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Association of Antipsychotic Drug Exposure in Pregnancy With Risk of Neurodevelopmental Disorders
A National Birth Cohort Study

Loreen Straub, MD, MS; Sonia Hernández-Díaz, MD, DrPH; Brian T. Bateman, MD, MS; Katherine L. Wisner, MD, MS; Kathryn J. Gray, MD, PhD; Page B. Pennell, MD; Barry Lester, PhD; Christopher J. McDougle, MD; Elizabeth A. Suarez, MPH, PhD; Yanmin Zhu, MS, PhD; Heidi Zakoul, BA; Helen Mogun, MS; Krista F. Huybrechts, MS, PhD

IMPORTANCE Although antipsychotic drugs cross the placenta and animal data suggest potential neurotoxic effects, information regarding human neurodevelopmental teratogenicity is limited.

OBJECTIVE To evaluate whether children prenatally exposed to antipsychotic medication are at an increased risk of neurodevelopmental disorders (NDD).

DESIGN, SETTINGS, AND PARTICIPANTS This birth cohort study used data from the Medicaid Analytic eXtract (MAX, 2000-2014) and the IBM Health MarketScan Research Database (MarketScan, 2003-2015) for a nationwide sample of publicly (MAX) and privately (MarketScan) insured mother-child dyads with up to 14 years of follow-up. The MAX cohort consisted of 2 034 883 children who were not prenatally exposed and 9551 who were prenatally exposed to antipsychotic medications; the MarketScan consisted of 1 306 408 and 1221 children, respectively. Hazard ratios were estimated through Cox proportional hazards regression, using propensity score overlap weights for confounding control. Estimates from both cohorts were combined through meta-analysis.

EXPOSURES At least 1 dispensing of a medication during the second half of pregnancy (period of synaptogenesis), assessed for any antipsychotic drug, at the class level (atypical and typical), and for the most commonly used drugs (aripiprazole, olanzapine, quetiapine, risperidone, and haloperidol).

MAIN OUTCOMES AND MEASURES Autism spectrum disorder, attention-deficit/hyperactivity disorder, learning disability, speech or language disorder, developmental coordination disorder, intellectual disability, and behavioral disorder, identified using validated algorithms, and the composite outcome of any NDD. Data were analyzed from April 2020 to January 2022.

RESULTS The MAX cohort consisted of 2 034 883 unexposed pregnancies and 9551 pregnancies with 1 or more antipsychotic drug dispensings among women with a mean (SD) age of 26.8 (6.1) years, 204 (2.1%) of whom identified as Asian/Pacific Islander, 2720 (28.5%) as Black, 500 (5.2%) as Hispanic/Latino, and 5356 (56.1%) as White. The MarketScan cohort consisted of 1 306 408 unexposed and 1221 exposed pregnancies among women with a mean (SD) age of 33.1 (5.0) years; race and ethnicity data were not available. Although the unadjusted results were consistent with an approximate 2-fold increased risk for most exposure-outcome contrasts, risks were no longer meaningfully increased after adjustment (eg, pooled unadjusted vs adjusted hazard ratios [95% CI] for any NDD after any antipsychotic exposure: 1.91 [1.79-2.03] vs 1.08 [1.01-1.17]), with the possible exception of aripiprazole (1.36 [1.14-1.63]). Results were consistent across sensitivity analyses.

CONCLUSIONS AND RELEVANCE The findings of this birth cohort study suggest that the increased risk of NDD seen in children born to women who took antipsychotic drugs late in pregnancy seems to be explained by maternal characteristics and is not causally related with prenatal antipsychotic exposure. This finding highlights the importance of closely monitoring the neurodevelopment of the offspring of women with mental illness to ensure early intervention and support. The potential signal for aripiprazole requires replication in other data before causality can be assumed.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Loreen Straub, MD, MS, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont St, Ste 3030, Boston, MA 02120 (lstraub@bwh.harvard.edu).

Antipsychotic medications are among the most commonly prescribed drug classes in the US.[1] The clinical uses of antipsychotic drugs extend beyond psychotic disorders and include bipolar, major depressive, and anxiety disorders, all of which are common among women of childbearing age.[2] This expansion of approved and off-label indications, coupled with unimpaired fecundity with newer prolactin-sparing agents, has produced a more than doubling of antipsychotic drug use during pregnancy in the 2000s.[3,4] Antipsychotic drugs are highly lipophilic and cross the placenta.[5] While the risks of congenital malformations and short-term neonatal complications associated with in utero exposure to antipsychotic drugs have been evaluated by epidemiologic studies,[6-12] little information is available on human neurodevelopmental teratogenicity despite animal data suggesting a potential neurotoxic effect.[13]

Preclinical studies in adult rats prenatally exposed to antipsychotic drugs have demonstrated structural effects on the central nervous system with lasting neurofunctional sequelae, including deficits in learning and memory acquisition and retention.[14,15] Mechanisms such as neuronal apoptosis by interference of antipsychotic drugs with normal neurotransmitter function during synaptogenesis and aberrant neuronal network organization may play a role.[16,17] The observed neurocognitive effects are not uniform across individual agents, which has been attributed to their different receptor activity profiles.[14,15,18,19]

Longitudinal studies that evaluate the association between in utero antipsychotic exposure and long-term neurodevelopmental disorders (NDD) in humans are challenging to conduct because they require large patient cohorts followed over long time periods and the potential for confounding. Until recently, available data were mainly derived from case reports and small case-series.[13] Findings from 2 new population-based cohort studies did not suggest a substantial increase in risk of attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) after prenatal exposure to antipsychotic drugs; however, the association of individual antipsychotic drugs, the potential dose-response effects, and the risk of other specified NDDs remains unknown.[20,21] Therefore, we conducted a large-scale epidemiologic study nested in nationwide health care utilization databases, including broad information for confounding control by treatment indication and associated factors, to evaluate the association between in utero exposure to antipsychotic drugs and NDDs in children.

Key Points

Question Is prenatal exposure to antipsychotic medication associated with increased risk of a neurodevelopmental disorder?

Findings This birth cohort study of 3.4 million children nested in nationwide health care utilization data with as many as 14 years of follow-up, after accounting for treatment indications and other potential confounders, found no meaningfully increased risk of neurodevelopmental disorders for prenatal antipsychotic exposure, with the possible exception of exposure to aripiprazole.

Meaning The findings of this birth cohort study suggest that antipsychotic medications may not have important neurotoxic effects; the potential signal identified for aripiprazole requires replication in other data before causality can be assumed.

Methods

This large cohort study was reviewed and approved by the Institutional Review Board of Brigham and Women's Hospital, which waived the need for informed consent because the research used only deidentified databases. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies.

Data Sources and Study Cohort

We used cohorts of publicly and privately insured mothers and their children nested in the nationwide Medicaid Analytic eXtract (MAX) for 2000 to 2014 (most recent years available at the time of study conduct) and the IBM Health MarketScan Research Database (MarketScan) for 2003 to 2015. Both data sources included information on demographics, insurance enrollment, diagnosis and procedure claims during hospitalizations, outpatient and emergency department visits, and outpatient medication dispensings. The development of these mother-child cohorts has been described previously.[22,23] Mothers (12-55 years old) were required to be continuously insured from 3 months before until 1 month after pregnancy. Children were followed from their date of birth until whichever came first: their continuous enrollment ended; they developed the specific NDD of interest; the study period ended; or they died. Children with a known chromosomal or genetic abnormality were excluded (eFigures 1 and 2 in the Supplement).

Exposure to Antipsychotic Drugs

In primary analyses, children were considered exposed if their mother filled a prescription for any antipsychotic medication during the second half of pregnancy (>18 gestational weeks), the period of synaptogenesis.[16] In secondary analyses—given the uncertainty around the putative biological mechanism(s) and etiologically relevant time window—we also evaluated risks associated with early pregnancy exposure, defined as filling a prescription during the first half of pregnancy (eFigures 1 and 2 in the Supplement). For both periods, we further assessed exposure to atypical and typical antipsychotic drugs (eTable 1 in the Supplement for the specific medications included), and to the most commonly used individual medications (aripiprazole, olanzapine, quetiapine, risperidone, and haloperidol; groups not mutually exclusive). Unexposed children were those born to mothers with no antipsychotic dispensing from 90 days before pregnancy until birth.

Neurodevelopmental Disorders

The NDDs most commonly diagnosed in the US[24-26] were considered: (1) ASD; (2) ADHD; (3) learning disability; (4) developmental speech or language disorder; (5) developmental coordination disorder (DCD); (6) intellectual disability; (7)

behavioral disorder, including disturbance of conduct and emotions; and (8) any NDD (the presence of any of the specific disorders 1-7; eTable 2 in the Supplement). Despite the heterogeneity of NDD, a composite outcome was considered given the frequent co-occurrence of these disorders and the potential for shared mechanisms across NDDs (eg, the neurotoxic effects of medications on the developing brain). The presence of individual NDDs was defined using validated algorithms that have been shown to identify the outcomes with generally high positive predictive values[27] and to generate event rates consistent with US statistics.[28]

Covariates

A broad range of potential (proxies for) confounders was considered, including: treatment indications, lifestyle behaviors, proxies for severity of underlying mental health-related illnesses, exposure to other psychotropics and nonpsychotropic medications, demographic factors, other maternal comorbidities,[29] and county-level measures of socioeconomic status (SES; data available for MAX only; details in the **Table** and eTable 3 and eFigure 2 in the Supplement). Treatment indications, lifestyle behaviors, and maternal conditions were assessed from 3 months before pregnancy to the end of the respective exposure assessment period; proxies for severity of mental health-related illness and other prescription medication exposures were assessed from 3 months prior to pregnancy until the end of the first half of pregnancy.

The MAX data were merged with county-level data on various SES measures provided by the US Department of Agriculture,[30] after linkage of maternal zip codes with corresponding Federal Information Processing System county codes using crosswalk files provided by the US Department of Housing and Urban Development[31] (Table).

We further assessed balance on various neonatal, childhood, and maternal postpartum characteristics. While occurring subsequent to exposure, these variables could be (proxies for) confounders—eg, manifestations of the severity of maternal mental illness—or indicators of how much of the potential effect of in utero antipsychotic exposure on NDDs may be mediated through perinatal outcomes or a mother's mental health postpartum and its influence on the child's environment.

Statistical Analysis

Hazard ratios (HR) from both cohorts were combined using fixed effects meta-analysis.[32] Covariate balance between exposed and unexposed pregnancies was compared using standardized differences. Standardized difference, as detailed in the Table, was estimated using the following equation:

$$\frac{\bar{x}_{exp}-\bar{x}_{ref}}{\sqrt{\frac{s^2_{exp}+s^2_{ref}}{2}}}$$

where $\bar{x}$ represented the sample mean and S^2 the sample variance of the covariate in the antipsychotic exposed (exp) and the reference group (ref).

Crude and propensity score (PS) weighted cumulative incidence curves with 95% CIs stratified by exposure were assessed using Kaplan-Meier analyses (**Figure 1**; eFigures 3 and 4 in the Supplement). We used PS overlap weights for confounding control.[33] Cohort characteristics stratified by exposure were only presented before PS overlap weighting was implemented because this approach, by definition, creates perfect balance (that is, a standardized difference of 0) for all covariates included in the PS model.[32]

Unadjusted and adjusted HRs with 95% CIs for each exposure-outcome contrast were estimated through Cox proportional hazards regression (**Figures 2** and **3**; eTable 4 in the Supplement).[32] The fully adjusted models accounted for all (proxies for) confounders described (Table; eTable 3 in the Supplement) without variable selection (neonatal, childhood, and maternal postpartum characteristics were not accounted for).

A range of sensitivity analyses were conducted to evaluate the robustness of the findings (**Figure 4**; eTables 4 and 5 in the Supplement). First, to account for potential residual confounding, we used high-dimensional PS (hdPS) analyses that included 200 empirically defined covariates in addition to the investigator-defined variables.[34] Second, to assess the effect of exposure misclassification, we redefined exposure as having 2 or more dispensings of the medication of interest during the assessment period, the assumption being that if patients refill a prescription, they are likely to also consume the medication. Third, we evaluated the association between exposure duration and NDD risk using strata based on days' supply (≤30, >30 to ≤60, >60 days). Fourth, to address potential outcome misclassification owing to early preliminary diagnoses, we required the outcome to be recorded at age 3 years or older. Fifth, we assessed whether antipsychotic exposure increased the risk of being diagnosed with multiple NDDs. Finally, as there is potential for selection bias owing to informative censoring, we accounted for inverse probability of censoring weights in addition to PS overlap weights for analyses of any antipsychotic exposure during the second half of pregnancy.[35-37]

Furthermore, we conducted several post hoc exploratory analyses for aripiprazole to follow up on a potential signal observed (eTables 6, 7, and 8 in the Supplement). First, we conducted a dose-response analysis using the total cumulative dose of aripiprazole dispensings overlapping with the respective assessment period. Second, we redefined the reference group as women who had 1 or more aripiprazole prescriptions dispensed from 90 to 31 days prior to pregnancy but no antipsychotic drug dispensing from 30 days before pregnancy to delivery (discontinuers). Women who discontinued aripiprazole before pregnancy might be more comparable with women exposed to aripiprazole during pregnancy than women who had never been exposed to any antipsychotic. Third, in an attempt to isolate the etiologically relevant window, we assessed the neurodevelopmental effect of aripiprazole for women with late (second half of pregnancy) but not early (first half of pregnancy) exposure, and early but not late exposure, respectively. Fourth, to evaluate whether aripiprazole being a more recently approved antipsychotic medication is preferentially used for severe treatment-resistant conditions, we explored potential differences between women exposed to aripiprazole vs other antipsychotic drugs in terms of patient characteristics and antipsychotic exposure during the year

Table. Selected Characteristics of Publicly (MAX) and Privately (MarketScan) Insured Women With or Without Exposure to Antipsychotic Medications (≥1 Dispensation) in Second Half of Pregnancy

Characteristic	Public insurance (MAX 2000-2014)			Private insurance (MarketScan 2000-2015)		
	No. (%)		Standardized difference[a]	No. (%)		Standardized difference[a]
	Exposed	Unexposed		Exposed	Unexposed	
Total	9551	2 034 883		1214	1 306 408	
Demographic information						
Age, mean (SD), y	26.8 (6.1)	24.4 (5.8)	0.41	33.1 (5.0)	32.0 (4.6)	0.24
Race and ethnicity[b]						
Asian/Pacific Islander	204 (2.1)	75 181 (3.7)	−0.09	NA	NA	NA
Black/African American	2720 (28.5)	674 009 (33.1)	−0.10	NA	NA	NA
Hispanic/Latino	500 (5.2)	293 701 (14.4)	−0.31	NA	NA	NA
Other/unknown	771 (8.1)	168 003 (8.3)	−0.01	NA	NA	NA
White	5356 (56.1)	823 989 (40.5)	0.32	NA	NA	NA
Treatment indications						
Schizophrenia or schizoaffective disorder	1351 (14.2)	2493 (0.1)	0.57	53 (4.4)	93 (<0.1)	0.30
Bipolar disorder	5139 (53.8)	36 336 (1.8)	1.43	613 (50.5)	5118 (0.4)	1.41
Depression	4923 (51.5)	168 662 (8.3)	1.07	554 (45.6)	63 588 (4.9)	1.06
Psychosis	959 (10.0)	4753 (0.2)	0.46	64 (5.3)	615 (0.1)	0.33
Anxiety	3241 (33.9)	103 515 (5.1)	0.78	416 (34.3)	49 917 (3.8)	0.84
Epilepsy or convulsions	535 (5.6)	22 304 (1.1)	0.25	27 (2.2)	5799 (0.4)	0.16
Other MH disorders[c]	749 (7.8)	24 267 (1.2)	0.32	81 (6.7)	8477 (0.7)	0.32
Attention-deficit/hyperactivity disorder	609 (6.4)	15 940 (0.8)	0.30	48 (4.0)	6310 (0.5)	0.24
Behavioral disorder	418 (4.4)	16 346 (0.8)	0.23	9 (0.7)	312 (<0.1)	0.12
Other neurodevelopmental disorders[d]	205 (2.2)	6115 (0.3)	0.17	7 (0.6)	276 (<0.1)	0.10
Lifestyle behaviors						
Smoking	2362 (24.7)	172 887 (8.5)	0.45	86 (7.1)	15 248 (1.2)	0.30
Alcohol dependence	754 (7.9)	19 179 (0.9)	0.34	35 (2.9)	1290 (0.1)	0.23
Substance use disorder	2250 (23.6)	69 199 (3.4)	0.62	66 (5.4)	2576 (0.2)	0.32
Proxy for severity of MH-related illness, mean (SD)						
No. of distinct MH-related diagnoses	3.2 (3.1)	0.3 (0.9)	1.28	2.6 (2.6)	0.1 (0.6)	1.32
No. of distinct MH-related ED visits	0.4 (1.0)	0.0 (0.2)	0.45	0.4 (1.3)	0.0 (0.1)	0.40
No. of distinct MH-related hospitalizations	0.5 (1.4)	0.0 (0.2)	0.43	0.3 (1.2)	0.0 (0.1)	0.37
No. of non-antipsychotic psychotropic dispensings	2.3 (2.2)	0.2 (0.7)	1.29	2.5 (2.3)	0.2 (0.6)	1.44
Other prescription medication exposure						
Benzodiazepines	2896 (30.3)	65 058 (3.2)	0.78	426 (35.1)	48 764 (3.7)	0.86
Antidepressants	5864 (61.4)	181 105 (8.9)	1.32	763 (62.9)	99 618 (7.6)	1.42
Anticonvulsants	2783 (29.1)	39 746 (2.0)	0.81	381 (31.4)	13 622 (1.0)	0.90
Psychostimulants	718 (7.5)	14 690 (0.7)	0.35	99 (8.2)	9920 (0.8)	0.36
Anxiolytics	480 (5.0)	9008 (0.4)	0.28	52 (4.3)	3002 (0.2)	0.28
Opioids	4516 (47.3)	503 477 (24.7)	0.48	344 (28.3)	169 743 (13.0)	0.39
Corticosteroids	2216 (23.2)	268 368 (13.2)	0.26	274 (22.6)	190 326 (14.6)	0.21
Other maternal comorbidities						
Pregestational diabetes	999 (10.5)	119 237 (5.9)	0.17	175 (14.4)	104 580 (8.0)	0.20
Pregestational hypertension	812 (8.5)	95 704 (4.7)	0.15	114 (9.4)	74 312 (5.7)	0.14
Hyperemesis/NVP	3024 (31.7)	365 671 (18.0)	0.32	272 (22.4)	105 927 (8.1)	0.41
Obstetric Comorbidity Index[29]						
0	3034 (31.8)	1 117 471 (54.9)	−0.48	355 (29.2)	565 046 (43.3)	−0.29
1	2049 (21.5)	459 519 (22.6)	−0.03	293 (24.1)	346 562 (26.5)	−0.06
2	1774 (18.6)	240 741 (11.8)	0.19	232 (19.1)	205 286 (15.7)	0.09
≥3	2694 (28.2)	217 152 (10.7)	0.45	334 (27.5)	189 514 (14.5)	0.32

(continued)

Table. Selected Characteristics of Publicly (MAX) and Privately (MarketScan) Insured Women With or Without Exposure to Antipsychotic Medications (≥1 Dispensation) in Second Half of Pregnancy (continued)

Characteristic	Public insurance (MAX 2000-2014)			Private insurance (MarketScan 2000-2015)		
	No. (%)		Standardized difference[a]	No. (%)		Standardized difference[a]
	Exposed	Unexposed		Exposed	Unexposed	
County-level SES measures						
Proximity to metropolitan area[e]						
Metropolitan	8159 (85.4)	1 724 309 (84.7)	0.02	NA	NA	NA
Urban	1069 (11.2)	238 445 (11.7)	−0.02	NA	NA	NA
Rural	174 (1.8)	40 988 (2.0)	−0.01	NA	NA	NA
Unemployment rate, quartile						
Low	3157 (33.6)	499 810 (25.0)	0.19	NA	NA	NA
Low-moderate	2440 (26.0)	488 079 (24.4)	0.04	NA	NA	NA
Moderate-high	2000 (21.3)	520 272 (26.0)	−0.11	NA	NA	NA
High	1805 (19.2)	494 552 (24.7)	−0.13	NA	NA	NA
Poverty rate, quartile						
Low	2844 (30.3)	502 523 (25.1)	0.12	NA	NA	NA
Low-moderate	1818 (19.3)	502 979 (25.1)	−0.14	NA	NA	NA
Moderate-high	2642 (28.1)	495 803 (24.8)	0.08	NA	NA	NA
High	2098 (22.3)	501 382 (25.0)	−0.06	NA	NA	NA
% Of county with ≤ HS, quartile				NA	NA	NA
Low	2778 (29.6)	496 790 (24.8)	0.11	NA	NA	NA
Low-moderate	2200 (23.4)	508 921 (25.4)	−0.05	NA	NA	NA
Moderate-high	2143 (22.8)	501 312 (25.0)	−0.05	NA	NA	NA
High	2281 (24.3)	495 702 (24.8)	−0.01	NA	NA	NA

Abbreviations: ED, emergency department; HS, high school diploma; MarketScan, IBM Health MarketScan Research Database; MAX, Medicaid Analytic Extract; MH, mental health; NA, data not available in MarketScan; NVP, nausea and vomiting in pregnancy; SES, socioeconomic status.

[a] For the standardized differences estimation equation, refer to the Statistical Analysis section.

[b] Based on data submitted to the Centers for Medicare & Medicaid Services by each state from collected and coded Medicaid applications. For race and ethnicity, the category *other/unknown* included American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, Hispanic/Latino, more than 1 race, and unknown; category *Hispanic/Latino* included this ethnicity with missing race information, whereas *other/unknown* included Hispanic/Latino with 1 or more races.

[c] Includes delirium, dementia, tic disorder, somatoform spectrum disorder, eating disorder, psychotherapy, and self-inflicted injury.

[d] Includes autism spectrum disorder, speech/language disorder, developmental coordination disorder, intellectual disability, and learning disorder.

[e] Metropolitan was defined as a county in a metropolitan area or with ≥20 000 residents adjacent to a metropolitan area; urban was a county with ≥20 000 residents not adjacent to a metropolitan area or with 2500-19 999 residents; and rural was a county with <2500 residents. Unemployment rate, poverty rate, and rate of educational attainment reflect year-specific quartiles (see the Methods section).

before pregnancy. Lastly, we assessed differences in NDD co-occurrence patterns between children who were prenatally exposed to aripiprazole and children who were not exposed.

All analyses were conducted from April 2020 to January 2022, separately for each cohort using SAS version 9.4 (SAS Institute Inc). No adjustments were made for multiple comparisons. Statistical tests were 2-tailed and P values < .05 were considered statistically significant.

Results

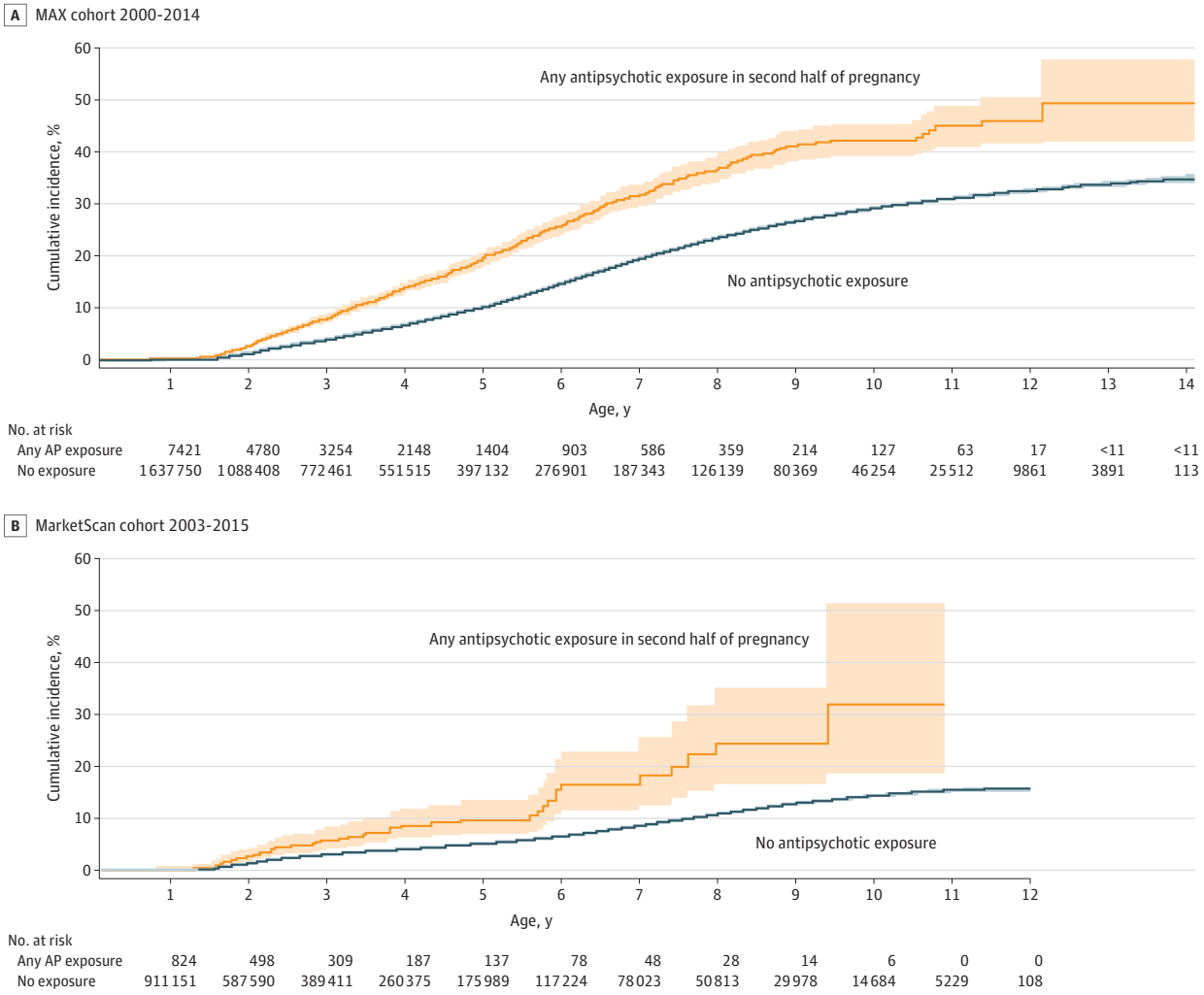
Cohort Characteristics

The publicly insured (MAX) cohort consisted of 2 034 883 unexposed pregnancies, 9551 with 1 or more antipsychotic drug dispensings during the second half (irrespective of earlier exposure), and 19 804 with 1 or more antipsychotic dispensing during the first half of pregnancy (irrespective of late pregnancy exposure). Numbers in the privately insured (MarketScan) cohort were respectively: 1 306 408, 1221, and 1986 pregnancies. In the publicly insured cohort with antipsychotic exposure during the second half of pregnancy, the women had a mean (SD) age of 26.8 (6.1) years, and 204 (2.1%) identified as Asian/Pacific Islander, 2720 (28.5%) as Black, 500 (5.2%) as Hispanic/Latino, and 5356 (56.1%) as White; in the privately insured cohort, the exposed women had a mean (SD) age of 33.1 (5.0) years; race and ethnicity data were not available. Additional details on cohort characteristics are available in the Table.

The vast majority of exposures were to atypical antipsychotic drugs (≈90% in both cohorts and assessment periods), with quetiapine being the most commonly dispensed (≈40% of all exposed), followed by aripiprazole (16%-23%) (eFigure 1 in the Supplement). Most of the women were dispensed only 1 type of antipsychotic drug during pregnancy (eTable 9 in the Supplement).

Women taking any antipsychotic medication during pregnancy were more likely to be of older age (≥35 years) and White,

Figure 1. Cumulative Incidence of Any NDD in Children, by AP Exposure in Second Half of Pregnancy



A, Among the MAX (privately insured) cohort. B, Among the MarketScan (publicly insured) cohort. Cell sizes of <11 individuals are suppressed per the Centers for Medicaid & Medicare Services' policy. Solid lines represent cumulative incidences; shaded areas denote 95% CIs; AP, antipsychotic medication; MarketScan, IBM Health MarketScan Research Database; MAX, the Medicaid Analytic Extract; and NDD, neurodevelopmental disorders.

have psychiatric or neurologic conditions and other comorbidities, be dispensed other drugs during pregnancy, and have unhealthy lifestyle behaviors (eg, alcohol dependence, smoking, substance use disorder). County-level SES information did not indicate strong differences between exposed and unexposed women. Similar discrepancies were observed for atypical and typical antipsychotic drugs, each drug considered, both exposure assessment periods, and both cohorts (Table; eTable 3 in the Supplement).

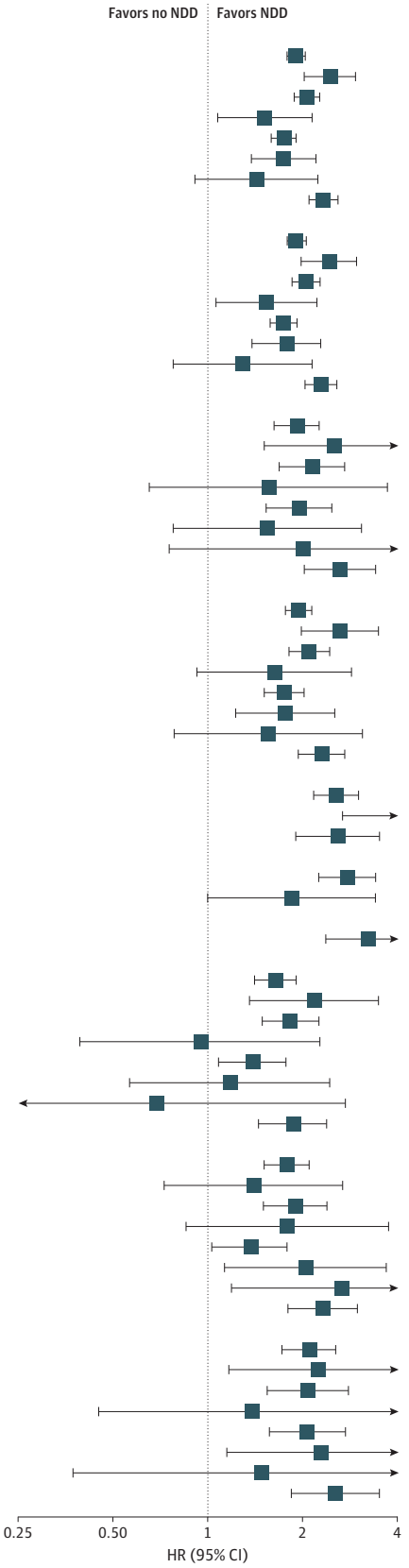
After PS overlap weighting, all covariates in the PS model were by definition perfectly balanced between exposed and unexposed. Even though neonatal, childhood, and maternal postpartum characteristics were not included in the PS model, these variables were generally very balanced after PS overlap weighting for all exposure-reference contrasts (eTable 10 in the Supplement).

Cumulative Incidence and Hazard Ratio of NDDs

By 8 years of age—the age at which most NDDs are expected to have been diagnosed—37.3% (95% CI, 34.8%-40.0%) of all publicly insured children born to mothers with second half of pregnancy antipsychotic exposure had been diagnosed with any NDD compared with 23.7% (23.6%-23.8%) of children who were not exposed; respectively, these incident rates were 24.5% (22.2%-27.1%) and 14.3% (14.1%-14.4%) for ADHD and 3.5% (2.8%-4.4%) and 1.6% (1.6%-1.7%) for ASD. Among privately insured children, cumulative incidences were 24.5% (16.7%-35.1%) and 11.0% (10.8%-11.2%) for any NDD, 17.5% (10.2%-29.1%) and 5.8% (5.7%-6.0%) for ADHD, and 3.8% (1.7%-8.5%) and 1.3% (1.2%-1.3%) for ASD, respectively. Similar patterns of higher incidence among prenatally exposed vs unexposed and among publicly vs privately insured children were observed for all other outcomes and

Figure 2. Unadjusted Estimates of NDDs in Children, by AP Exposure in Second Half of Pregnancy

Source	HR (95% CI)
Any antipsychotic	
Any neurodevelopmental disorder	1.91 (1.79-2.03)
ASD	2.44 (2.02-2.96)
ADHD	2.07 (1.88-2.28)
Learning difficulty	1.51 (1.07-2.14)
Speech/language disorder	1.74 (1.59-1.91)
DCD	1.74 (1.37-2.21)
Intellectual disability[a]	1.43 (0.91-2.24)
Behavioral disorder	2.33 (2.09-2.59)
Atypical antipsychotics	
Any neurodevelopmental disorder	1.91 (1.79-2.05)
ASD	2.42 (1.97-2.97)
ADHD	2.05 (1.85-2.27)
Learning difficulty	1.54 (1.06-2.23)
Speech/language disorder	1.74 (1.58-1.92)
DCD	1.78 (1.38-2.28)
Intellectual disability[a]	1.29 (0.78-2.14)
Behavioral disorder	2.29 (2.04-2.56)
Typical antipsychotics	
Any neurodevelopmental disorder	1.91 (1.62-2.26)
ASD[a]	2.51 (1.51-4.16)
ADHD	2.14 (1.68-2.72)
Learning difficulty[a]	1.55 (0.65-3.73)
Speech/language disorder[a]	1.95 (1.53-2.47)
DCD[a]	1.54 (0.77-3.07)
Intellectual disability[a]	2.00 (0.75-5.33)
Behavioral disorder[a]	2.63 (2.03-3.41)
Quetiapine	
Any neurodevelopmental disorder	1.94 (1.76-2.14)
ASD	2.62 (1.97-3.49)
ADHD	2.10 (1.81-2.45)
Learning difficulty[a]	1.63 (0.92-2.87)
Speech/language disorder	1.75 (1.51-2.02)
DCD	1.76 (1.22-2.53)
Intellectual disability[a]	1.56 (0.78-3.11)
Behavioral disorder	2.30 (1.93-2.73)
Aripiprazole	
Any neurodevelopmental disorder	2.56 (2.17-3.01)
ASD	4.16 (2.68-6.45)
ADHD	2.58 (1.90-3.50)
Learning difficulty[b]	-
Speech/language disorder	2.77 (2.25-3.41)
DCD	1.84 (0.99-3.42)
Intellectual disability[b]	-
Behavioral disorder[a]	3.21 (2.37-4.34)
Olanzapine	
Any neurodevelopmental disorder	1.63 (1.40-1.90)
ASD[a]	2.17 (1.35-3.49)
ADHD	1.83 (1.48-2.25)
Learning difficulty[a]	0.95 (0.39-2.27)
Speech/language disorder	1.39 (1.08-1.77)
DCD[a]	1.17 (0.56-2.44)
Intellectual disability[a]	0.68 (0.17-2.74)
Behavioral disorder[a]	1.86 (1.45-2.39)
Risperidone	
Any neurodevelopmental disorder	1.78 (1.51-2.09)
ASD[a]	1.39 (0.73-2.68)
ADHD	1.89 (1.49-2.38)
Learning difficulty[a]	1.79 (0.85-3.75)
Speech/language disorder[a]	1.36 (1.03-1.79)
DCD[a]	2.05 (1.13-3.70)
Intellectual disability[a]	2.66 (1.19-5.92)
Behavioral disorder[a]	2.32 (1.80-3.00)
Haloperidol	
Any neurodevelopmental disorder[a]	2.10 (1.72-2.55)
ASD[a]	2.23 (1.16-2.28)
ADHD[a]	2.08 (1.54-2.81)
Learning difficulty[a]	1.39 (0.45-4.30)
Speech/language disorder[a]	2.07 (1.56-2.75)
DCD[a]	2.29 (1.15-4.58)
Intellectual disability[a]	1.48 (0.37-5.92)
Behavioral disorder[a]	2.54 (1.84-3.50)



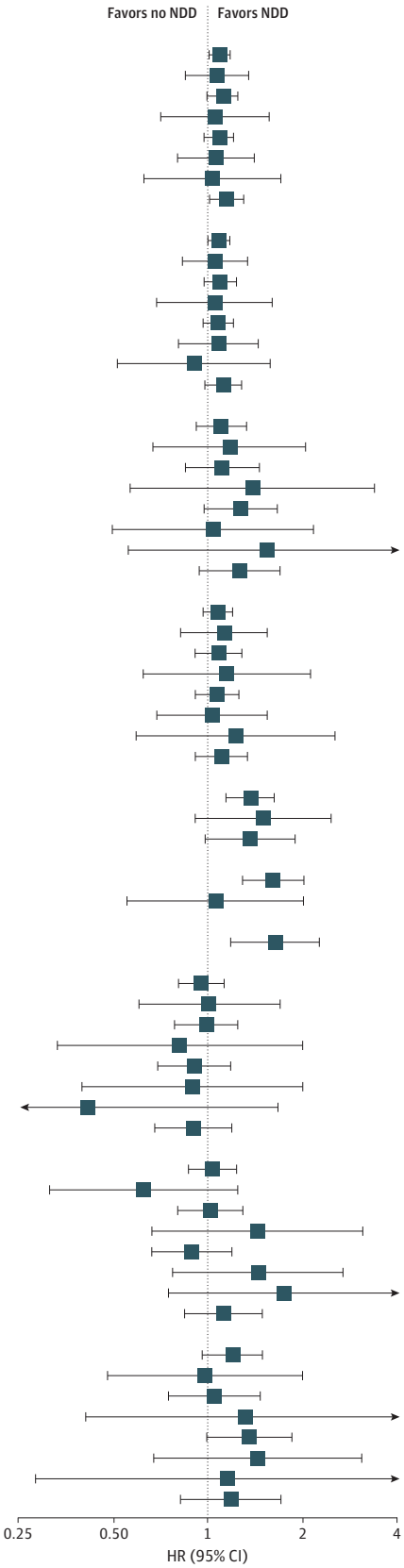
Pooled unadjusted estimates, propensity score overlap weighting; ADHD denotes attention-deficit/hyperactivity disorder; AP, antipsychotic medication; ASD, Autism Spectrum Disorder; DCD, Developmental Coordination Disorder; HR, hazard ratio; MarketScan, IBM Health MarketScan Research Database; MAX, Medicaid Analytic Extract; and NDDs, neurodevelopmental disorders.

[a] Results present the MAX cohort only to suppress unstable estimates based on ≤1 exposed in MarketScan cohort.

[b] No results presented to suppress unstable estimates based on ≤1 exposed in MAX and MarketScan cohorts.

Figure 3. Adjusted Estimates of NDDs in Children, by AP Exposure in Second Half of Pregnancy

Source	HR (95% CI)
Any antipsychotic	
Any neurodevelopmental disorder	1.08 (1.01-1.17)
ASD	1.06 (0.85-1.34)
ADHD	1.11 (0.99-1.24)
Learning difficulty	1.05 (0.70-1.57)
Speech/language disorder	1.08 (0.97-1.21)
DCD	1.06 (0.80-1.40)
Intellectual disability[a]	1.03 (0.62-1.70)
Behavioral disorder	1.14 (1.00-1.29)
Atypical antipsychotics	
Any neurodevelopmental disorder	1.08 (1.00-1.17)
ASD	1.05 (0.82-1.33)
ADHD	1.09 (0.97-1.23)
Learning difficulty	1.05 (0.68-1.60)
Speech/language disorder	1.08 (0.96-1.21)
DCD	1.08 (0.80-1.44)
Intellectual disability[a]	0.90 (0.51-1.57)
Behavioral disorder	1.11 (0.97-1.28)
Typical antipsychotics	
Any neurodevelopmental disorder	1.10 (0.91-1.32)
ASD[a]	1.17 (0.67-2.04)
ADHD	1.11 (0.84-1.45)
Learning difficulty[a]	1.39 (0.56-3.40)
Speech/language disorder[a]	1.27 (0.97-1.65)
DCD[a]	1.04 (0.49-2.17)
Intellectual disability[a]	1.53 (0.56-4.23)
Behavioral disorder[a]	1.26 (0.93-1.70)
Quetiapine	
Any neurodevelopmental disorder	1.07 (0.96-1.19)
ASD	1.12 (0.81-1.54)
ADHD	1.08 (0.91-1.28)
Learning difficulty[a]	1.14 (0.62-2.12)
Speech/language disorder	1.06 (0.91-1.25)
DCD	1.03 (0.69-1.54)
Intellectual disability[a]	1.22 (0.59-2.54)
Behavioral disorder	1.10 (0.91-1.33)
Aripiprazole	
Any neurodevelopmental disorder	1.36 (1.14-1.63)
ASD	1.49 (0.91-2.47)
ADHD	1.36 (0.98-1.89)
Learning difficulty[b]	-
Speech/language disorder	1.61 (1.28-2.02)
DCD	1.05 (0.55-2.01)
Intellectual disability[b]	-
Behavioral disorder[a]	1.63 (1.18-2.26)
Olanzapine	
Any neurodevelopmental disorder	0.95 (0.80-1.12)
ASD[a]	1.00 (0.60-1.69)
ADHD	0.98 (0.78-1.24)
Learning difficulty[a]	0.81 (0.33-2.00)
Speech/language disorder	0.90 (0.69-1.18)
DCD[a]	0.89 (0.40-2.01)
Intellectual disability[a]	0.41 (0.10-1.67)
Behavioral disorder[a]	0.90 (0.67-1.19)
Risperidone	
Any neurodevelopmental disorder[c]	1.03 (0.86-1.23)
ASD[a]	0.62 (0.31-1.24)
ADHD[c]	1.01 (0.78-1.30)
Learning difficulty[a]	1.43 (0.66-3.10)
Speech/language disorder[a]	0.88 (0.66-1.19)
DCD[a]	1.44 (0.77-2.69)
Intellectual disability[a]	1.74 (0.75-4.06)
Behavioral disorder[a]	1.12 (0.84-1.48)
Haloperidol	
Any neurodevelopmental disorder[a]	1.19 (0.96-1.48)
ASD[a]	0.98 (0.48-2.01)
ADHD[a]	1.04 (0.75-1.46)
Learning difficulty[a]	1.30 (0.41-4.15)
Speech/language disorder[a]	1.35 (0.99-1.85)
DCD[a]	1.44 (0.67-3.09)
Intellectual disability[a]	1.15 (0.28-4.72)
Behavioral disorder[a]	1.18 (0.82-1.71)



Pooled adjusted estimates, using propensity score overlap weighting; ADHD denotes attention-deficit/hyperactivity disorder; AP, antipsychotic medication; ASD, Autism Spectrum Disorder; DCD, Developmental Coordination Disorder; HR, hazard ratio; MarketScan, IBM Health MarketScan Research Database; MAX, Medicaid Analytic Extract; and NDDs, neurodevelopmental disorders.

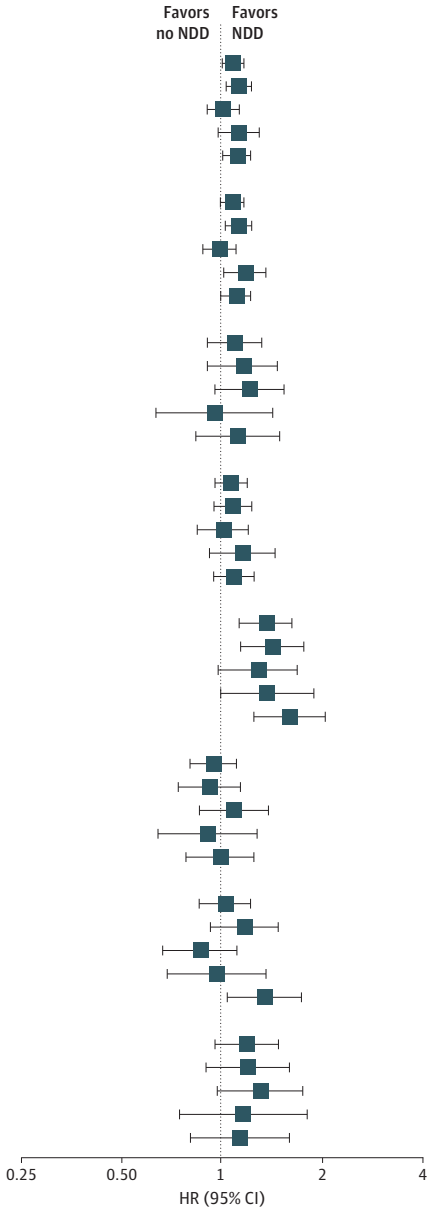
[a] Results present the MAX cohort only to suppress unstable estimates based on ≤1 exposed in MarketScan cohort.

[b] No results presented to suppress unstable estimates based on ≤1 exposed in MAX and MarketScan cohorts.

[c] Fully adjusted model did not converge in MarketScan. MarketScan results are adjusted for treatment indication, lifestyle behavior, proxies for severity of mental illness, and concomitant use of other psychotropic drugs; thus, pooled estimates were based on fully adjusted results in MAX and partially adjusted in MarketScan.

Figure 4. Sensitivity Analyses of Adjusted Estimates of Any NDD in Children, by AP Exposure in Second Half of Pregnancy

Source	HR (95% CI)
Any antipsychotic	
Adjusted main analysis	1.08 (1.01-1.17)
≥2 Dispensings	1.13 (1.03-1.23)
≤30-d Supply	1.01 (0.91-1.13)
>30- and ≤60-d Supply	1.13 (0.98-1.30)
>60-d Supply	1.11 (1.01-1.23)
Atypical antipsychotics	
Adjusted main analysis	1.08 (1.00-1.17)
≥2 Dispensings	1.13 (1.03-1.24)
≤30-d Supply	0.99 (0.88-1.11)
>30- and ≤60-d Supply	1.18 (1.02-1.37)
>60-d Supply	1.11 (1.00-1.22)
Typical antipsychotics	
Adjusted main analysis	1.10 (0.91-1.32)
≥2 Dispensings[b]	1.16 (0.91-1.48)
≤30-d Supply[a]	1.22 (0.96-1.54)
>30- and ≤60-d Supply[a]	0.96 (0.64-1.43)
>60-d Supply[b]	1.12 (0.84-1.50)
Quetiapine	
Adjusted main analysis	1.07 (0.96-1.19)
≥2 Dispensings	1.09 (0.95-1.24)
≤30-d Supply	1.01 (0.85-1.20)
>30- and ≤60-d Supply	1.16 (0.92-1.45)
>60-d Supply	1.09 (0.95-1.25)
Aripiprazole	
Adjusted main analysis	1.36 (1.14-1.63)
≥2 Dispensings	1.43 (1.15-1.77)
≤30-d Supply[a]	1.29 (0.98-1.69)
>30- and ≤60-d Supply[a]	1.38 (0.99-1.90)
>60-d Supply[a]	1.61 (1.26-2.06)
Olanzapine	
Adjusted main analysis	0.95 (0.80-1.12)
≥2 Dispensings	0.92 (0.75-1.14)
≤30-d Supply[a]	1.09 (0.86-1.39)
>30- and ≤60-d Supply[b]	0.91 (0.65-1.28)
>60-d Supply[a]	0.99 (0.79-1.25)
Risperidone	
Adjusted main analysis	1.03 (0.86-1.23)
≥2 Dispensings[a]	1.17 (0.93-1.48)
≤30-d Supply[b]	0.87 (0.67-1.12)
>30- and ≤60-d Supply[b]	0.97 (0.69-1.37)
>60-d Supply[a]	1.35 (1.04-1.74)
Haloperidol	
Adjusted main analysis[b]	1.19 (0.96-1.48)
≥2 Dispensings[b]	1.20 (0.90-1.60)
≤30-d Supply[b]	1.31 (0.98-1.76)
>30- and ≤60-d Supply[b]	1.17 (0.75-1.81)
>60-d Supply[b]	1.14 (0.81-1.60)



Pooled adjusted estimates, using propensity score overlap weighting; AP denotes antipsychotic medications; HR, hazard ratio; MarketScan, IBM Health MarketScan Research Database; MAX, Medicaid Analytic Extract; and NDD, neurodevelopmental disorder.

[a] MarketScan results are unadjusted (adjusted models did not converge); thus, pooled estimates were based on adjusted results in MAX and unadjusted in MarketScan.

[b] Results present the MAX cohort only to suppress unstable estimates based on ≤1 exposed in MarketScan cohort.

both exposure assessment periods (Figure 1; eFigure 3 in the Supplement).

Pooled unadjusted analyses were generally consistent, with an approximate 2-fold increased risk for most exposure-outcome contrasts and for both assessment periods (Figure 2; eTable 4 in the Supplement). However, adjusted results did not suggest a substantially increased risk for any exposure-outcome association, eg, for second-half exposure (pooled unadjusted $HR_{\text{any NDD}}$, 1.91 [95% CI, 1.79-2.03] vs pooled adjusted HR $[paHR]_{\text{any NDD}}$, 1.08 [95% CI, 1.01-1.17]), with the possible exception of aripiprazole (Figure 3; eTable 4 in the Supplement). For children whose mothers were dispensed aripiprazole during the second half of pregnancy, risks remained increased for any NDD (paHR, 1.36 [95% CI, 1.14-1.63]), as well as for ASD (paHR, 1.49 [95% CI, 0.91-2.47]), ADHD (paHR, 1.36 [95% CI, 0.98-1.89]), speech or language disorder (paHR, 1.61 [95% CI, 1.28-2.02]), and behavioral disorder (paHR, 1.63 [95% CI, 1.18-2.26]). Increased risks for NDD were also observed for exposure to aripiprazole in the first half of pregnancy (eTable 4 in the Supplement).

Sensitivity Analyses

Using hdPS and changing the outcome assessment period to 3 years of age or older did not meaningfully affect the findings (eTable 4 in the Supplement). Redefining exposure as 2 or more dispensings during the respective assessment period tended to slightly strengthen the associations, although they were less precisely estimated and remained generally close to

the null (Figure 4; eTable 4 in the Supplement). We found no evidence supporting a potential association between days' supply and NDDs. Although risk estimates occasionally suggested this association (eg, for any NDD among those aripiprazole- and risperidone-exposed), CIs were wide and overlapping and full confounding adjustment was not always possible in the privately insured cohort because of the relatively low numbers of women within strata (Figure 4; eTable 4 in the Supplement). There was also no substantial difference in risk of having 2 or more different NDDs diagnosed vs 1 NDD, with the possible exception of aripiprazole for which the overall results were driven by increased risks for 2 or more NDDs (paHR for second half of pregnancy, 1.48 [95% CI, 1.11-1.99]; for first half of pregnancy, 1.45 [95% CI, 1.20-1.74]) (eTable 4 in the Supplement). Accounting for censoring weights did not change the findings (eTable 5 in the Supplement).

Post Hoc Exploratory Analyses of Aripiprazole Exposure

No clear dose-response relationship was found based on cumulative aripiprazole dose, although wide CIs hampered the interpretation of the observed estimates. Comparing pregnancies that were aripiprazole exposed with those who discontinued prior to pregnancy did not considerably affect the estimates. Associations were slightly stronger for late exposure only than for early exposure only (eTable 6 in the Supplement).

A review of patient characteristics and prior antipsychotic exposure did not provide strong evidence that aripiprazole is systematically prescribed in patients with more severe illness and/or inadequate response to other antipsychotic drugs (eTable 3 and 7 in the Supplement). There were no striking differences in the combinations of NDDs between the aripiprazole exposed and the reference group (eTable 8 in the Supplement).

Discussion

This birth cohort study of 3.4 million children with up to 14 years of follow-up found that, although NDD incidence was higher among those children exposed to antipsychotic drugs vs not exposed during the second half of pregnancy, risks were no longer meaningfully increased after adjustment for confounding by maternal characteristics and other factors that may negatively affect the fetal environment—with the possible exception of aripiprazole. Results were consistent across a range of prespecified sensitivity analyses. Post hoc analyses to explore the positive association observed for aripiprazole did not allow us to rule out causality.

Two recent systematic reviews have summarized the evidence regarding neurobehavioral teratogenicity of intrauterine antipsychotic exposure.[13,38] Preclinical studies—mostly conducted in rodents—have consistently reported adverse neurodevelopmental effects of prenatal antipsychotic exposure.[38] Most clinical data derive from case reports and small case-series studies, and results have been inconsistent. Findings from case-control and cohort studies were judged to be of limited clinical relevance because of their small sample sizes and because between-study comparisons are hampered by substantial differences in methodology and follow-up duration.[13] The most consistent findings from those studies concern a (transient) delay in motor development—not confirmed by the present study. Because most studies had follow-up periods of less than 2 years, later-onset neurodevelopmental sequelae have not been well characterized. Both of the systematic reviews concluded that the limited human evidence makes it impossible to confirm or exclude long-lasting harmful neurocognitive effects in the offspring, and large high-quality studies are needed to support evidence-based clinical advice.[13,38] Recently, 2 cohort studies including 706 children exposed to antipsychotic drugs in Hong Kong and 15 466 children exposed in 5 Nordic countries reported no association between antipsychotic exposure at any time point during pregnancy and the risk of ASD or ADHD.[20,21] However, the effects of individual antipsychotic drugs, potential dose-response relationships, and the association with other specific NDDs were not assessed. Therefore, our study addresses an important evidence gap.

We interpreted the overall findings by considering results of both main and sensitivity analyses. We focused on the magnitude of the association, precision of the estimates (reflected by the width of the 95% CI), and consistency across analyses, rather than statistical significance of individual contrasts.[39,40] It is important to state that the probability of finding 1 or more associations that meet the critical point for statistical significance (conventionally, $P < .05$)—the probability of a type I error—increases in proportion to the number of associations tested. Given the large number of associations examined by this study (ie, different exposures, exposure windows, outcomes; multiple sensitivity analyses), we fully expected to observe some associations that reached statistical significance by chance alone. This further underscores the importance of interpreting the findings based on the entirety of the evidence.

Although the evidence for most exposures points to a null association, consistent findings of a potential small increased risk for aripiprazole across different analyses required further investigation. Post hoc exploratory analyses were conducted in an effort to exclude alternative explanations. Aripiprazole was approved for use more recently than the other antipsychotic drugs we considered, and therefore, may be prescribed preferentially to patients with more severe illness and/or to patients unresponsive to other antipsychotic treatment. Although illness severity and treatment response cannot be directly assessed in the present study data, comparing the characteristics of patients treated with aripiprazole vs other antipsychotic drugs—including proxies for disease severity and number of different antipsychotic drugs taken before pregnancy—did not reveal clear differences, suggesting that this explanation is unlikely.

Next, in a nonrandomized study evaluating NDD risk in children with vs without prenatal antipsychotic exposure, the main concern is confounding, particularly by factors challenging to assess in secondary data, such as family environment, genetic predisposition, and approach to parenting, in the setting of maternal mental illness. Given that we did not observe an association for the other antipsychotic medications and expect similar confounding mechanisms across treatments and given the consistent findings for the discontinuers analysis, confounding by these factors seems unlikely.

Lastly, unlike other antipsychotic drugs, aripiprazole reduces dopaminergic neurotransmission through D2 partial agonism, not D2 antagonism.[41] This action can result in lactation problems owing to prolactin reduction. Therefore, a potential hypothesis is that aripiprazole's association with NDDs may be mediated through a reduction in breastfeeding.[42,43] Our data did not include information on breastfeeding, which may be an important avenue to explore in future studies.

Strengths and Limitations

The strengths of our study were the following: (1) the use of mother-child linked birth cohorts of publicly and privately insured individuals nested in nationally representative data sources; (2) the large study size that enabled the evaluation of individual antipsychotic drugs, different exposure windows, and specific NDDs; (3) use of validated outcome definitions[27]; and (4) careful attention to a broad range of potential confounding variables and extensive sensitivity analyses to evaluate the robustness of the findings to exposure and outcome misclassification, residual confounding, and selection bias.

Because of their large size and long-term follow-up periods, birth cohorts nested in administrative databases or registries are an essential data source for studying perinatal risk factors for NDDs in humans; however, the data may also present some challenges. Experience has taught us that many of these challenges can be overcome through careful design and analytic approaches—eg, adherence to the principles of target trial emulation whenever possible,[44] the use of highly specific outcome definitions, data-driven approaches to identify proxies for residual confounding[34]—all of which were implemented.[45] Given that we expected upward confounding when comparing antipsychotic-exposed with unexposed pregnancies and in light of our null findings in adjusted analyses, residual confounding was not a concern, with the possible exception of aripiprazole.

Misclassification of exposure, on the other hand, was a potential concern. If women who filled a prescription for an antipsychotic medication but did not actually take it, results could be biased toward the null. To address the possibility of these false positives, we required women to have refilled a prescription at least once during the respective exposure window in secondary analyses, which did not substantially alter the findings. Moreover, there was no evidence of a dose-response relationship based on number of days' supply. Therefore, exposure misclassification was unlikely to explain the null findings. Also, consistency of the results when accounting for censoring weights does not support the presence of selection bias from informative censoring.

Conclusions

This birth cohort study found that the most commonly prescribed antipsychotic medications do not appear to meaningfully increase NDD risk in offspring after accounting for confounding. The potential signal identified for aripiprazole requires replication in other data sources before causality can be assumed.

These findings provide much needed clarity regarding NDD risk and may help to inform treatment decision-making in pregnancy, which is a sophisticated trade-off between benefits and risks. The benefits of antipsychotic treatment for pregnant women with severe mental illness are undisputed. Although the observed 2-fold increase in risk of NDD is not causally related with in utero exposure to antipsychotic drugs, it does highlight the importance of closely monitoring the neurodevelopment of the offspring of women with mental illness to ensure that early intervention and support can be instituted when needed.

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Author Affiliations: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Straub, Bateman, Suarez, Zhu, Zakoul, Mogun, Huybrechts); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Hernández-Díaz); Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Bateman); Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California (Bateman); The Asher Center for the Study and Treatment of Depressive Disorders, Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Wisner); Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Wisner); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts (Gray); Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Pennell); Center for the Study of Children at Risk, Departments of Psychiatry and Pediatrics, Alpert Medical School of Brown University, and Women and Infants Hospital, Providence, Rhode Island (Lester); Lurie Center for Autism, Massachusetts General Hospital, Lexington (McDougle); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (McDougle).

Author Contributions: Drs Straub and Huybrechts, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Straub, Hernández-Díaz, Bateman, Lester, Huybrechts.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Straub, Bateman, Lester, Zakoul, Huybrechts.
Critical revision of the manuscript for important intellectual content: Straub, Hernández-Díaz, Bateman, Wisner, Gray, Pennell, Lester, McDougle, Suarez, Zhu, Mogun, Huybrechts.
Statistical analysis: Straub, Lester, Suarez, Mogun, Huybrechts.
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Supervision: Hernández-Díaz, Bateman, Wisner, Huybrechts.
Other—clinical expertise: Pennell.

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