity				
0	7090 (45.8)	1 850 721 (43.0)	2235 (51.0)	4174 (50.0)
1	4473 (28.9)	1 545 695 (35.9)	1154 (26.3)	2440 (29.2)
≥2	3770 (24.4)	889 425 (20.6)	953 (21.7)	1709 (20.5)
Missing	133 (0.9)	22 779 (0.5)	43 (1.0)	33 (0.4)
Maternal comorbidity				
Yes	1395 (9.0)	161 014 (3.7)	418 (9.5)	571 (6.8)
No	14 071 (91.0)	4 147 606 (96.3)	3967 (90.5)	7785 (93.2)
Maternal psychiatric disorders				
Psychotic or bipolar disorders	4385 (28.4)	8356 (0.2)	4385 (100.0)	8356 (100.0)
Other psychiatric disorders	5729 (37.0)	415 906 (9.6)	0 (0.0)	0 (0.0)
No recorded psychiatric conditions	5352 (34.6)	3 884 358 (90.2)	0 (0.0)	0 (0.0)
Use of known teratogens				
Yes	531 (3.4)	9503 (0.2)	291 (6.6)	250 (3.0)
No	14 935 (96.6)	4 299 117 (99.8)	4094 (93.4)	8106 (97.0)
Use of suspected teratogens				
Yes	3211 (20.8)	127 660 (3.0)	1508 (34.4)	2675 (32.0)
No	12 255 (79.2)	4 180 960 (97.0)	2877 (65.6)	5681 (68.0)
Other medications during pregnancy				
Yes	9937 (64.3)	647 209 (15.0)	2747 (62.6)	4171 (49.9)
No	5529 (35.7)	3 661 411 (85.0)	1638 (37.4)	4185 (50.1)

Continued

Table 1 Continued

	Full study population		Maternal psychotic or bipolar disorders	
	Exposed (n=15 466)	Unexposed (n=4 308 620)	Exposed (n=4385)	Unexposed (n=8356)
Children characteristics	n (%)	n (%)	n (%)	n (%)
Sex				
Male	7758 (50.2)	2 211 376 (51.3)	2289 (52.2)	4284 (51.3)
Female	7708 (49.8)	2 097 244 (48.7)	2096 (47.8)	4072 (48.7)
Calendar year of birth				
1996–2005	2338 (15.1)	1 148 146 (26.6)	600 (13.7)	764 (9.1)
2006–2008	3645 (23.6)	808 282 (18.8)	612 (14.0)	1020 (12.2)
2009–2011	3040 (19.7)	851 673 (19.8)	1010 (23.0)	1876 (22.5)
2012–2014	3429 (22.2)	830 200 (19.3)	1175 (26.8)	2446 (29.3)
2015–2017	3014 (19.5)	670 319 (15.6)	988 (22.5)	2250 (26.9)

*BMI was not obtained from Denmark.
BMI, body mass index.

online supplemental table 2). We included country and birth year as strata variables in the models as these variables did not satisfy the proportional hazard assumption. Other variables were not found to seriously violate the proportional hazard assumption, judged from visual inspection of log cumulative hazard plots and smoothed plots of the scaled Schoenfeld residuals.[21] To account for missing covariate values, we used the simplified two-stage calibration method proposed by Hjellvik *et al*.[23] With this method, partly adjusted effect estimates from the full population are calibrated by fully adjusted effect estimates from a subset of the population that has no missing covariate values. Clustered robust SEs were used to account for clustering of siblings.

We conducted stratified analyses by timing of antipsychotic exposure (first trimester only; second or third trimester only; throughout pregnancy, that is, first trimester and second or third trimester) and type of antipsychotic (typical only, atypical only). To evaluate the impact of confounding by indication, we performed analyses stratified by maternal psychiatric disorder.

We pooled data from Finland, Iceland, Norway and Sweden and analysed these as one cohort while data from Denmark were analysed separately, in compliance with national data protection regulations. The resulting effect estimates from the pooled cohort and the Danish cohort were combined at the final stage by a fixed effects meta-analysis approach.

Secondary analyses

We conducted four separate analyses to further explore the impact of potential confounding by indication and unmeasured confounding. First, we compared risks of ADHD and ASD in children whose mothers used antipsychotics during pregnancy *versus* those who only used antipsychotics prepregnancy (a prescription fill from 12 months to 90 days before LMP). Furthermore, we stratified this analysis by maternal psychiatric disorder. Second, to quantify the influence of maternal psychiatric disorder, we compared the risks of ADHD and ASD in children whose mothers had discontinued antipsychotic use before pregnancy (prepregnancy use only) *versus* those who had no recorded use of antipsychotic use before or during pregnancy. Third, to isolate the association between maternal psychotic or bipolar disorder and child neurodevelopment, we restricted the analysis to children whose mothers did not use any antipsychotics before or during pregnancy and compared risks of ADHD and ASD among those whose mothers had a psychotic or bipolar disorder *versus* those who did not. Finland only provided prescription data from 90 days before LMP until birth and, therefore, did not contribute to these secondary analyses.

Finally, we conducted a sibling analysis to further adjust for unmeasured confounding from family-related factors not captured in the study data, for example, genetic and social factors. We restricted the cohort to women with at least two children in our data and analysed siblings who were discordant for both exposure and outcome. We then compared the risks of ADHD and ASD in sibling clusters exposed and unexposed to antipsychotics *in utero*.

Sensitivity analyses

To reduce the possibility of exposure misclassification, we redefined the primary exposure definition requiring at least two filled antipsychotic prescriptions (from LMP to birth) for a child to be categorised as exposed in utero. Furthermore, as data were not available from the Norwegian Patient Registry before 2008, we conducted a sensitivity analysis restricting the Norwegian cohort to births after 2008 to test the robustness of the data included in the primary analysis from Norway. Finally, we conducted *post hoc* sensitivity analyses to elucidate whether the sibling analysis was impacted by selection bias, as the sibling comparison was by necessity restricted to a highly selected sample, that is, children with at least one sibling, and who were discordant on exposure *in utero* (see details in Supplement, online supplemental table 11, table 12).

All analyses were conducted in R (V.4.0.0). The research was approved by applicable ethics review boards and/or register controllers in all study countries.

RESULTS

We identified 4 324 086 children eligible to be included in the study cohort (online supplemental figure 1). Overall, 15 466 children (0.4%) were exposed to antipsychotics *in utero*; thereof 6478 (41.9%) in the first trimester only, 3349 (21.7%) in the second or third trimester only and 5639 (36.4%) throughout the pregnancy period. Maternal age, smoking, BMI, education, cohabitation and use of other medications in pregnancy differed between exposed and unexposed children (table 1). Among children, whose mothers had a diagnosis of psychotic or bipolar disorder, 4385 (34.4%) were exposed to antipsychotics *in utero*; among those whose mothers had other psychiatric disorders, 5729 (1.4%) were exposed.

Table 2 HRs and 95% CIs comparing the risk for ADHD in exposed and unexposed children by timing and type of antipsychotic exposure

	Number with ADHD/N	Person-years at risk	Hazard ratio (95% CI)		
			Crude	Model 1*	Model 2†
Antipsychotic exposure					
Unexposed	71775/4 308 620	41 863 339	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Exposed anytime during pregnancy	482/15 466	130 211	2.28 (2.08 to 2.49)	2.00 (1.83 to 2.19)	1.10 (1.00 to 1.21)
Timing of antipsychotic exposure					
First trimester only	210/6478	56 144	2.17 (1.90 to 2.49)	1.72 (1.51 to 1.97)	1.07 (0.93 to 1.23)
Second/third trimester only	103/3349	28 534	2.24 (1.84 to 2.72)	2.09 (1.72 to 2.54)	1.08 (0.89 to 1.32)
First trimester and second/third trimester	169/5639	45 534	2.45 (2.10 to 2.85)	2.46 (2.11 to 2.85)	1.06 (0.90 to 1.25)
Type of antipsychotic exposure					
Typical antipsychotics only	272/6896	75 179	1.84 (1.63 to 2.08)	1.71 (1.51 to 1.93)	1.11 (0.98 to 1.26)
Atypical antipsychotics only	166/7752	48 100	3.11 (2.67 to 3.62)	2.40 (2.06 to 2.79)	1.00 (0.85 to 1.17)

*Adjusted for source country, birth year, sex of child, maternal age, and parity.
†Adjusted for source country, birth year, sex of child, maternal age, parity, maternal education, cohabitation, mother born within source country, BMI, smoking, maternal comorbidity, use of known teratogens, use of suspected teratogens, other medications during pregnancy.
ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Antipsychotics and ADHD

During 41 993 550 years of total follow-up time with a median of 9.8 years (25th to 75th percentile 5.5–14.3 years), we identified 72 257 children with ADHD, of whom 482 (3.1%) were exposed to antipsychotics *in utero* and 71 775 unexposed (1.7%). Comparing the risk of ADHD among exposed and unexposed children yielded a crude HR of 2.28 (95% CI 2.08 to 2.49). As presented in table 2, the association was attenuated with full adjustment (HR, 1.10; 95% CI 1.00 to 1.21). The HRs for ADHD remained similar across trimester of exposure and type of antipsychotics (table 2).

Stratifying by maternal psychiatric disorder yielded adjusted HRs of 0.90 (95% CI 0.70 to 1.15), 0.96 (95% CI 0.82 to 1.12) and 1.44 (95% CI 1.25 to 1.66), respectively, for psychotic or bipolar disorders; other psychiatric disorders; or no recorded psychiatric conditions (figure 1, online supplemental table 3).

Antipsychotics and ASD

During 42 113 726 years of total follow-up time with a median of 9.9 years (25th to 75th percentile, 5.5–14.3 years), we identified 38 674 children with ASD, of whom 238 (1.5%) were exposed to antipsychotics *in utero* and 38 436 (0.9%) unexposed. Comparing the risk of ASD among exposed and unexposed children yielded a crude HR of 2.12 (95% CI 1.86 to 2.41) and a fully adjusted HR of 1.12 (95% CI 0.97 to 1.29). The HRs for ASD remained similar across trimester of exposure but was slightly elevated with atypical antipsychotic exposure (table 3). Stratifying by maternal psychiatric disorder yielded fully adjusted HRs of 1.28 (95% CI 0.95 to 1.71), 1.09 (95% CI 0.86 to 1.37) and 1.27 (95% CI 1.00 to 1.60), respectively, for psychotic or bipolar disorders; other psychiatric disorders and no recorded psychiatric conditions (figure 2, online supplemental table 7).

Secondary analyses

To explore the role of confounding by indication, we conducted several secondary analyses implementing different comparisons with varying patterns of maternal antipsychotic use and underlying psychiatric disorders as well as sibling comparisons.

(1) Use in pregnancy versus prepregnancy use only: the risk of neurodevelopmental outcomes in children was decreased when maternal use of antipsychotics in pregnancy was compared with prepregnancy use only, yielding a fully adjusted HR 0.74 (95% CI 0.62 to 0.87) for ADHD (figure 1, online supplemental table 4) and 0.88 (95% CI 0.70 to 1.10) for ASD (figure 2, online supplemental table 8). The estimates remained similar, when stratified by maternal psychiatric disorder.

(2) Pre-pregnancy use only versus no use during or before pregnancy: comparing maternal prepregnancy antipsychotic use with no use before or during pregnancy yielded a fully adjusted HR of 1.44 (95% CI 1.29 to 1.60) for ADHD (figure 1, online supplemental table 4) and 1.39 (95%CI, 1.19 to 1.63) for ASD (figure 2, online supplemental table 8).

(3) No use with psychotic disorder versus no use without psychotic disorder: restricting the analysis to children whose mothers had no use of antipsychotics before or during pregnancy yielded a fully adjusted HR of 1.79 (95% CI 1.52 to 2.11) for ADHD (figure 1, online supplemental table 4) and 1.89 (95% CI 1.54 to 2.30) for ASD (figure 2, online supplemental table 8).

(4) Sibling analysis: restricting the analysis to the 1 832 862 sibling clusters in our data, we identified 7424 siblings who were discordant for maternal antipsychotic use (online supplemental figure 1). Of these, 644 and 254 sibling clusters were discordant for both maternal antipsychotic use and ADHD and ASD, respectively. Comparing these siblings, we observed a fully adjusted HR of 1.14 (95% CI 0.79 to 1.64) for ADHD (figure 1, online supplemental table 4) and 1.34 (95% CI 0.75 to 2.39) for ASD (figure 2, online supplemental table 8).

Sensitivity analyses

The sensitivity analyses yielded results that were consistent with those observed in the primary analysis. Redefining antipsychotic exposure *in utero* as at least two filled prescriptions for an antipsychotic yielded HRs consistent with those observed in the primary analysis (online supplemental table 5, table 9). Restricting the Norwegian cohort to births after 2008 yielded results that were similar to those from the primary analyses (online supplemental table 6, table 10).

DISCUSSION

Main findings

In a multinational cohort study of over 4 million singleton births, followed through the Nordic health registers for a median of 10 years, we did not find convincing evidence of an increased risk of ADHD or ASD in children exposed to antipsychotics *in*

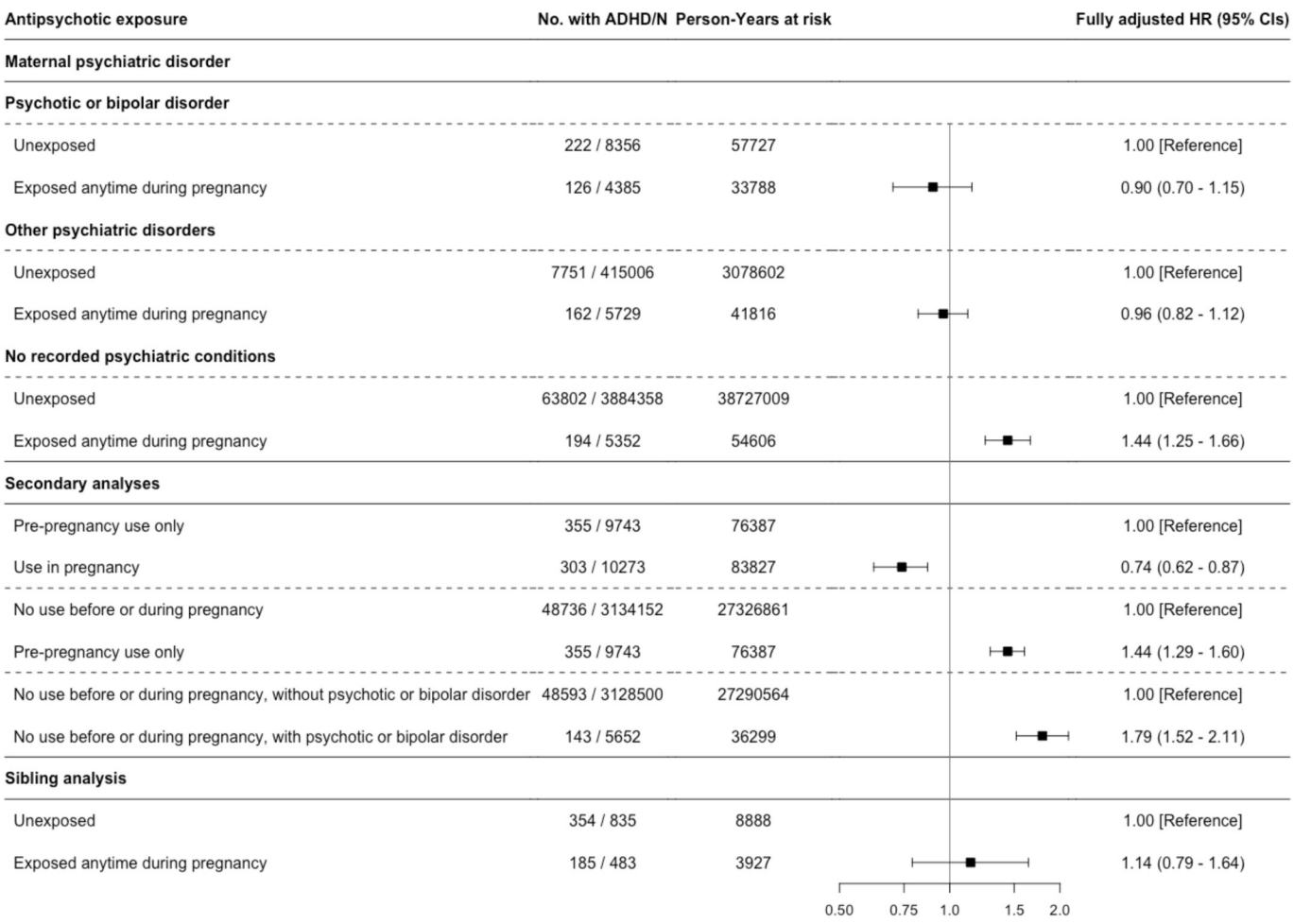

Figure 1 HRs for child ADHD comparing the risk by varying patterns of maternal antipsychotic use and psychiatric disorders and in siblings exposed and unexposed to antipsychotics *in utero*. ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio; CI, confidence interval.

utero. We observed an adjusted hazard estimate of 1.10 (95% CI 1.00 to 1.21) for ADHD and 1.12 (95% CI 0.97 to 1.29) for ASD with any antipsychotic exposure *in utero*. When accounting for maternal psychotic, bipolar and other psychiatric disorders in stratified analyses, there was, however, no indication of increased risk with pregnancy exposure.

Overall, our findings did not vary by trimester of exposure. We observed a slightly elevated hazard estimate for ASD with use of atypical antipsychotics warranting further investigation. The main findings remained consistent across several secondary and sensitivity analyses, where we implemented different comparisons in different subgroups, including siblings discordant for

Table 3 HRs and 95% CIs comparing the risk for ASD in exposed and unexposed children by timing and type of antipsychotic exposure

			Hazard ratio (95% CI)		
	Number with ASD/N	Person-years at risk	Crude	Model 1*	Model 2†
Antipsychotic exposure					
Unexposed	38436/4 308 620	41 982 697	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Exposed anytime during pregnancy	238/15 466	131 029	2.12 (1.86 to 2.41)	2.11 (1.86 to 2.40)	1.12 (0.97 to 1.29)
Timing of antipsychotic exposure					
First trimester only	105/6478	56 420	2.14 (1.76 to 2.59)	1.96 (1.62 to 2.38)	1.19 (0.97 to 1.44)
Second/third trimester only	47/3349	28 781	1.96 (1.47 to 2.61)	2.11 (1.58 to 2.80)	1.11 (0.83 to 1.48)
First trimester and second/third trimester	86/5639	45 826	2.24 (1.80 to 2.78)	2.35 (1.90 to 2.91)	1.04 (0.82 to 1.30)
Type of antipsychotic exposure					
Typical antipsychotics only	113/6896	75 823	1.60 (1.33 to 1.93)	1.66 (1.38 to 2.00)	1.06 (0.87 to 1.28)
Atypical antipsychotics only	110/7752	48 166	3.09 (2.56 to 3.73)	2.91 (2.41 to 3.52)	1.26 (1.03 to 1.54)

*Adjusted for source country, birth year, sex of child, maternal age, and parity.
†Adjusted for source country, birth year, sex of child, maternal age, parity, maternal education, cohabitation, mother born within source country, BMI, smoking, maternal comorbidity, use of known teratogens, use of suspected teratogens, other medications during pregnancy.
ASD, autism spectrum disorder; BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Antipsychotic exposure	No. with ASD/N	Person-Years at risk	Fully adjusted HR (95% CIs)
Maternal psychiatric disorder			
Psychotic or bipolar disorder			
Unexposed	139 / 8356	57891	1.00 [Reference]
Exposed anytime during pregnancy	91 / 4385	33851	1.28 (0.95 - 1.71)
Other psychiatric disorders			
Unexposed	3829 / 415906	3089835	1.00 [Reference]
Exposed anytime during pregnancy	76 / 5729	42108	1.09 (0.86 - 1.37)
No recorded psychiatric conditions			
Unexposed	34468 / 3884358	38834971	1.00 [Reference]
Exposed anytime during pregnancy	71 / 5352	55070	1.27 (1.00 - 1.60)
Secondary analyses			
Pre-pregnancy use only	174 / 9743	76873	1.00 [Reference]
Use in pregnancy	174 / 10273	84178	0.88 (0.70 - 1.10)
No use before or during pregnancy	30815 / 3134152	27377539	1.00 [Reference]
Pre-pregnancy use only	174 / 9743	76873	1.39 (1.19 - 1.63)
No use before or during pregnancy, without psychotic or bipolar disorder	30716 / 3128500	27341143	1.00 [Reference]
No use before or during pregnancy, with psychotic or bipolar disorder	99 / 5652	36395	1.89 (1.54 - 2.30)
Sibling analysis			
Unexposed	115 / 304	3042	1.00 [Reference]
Exposed anytime during pregnancy	82 / 186	1504	1.34 (0.75 - 2.39)

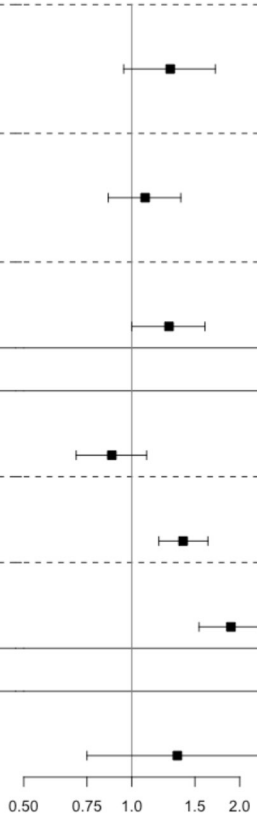

Figure 2 HRs for child ASD comparing the risk by varying patterns of maternal antipsychotic use and psychiatric disorders and in siblings exposed and unexposed to antipsychotics *in utero*. ASD, autism spectrum disorder; HR, hazard ratio; CI, confidence interval.

maternal antipsychotic use and outcome, and varied the exposure definition. Notably, our results clearly show an association between underlying maternal psychotic and bipolar disorders, that is, the main indications for antipsychotic use and children's risk of neurodevelopmental outcomes.

Interpretation and previous studies

Published data on the association between prenatal antipsychotic use and the risk of neurodevelopmental outcomes in children are lacking. The patterns observed in our study align with population-based data from Petersen *et al* showing that women prescribed antipsychotics in pregnancy were at increased risk of giving birth to a child with neurodevelopmental disorders, but once health and lifestyle factors and concomitant medication had been accounted for the association disappeared.[13] While our results do not suggest an increased risk of child ADHD or ASD following *in utero* antipsychotic exposure, these outcomes were strongly associated with maternal diagnosis of psychotic and bipolar disorders. Having a parent with a severe mental illness such as schizophrenia or bipolar disorder has been shown to significantly increase the risk of ASD and ADHD.[24] Furthermore, previous studies have reported that maternal bipolar disorder and schizophrenia are associated with adverse birth outcomes, including preterm birth,[24–26] which in itself has been proposed as a risk factor for ADHD in children.[27] Our results firmly suggest that shared familial environment and genetics play a critical role when evaluating the long-term safety of antipsychotic use in pregnancy. Recent epidemiologic and genetic research points to high heritability of both ADHD and ASD and shared genetic risk for these neurodevelopmental disorders with schizophrenia, other psychotic and bipolar disorders.[28–30] Interestingly, we observed a decreased risk of ADHD and ASD with continuation of antipsychotic treatment in pregnancy compared with prepregnancy use only. There may be no clear explanation for this, but treatment continuation in pregnancy could be a marker for a well-treated stable disease without breakthrough symptoms.

Indications for antipsychotics have expanded in recent years with frequent off-label use. The elevated HR for both ADHD and ASD, observed among children whose mothers used antipsychotics during pregnancy without a recorded psychiatric disorder, might be explained by unmeasured confounding due to unspecific psychiatric symptoms not captured in our data, for example, anxiety, insomnia or nausea.[1–4]

Strengths and limitations

Our study overcomes many of the limitations associated with prior observational studies of medication safety during pregnancy. With nationwide cohorts pooled across five countries and over 41 million years of follow-up of children from birth onwards, the study represents some of the largest cohorts assembled for the study of medication safety in pregnancy. Information on medication exposures was based on filled prescriptions and, thus, free from recall bias and primary non-adherence. We addressed the issue of confounding by indication with analyses stratified by maternal psychotic and bipolar disorders (main indications) and other psychiatric disorders (other

possible indications). Our findings are further strengthened by secondary analyses suggesting positive associations between maternal psychiatric disease and children's risk of ADHD, but not between treatment with antipsychotics during pregnancy and ADHD in children. In sibling analyses, we were able to address residual confounding by time-invariant factors shared within a family, for example, genetic predisposition and social environment. But a sibling analysis reduces the size of the study cohort since only sibling pairs discordant for both exposure and outcome are informative and contribute to the effect estimate, leading to less precise effect estimates with wider CIs. While the sibling sample may represent a selected part of the population, for example, in terms of maternal fertility, age and severity of illness, our *post hoc* sensitivity analyses suggested that selection bias did not substantially affect these estimates (online supplemental table 11, table 12). Children's exposure status did not appear to be related to birth order and residual confounding by unmeasured familial factors appeared unsubstantial once we had accounted for all measured confounders.

The study also has limitations. First, even though the data sources contained vast amounts of patient-level information, data on maternal education, parity, cohabitation, maternal country of birth, maternal smoking and BMI were not complete. To counteract these limitations, we implemented a two-stage calibration method to address missing covariate values.[23] Furthermore, we lacked direct information on the underlying indication for which antipsychotics were prescribed and measurements about change in psychiatric disorders over the course of pregnancy. Second, although we minimised the influence of confounding by indication in stratified analyses and by adjusting for recorded maternal psychiatric disorders, some residual confounding by indication is still possible because of potential confounding factors not captured in the Nordic registers. Third, the cohort was restricted to live births, which could have resulted in underestimation of HRs due to selection bias. This bias would occur if *in utero* antipsychotic exposure was positively related to terminations and stillbirth, which in turn could lead to a diminished risk of ADHD and ASD in childhood (because children had not survived long enough to experience the outcome). However, the differences in the proportion of non-live births among women who received antipsychotics during pregnancy versus those who did not would have to be greater than seems plausible to fully account for the observed null findings. Fourth, we did not have reliable data on dispensed doses of antipsychotics, which hindered our ability to evaluate a potential dose-response association. Finally, as in all studies based on data on filled prescriptions, it remains uncertain whether and when the women consumed the dispensed medication. We addressed the possibility of misclassified medication exposure by conducting a sensitivity analysis requiring at least two prescription fills during the relevant exposure window, which did not lead to meaningful change of the primary results.

CONCLUSION

In conclusion, our findings suggest little or no increased risk of ADHD or ASD with exposure to antipsychotics *in utero*. The increased risk observed among children whose mothers had non-specified conditions is likely due to residual confounding. Corroborating previous research, we observed a strong association between the neurodevelopmental outcomes and maternal psychotic and bipolar disorders. Results regarding child neurodevelopment are reassuring for women who need antipsychotics during pregnancy.

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Correction notice This article has been corrected since it first published. Buket Öztürk Essen has been changed to Buket Öztürk Esen.

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Contributors HZ and OH contributed to all the aspects of this study. JMC, ØK, CEC, ML, VH and SPU were involved in preparation of analytic datasets, designing the study, and preparation of the final manuscript. JMC and JR were involved in drafting the manuscript. KF, KE, HK, JR, MG, M-HB, MN, BO and SEH were involved in designing the study and preparation of the final manuscript. HZ, OH, JMC, ØK, CEC, ML, VH, SPU, KF, HK, MG, MN and SPU had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HZ and OH are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests CEC, HK, and JR are employees of the Centre for Pharmacopidemiology at Karolinska Institutet, which receives funding from pharmaceutical companies and regulatory authorities for drug safety/utilisation studies, unrelated to the submitted work. ØK, KF and JMC are employees of an institution, which received funding from pharmaceutical companies to conduct post-authorisation safety studies (PASS) of drugs unrelated to the submitted work (no personal fees). HZ is an employee of the Centre for Big Data Research in Health, UNSW Sydney which received funding from AbbVie Australia to conduct post-marketing drug utilisation research, unrelated to the submitted work.

Patient consent for publication Not applicable.

Ethics approval This research and access to the Nordic data was approved by the National Bioethics Committee, the Data Protection Authority in Iceland, the Directorate of Health, and all other relevant data custodians; the Norwegian Data Inspectorate in Norway and the Regional Ethics Committee for Medical Research of South/East Norway in Oslo, Norway; the Regional Ethical Research Board in Stockholm, Sweden; the Finnish Institute for Health and Welfare and the Social Insurance Institute in Finland. No ethics approval was required in Denmark and Finland.

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REFERENCES

1 Alexander GC, Gallagher SA, Mascola A, *et al*. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. *Pharmacoepidemiol Drug Saf* 2011;20:177–84.
2 Gjerden P, Bramness JG, Tvete IF, *et al*. The antipsychotic agent quetiapine is increasingly not used as such: dispensed prescriptions in Norway 2004-2015. *Eur J Clin Pharmacol* 2017;73:1173–9.
3 Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. *Cochrane Database Syst Rev* 2015;11:CD006271.
4 Seidel S, Aigner M, Ossege M. Antipsychotics for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2013;8:CD004844.
5 Reutfors J, Cesta CE, Cohen JM, *et al*. Antipsychotic drug use in pregnancy: a multinational study from ten countries. *Schizophr Res* 2020;220:106–15.
6 Horacek J, Bubenikova-Valesova V, Kopecek M, *et al*. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs* 2006;20:389–409.
7 Coughlin CG, Blackwell KA, Bartley C, *et al*. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. *Obstet Gynecol* 2015;125:1224–35.
8 Huybrechts KF, Hernández-Díaz S, Patorno E, *et al*. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry* 2016;73:938–46.
9 Vigod SN, Gomes T, Wilton AS, *et al*. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. *BMJ* 2015;350:h2298.
10 Galbally M, Snellen M, Power J. Antipsychotic drugs in pregnancy: a review of their maternal and fetal effects. *Ther Adv Drug Saf* 2014;5:100–9.
11 Gentile S, Fusco ML. Neurodevelopmental outcomes in infants exposed in utero to antipsychotics: a systematic review of published data. *CNS Spectr* 2017;22:273–81.
12 Ornoy A, Weinstein-Fudim L, Ergaz Z. Antidepressants, antipsychotics, and mood stabilizers in pregnancy: what do we know and how should we treat pregnant women with depression. *Birth Defects Res* 2017;109:933–56.
13 Petersen I, McCrea RL, Sammon CJ, *et al*. Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records. *Health Technol Assess* 2016;20:1–176.
14 Vucicevic L, Misirkic-Marjanovic M, Paunovic V, *et al*. Autophagy inhibition uncovers the neurotoxic action of the antipsychotic drug olanzapine. *Autophagy* 2014;10:2362–78.
15 Newport DJ, Calamaras MR, DeVane CL, *et al*. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. *Am J Psychiatry* 2007;164:1214–20.
16 Ludvigsson JF, Håberg SE, Knudsen GP, *et al*. Ethical aspects of registry-based research in the Nordic countries. *Clin Epidemiol* 2015;7:491–508.
17 Furu K, Wettermark B, Andersen M, *et al*. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol* 2010;106:86–94.
18 World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC/DDD index, 2020. Available: https://www.whocc.no/atc_ddd_index/ [Accessed Aug 2020].
19 Atladottir HO, Gyllenberg D, Langridge A, *et al*. The increasing prevalence of reported diagnoses of childhood psychiatric disorders: a descriptive multinational comparison. *Eur Child Adolesc Psychiatry* 2015;24:173–83.
20 Suren P, Havdahl A, Oyen AS. Diagnosing autism spectrum disorder among children in Norway. *Tidsskr Nor Laegeforen* 2019;139.
21 Lampi KM, Sourander A, Gissler M, *et al*. Brief report: validity of Finnish registry-based diagnoses of autism with the ADI-R. *Acta Paediatr* 2010;99:1425–8.
22 Surén P, Bakken IJ, Aase H, *et al*. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. *Pediatrics* 2012;130:e152–8.
23 Hjellvik V, De Bruin ML, Samuelsen SO, *et al*. Adjusting for unmeasured confounding using validation data: simplified two-stage calibration for survival and dichotomous outcomes. *Stat Med* 2019;38:2719–34.
24 McCoy BM, Rickert ME, Class QA, *et al*. Mediators of the association between parental severe mental illness and offspring neurodevelopmental problems. *Ann Epidemiol* 2014;24:629–34. 34 e1..
25 Bodén R, Lundgren M, Brandt L, *et al*. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. *BMJ* 2012;345:e7085.
26 Vigod SN, Fung K, Amartey A, *et al*. Maternal schizophrenia and adverse birth outcomes: what mediates the risk? *Soc Psychiatry Psychiatr Epidemiol* 2020;55:561–70.
27 Sucksdorff M, Lehtonen L, Chudal R, *et al*. Preterm birth and poor fetal growth as risk factors of Attention-Deficit/ hyperactivity disorder. *Pediatrics* 2015;136:e599–608.
28 Cheng C-M, Chang W-H, Chen M-H, *et al*. Co-Aggregation of major psychiatric disorders in individuals with first-degree relatives with schizophrenia: a nationwide population-based study. *Mol Psychiatry* 2018;23:1756–63.
29 Sullivan PF, Magnusson C, Reichenberg A, *et al*. Family history of schizophrenia and bipolar disorder as risk factors for autism. *Arch Gen Psychiatry* 2012;69:1099–103.
30 Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry* 2019;24:562–75.