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Online-only figures

Cohort selection: Exclusion criteria

i. Recorded pregnancies with missing birth date, birthweight, or gestational age at birth.
ii. Recorded pregnancies with invalid gestational age
    a. Invalid based on recorded GA: Children with recorded gestational length ≤154 days (≤gestational week 22+0) and >308 days (>gestational week 44+0),
    b. Invalid based on birthweight: GA & sex-specific BW z-score>4 SD and GA<35 weeks.
iii. Children diagnosed with fetal chromosomal/genetic anomalies or fetal alcohol syndrome, i.e., ICD-9 (27911, 7531, 7560, 7580-7583, 7585-7589, 7898, 76071) and ICD-10 codes (D821, Q619, Q751, Q754, Q87, Q90 – Q94, Q96–Q99, Q860) as recorded in the Nordic Medical Birth, Congenital Malformation or Patient Registers within the first year after date of birth (DOB).
iv. Children with a recorded birth weight <300 grams and >7000 grams.
v. Children where information on sex is missing/unknown/undefined.
vi. Recorded pregnancies solely exposed to prochlorperazine (but not any other antipsychotic drug) between LMP and birth.
vii. Recorded pregnancies solely exposed to antipsychotics between LMP-90 and LMP but not between LMP and birth.

We excluded children with missing or invalid data on birth date, gestational age or birth weight, those with missing data on sex, and those diagnosed with fetal chromosomal/genetic anomalies or fetal alcohol syndrome within the first year after birth (eFigure 1). Gestational age was essential to accurately assess exposure time windows during pregnancy, as the ascertainment of last menstrual period relied on this information. Since we used birth weight and sex in our algorithm to identify valid gestational age (see below), births with incomplete information on these variables had to be excluded. We also excluded children a chromosomal anomaly or fetal alcohol spectrum disorder diagnosed in the first year after birth. These diagnoses were not expected to be caused by antipsychotic exposure; we preferred to handle potential confounding by restriction rather than adjusting for these uncommon but strong risk factors.

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eTable 1. Antipsychotic medications, ATC classification codes and type

ATC	Exposure	Type
N05A	**Antipsychotics**	
N05AA	***Phenothiazines with alipathic side-chain***	
N05AA01	chlorpromazine	Typical
N05AA02	levomepromazine	Typical
N05AA03	promazine	Typical
N05AA04	acepromazine	Typical
N05AA05	triflupromazine	Typical
N05AA06	cyamemazine	Typical
N05AA07	chlorproethazine	Typical
N05AB	***Phenothiazines with piperazine structure***	
N05AB01	dixyrazine	Typical
N05AB02	fluphenazine	Typical
N05AB03	perphenazine	Typical
N05AB05	thiopropazate	Typical
N05AB06	trifluoperazine	Typical
N05AB07	acetophenazine	Typical
N05AB08	thioproperazine	Typical
N05AB09	butaperazine	Typical
N05AB10	perazine	Typical
N05AC	***Phenothiazines with piperidine structure***	
N05AC01	periciazine	Typical
N05AC02	thioridazine	Typical
N05AC03	mesoridazine	Typical
N05AC04	pipotiazine	Typical

N05AD	***Butyriohenone derivatives***	
N05AD01	haloperidol	Typical
N05AD02	trifluperidol	Typical
N05AD03	melperone	Typical
N05AD04	moperone	Typical
N05AD05	pipamperone	Typical
N05AD06	bromperidol	Typical
N05AD07	benperidol	Typical
N05AD08	droperidol	Typical
N05AD09	fluanisone	Typical
N05AE	***Indole derivatives***	
N05AE01	oxypertine	Typical
N05AE02	molindone	Typical
N05AE03	sertindole	Atypical
N05AE04	ziprasidone	Atypical
N05AE05	lurasidone	Atypical
N05AF	***Thioxanthene derivatives***	
N05AF01	flupentixol	Typical
N05AF02	clopenthixol	Typical
N05AF03	chlorprothixene	Typical
N05AF04	tiotixene	Typical
N05AF05	zuclopenthixol	Typical
N05AG	***Diphenylbutylpiperidine derivatives***	
N05AG01	fluspirilene	Typical
N05AG02	pimozide	Typical
N05AG03	penfluridol	Typical
N05AH	***Diazepines, oxazepines, thiazepines and oxepines***	

N05AH01	loxapine	Typical
N05AH02	clozapine	Atypical
N05AH03	olanzapine	Atypical
N05AH04	quetiapine	Atypical
N05AH05	asenapine	Atypical
N05AH06	clotiapine	Typical
N05AL	***Benzamides***	
N05AL01	sulpiride	Atypical
N05AL02	sultopride	Atypical
N05AL03	tiapride	Typical
N05AL04	remoxipride	Atypical
N05AL05	amisulpride	Atypical
N05AL06	veralipride	Typical
N05AL07	levosulpiride	Atypical
N05AX	***Other antipsychotics***	
N05AX07	prothipendyl	Typical
N05AX08	risperidone	Atypical
N05AX10	mosapramine	Atypical
N05AX11	zotepine	Atypical
N05AX12	aripiprazole	Atypical
N05AX13	paliperidone	Atypical
N05AX14	iloperidone	Atypical
N05AX15	cariprazine	Atypical
N05AX16	brexpiprazole	Atypical
N05AX17	pimavanserin	Atypical

ATC, Anatomical Therapeutic Chemical

eTable 2. Covariate definitions, source data, and relevant diagnostic, medication codes

Covariate	Time frame	Functional form of variable and comments	Data source[a]	definition	Codes ATC	Codes ICD-10	Codes ICPC
Calendar year of birth	Year of delivery	Continuous,1997-2017	MBR				
Maternal age	At delivery	Continuous	MBR				
Maternal age categories	At delivery	<20; 20-24; 25-29; 30-34; 35-39; ≥40	MBR				
Maternal education	In year of delivery	Compulsory education or less (ISCED: 0,1,2); Secondary education (ISCED: 3,4); Post-secondary education (ISCED: 5,6); Post-graduate education (ISCED: 7,8); Missing	NSI	Highest achieved education in year of birth, based on ISCED 2011 categorization as recorded by Statistics Institution			
Cohabitation	In year of delivery	No; Yes; Missing	MBR				
Maternal country of birth	n/a	Mother born in the country of delivery or not No; Yes	NSI MBR				
Parity	n/a	Number of previous deliveries 0; 1; ≥2	MBR				
Child sex	n/a	Female; Male	MBR				
BMI	In early pregnancy	Continuous. Set to missing for those with BMI values below 14 or above 55.	MBR	As recorded in MBR or calculated from maternal weight and height at first antenatal visit (kg/m2)			
BMI	In early pregnancy	Categorical	MBR				

Covariate	Time frame	Functional form of variable and comments	Data source[a]	definition	ATC	Codes ICD-10	Codes ICPC
		<18.5; 18.5 to <25; 2: 25 to <30; 30 to <35; >= 35; Missing					
Smoking	Early pregnancy	No; Yes; Missing Iceland: not available	MBR				
Maternal comorbidity	LMP - 365 days to birth	No; Yes	NPR MBR	≥1 diagnosis of listed maternal conditions			
Pre-existing diabetes						E10-E14	T89 T90 W85
Pre-existing hypertension						I10-I15 O10	K86 K87
Polycystic ovary syndrome						E28.2	
Migraine						G43	N89
Cluster headache						G44	N90
Epilepsy or convulsion, or epilepsy complicating pregnancy						G40 G41	N88
Maternal psychotic or bipolar disorders	LMP - 365 days to birth	No; Yes	NPR MBR	≥1 diagnosis of listed maternal conditions			
Bipolar disorders						F30-F31	
Schizophrenia and other psychotic disorders						F20-F29	
Other maternal psychiatric disorders	LMP - 365 days to birth	No; Yes	NPR MBR	≥1 diagnosis of listed maternal conditions			
Substance use disorder						F10-F19	
Depression and other mood disorders, excl. bipolar						F32-F39	

Covariate	Time frame	Functional form of variable and comments	Data source[a]	definition	Codes ATC	Codes ICD-10	Codes ICPC
Anxiety disorders						F40-F48	
Personality disorders						F60-F69	
Intellectual disability						F70-F79	
Disorders of psychological development						F80-F89	
Autism spectrum disorder						F84.0 F84.1 F84.5	
Attention/deficit-hyperactivity disorder						F90.0 F90.1 F90.2 F90.8 F90.9	
Suicide attempts						X60-X84 Y10-Y34	
Use of known teratogenic medications	LMP - 90 days to birth	No; Yes	PDR	≥1 prescription fills for any of listed medications			
Warfarin					B01AA03		
Antineoplastic agents					L01		
Isotretinoin					D10AD04 D10BA01 D10AD54		
Systemic retinoids for psoriasis dermatitis					D05BB D11AH04		
Misopristol					A02BB01 G02AD06 M01AB55 M01AE56		

Covariate	Time frame	Functional form of variable and comments	Data source[a]	definition	Codes		
					ATC	ICD-10	ICPC
Thalidomide					L04AX02		
Valproate					N03AG01		
Use of suspected teratogenic medications	LMP - 90 to birth	No; Yes	PDR	≥1 prescription fills for any of listed medications			
Lithium					N05AN01		
Antiepileptics excl. valproate					N03 [excl. N03AG01]		
Drugs acting on the renin-angiotensin system, incl. ACE inhibitors, ARBs					C09		
Antithyroid drugs					H03B		
Mycophenolic acid					L04AA13		
Leflunomide					L04AA13		
Teriflunomide					L04AA31		
Lenalidomide					L04AX04		
Pomalidomide					L04AX06		
Ergot alkaloids					N02C		
Other medications during pregnancy	LMP - 90 days to birth	No; Yes	PDR	≥1 prescription fills for any of listed medications			
Antidepressants					N06A		
Antidiabetics					A10		
Benzodiazepines					N05BA N05CD		
Triptans					N02CC		
Opioids					N02A		
Paracetamol					N02BE01		

MBR, Medical Birth Registry; Pop Reg, Population Register; NPR, National Patient Register; NPCD, Norwegian Primary Care Data; PDR, Prescription Drug Register; NSI, National Statistical Institute; ISCED, International Standard Classification of Education; ATC, Anatomical Therapeutic Chemical Classification; ICD International Classification of Disease; ICPC, International Classification of Primary Care; BMI, body mass index; n/a, not applicable; LMP, last menstrual period; AP, antipsychotic; ACE inhibitors, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers

[a]For Norway, only the MBR will provide information on maternal comorbidity from 2004 to 2008 since the Norwegian Patient Register was not available until 2009

eTable 3. Hazard ratios and 95% confidence intervals (CIs) comparing the risk for ADHD in exposed and unexposed children, stratified by maternal psychiatric disorder

			Hazard ratio (95% CI)		
Antipsychotic exposure	**No. with ADHD / N**	**Person-years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Maternal psychiatric disorder					
Psychotic or bipolar disorders					
Unexposed	222 / 8356	57727	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	126 / 4385	33788	0.87 (0.70 – 1.09)	0.94 (0.75 – 1.17)	0.90 (0.70 – 1.15)
Other psychiatric disorders					
Unexposed	7751 / 415906	3078602	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	162 / 14547	32998	1.57 (1.34 – 1.84)	1.39 (1.18 – 1.63)	0.96 (0.82 – 1.12)
No recorded psychiatric conditions					
Unexposed	63802 / 3884358	38727009	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	194 / 5352	54606	1.94 (1.68 – 2.23)	1.68 (1.46 – 1.93)	1.44 (1.25 – 1.66)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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

eTable 4. Hazard ratios and 95% confidence intervals (CIs) 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

			Hazard ratio (95% CI)		
Antipsychotic exposure	**No. with ADHD / N**	**Person-years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Maternal antipsychotic use (secondary analyses)					
Pre-pregnancy use only	355 / 9743	76387	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	303 / 10273	83827	0.69 (0.59 - 0.81)	0.73 (0.62 - 0.86)	0.74 (0.62 - 0.87)
No use before or during pregnancy	48736 / 15433823	15027190	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Pre-pregnancy use	355 / 9743	76387	2.77 (2.49 - 3.07)	2.61 (2.35 - 2.90)	1.44 (1.29 - 1.60)
No use before or during pregnancy without psychotic or bipolar disorders	48593 / 3128500	27290564	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
No use before or during pregnancy with psychotic or bipolar disorders	143 / 5652	36299	3.00 (2.54 - 3.53)	2.82 (2.39 - 3.32)	1.79 (1.52 - 2.11)
Maternal psychiatric disorder (secondary analyses)					
Psychotic and bipolar disorders					
Pre-pregnancy use only	33 / 1354	9057	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	63 / 2684	18861	0.89 (0.71 - 1.12)	0.81 (0.54 - 1.23)	0.81 (0.51 - 1.29)
Other psychiatric disorders					
Pre-pregnancy use only	171 / 4673	32646	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	104 / 3784	27075	0.69 (0.54 - 0.89)	0.69 (0.54 - 0.89)	0.70 (0.55 - 0.91)
No recorded psychiatric conditions					
Pre-pregnancy use only	151 / 3716	34685	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	136 / 3805	37890	0.65 (0.51 - 0.83)	0.75 (0.57 - 0.98)	0.85 (0.64 - 1.12)
Sibling analysis					
Unexposed	354 / 835	8888	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	185 / 483	3927	1.28 (0.98 - 1.67)	1.17 (0.84 - 1.62)	1.14 (0.79 - 1.64)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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

eTable 5. Hazard ratios and 95% confidence intervals (CIs) comparing the risk for ADHD in exposed and unexposed children, with antipsychotic exposure defined as ≥2 filled prescriptions

			Hazard ratio (95% CI)		
Antipsychotic exposure	**No. with ADHD / N**	**Person-years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Unexposed	71994 / 4315656	41924124	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	263 / 8430	69426	2.43 (2.15 - 2.74)	2.29 (2.03 - 2.58)	1.07 (0.94 - 1.22)
Type of antipsychotic exposure					
Typical antipsychotics only	114 / 2797	32508	1.77 (1.47 - 2.12)	1.84 (1.53 - 2.21)	1.04 (0.86 - 1.25)
Atypical antipsychotics only	105 / 4815	29985	3.18 (2.62 - 3.85)	2.55 (2.11 - 3.10)	1.02 (0.84 - 1.24)
Maternal psychiatric disorder					
Psychotic or bipolar disorders					
Unexposed	250 / 9468	66222	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	98 / 3273	25293	0.94 (0.74 - 1.19)	1.02 (0.80 - 1.30)	0.97 (0.74 - 1.28)
Other psychiatric disorders					
Unexposed	7830 / 418725	3099245	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	83 / 2910	21275	1.61 (1.30 - 2.00)	1.44 (1.16 - 1.79)	0.92 (0.74 - 1.14)
No recorded psychiatric conditions					
Unexposed	63914 / 3887463	38758658	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	82 / 2247	22958	1.99 (1.60 - 2.46)	1.90 (1.53 - 2.36)	1.53 (1.24 - 1.90)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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

eTable 6. Hazard ratios and 95% confidence intervals (CIs) comparing the risk for ADHD in exposed and unexposed children, with Norwegian cohort restricted to births after 2008

			Hazard ratio (95% CI)		
Antipsychotic exposure	**No. with ADHD / N**	**Person-years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Unexposed	64740 / 4087582	39311916	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	401 / 14037	113560	2.37 (2.14 - 2.61)	2.06 (1.86 - 2.27)	1.05 (0.94 - 1.16)
Timing of exposure					
First trimester only	171 / 5633	46250	2.38 (2.05 - 2.77)	1.82 (1.56 - 2.12)	1.05 (0.90 - 1.23)
Second/third trimester only	79 / 3046	25015	2.14 (1.71 - 2.67)	1.99 (1.60 - 2.49)	0.96 (0.77 - 1.21)
First trimester and second/third trimester	151 / 5358	42294	2.51 (2.14 - 2.95)	2.49 (2.13 - 2.92)	1.02 (0.86 - 1.21)
Type of antipsychotic exposure					
Typical antipsychotics only	207 / 5659	60673	1.86 (1.62 - 2.13)	1.73 (1.51 - 1.98)	1.06 (0.92 - 1.21)
Atypical antipsychotics only	151 / 7600	46425	3.13 (2.66 - 3.67)	2.34 (1.99 - 2.75)	0.93 (0.79 - 1.10)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity
[b]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

eTable 7. Hazard ratios and 95% confidence intervals (CIs) comparing the risk for ASD in exposed and unexposed children, stratified by maternal psychiatric disorder

			Hazard ratio (95% CI)		
Antipsychotic exposure	**No. with ASD / N**	**Person-years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Maternal psychiatric disorder					
Psychotic or bipolar disorders					
Unexposed	139 / 8356	57891	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	91 / 4385	33851	1.07 (0.82-1.40)	1.29 (0.98-1.69)	1.28 (0.95-1.71)
Other psychiatric disorders					
Unexposed	3829 / 415906	3089835	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	76 / 5729	42108	1.45 (1.16-1.82)	1.44 (1.15-1.80)	1.09 (0.86-1.37)
No recorded psychiatric conditions					
Unexposed	34468 / 3884358	38834971	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	71 / 5352	55070	1.49 (1.18-1.88)	1.54 (1.22-1.94)	1.27 (1.00-1.60)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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

eTable 8. Hazard rations and 95% confidence intervals (CIs) 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

Antipsychotic exposure	No. with ASD / N	Person-years at risk	Hazard ratio (95% CI) Crude	Model 1[a]	Model 2[b]
Maternal antipsychotic use (secondary analyses)					
Pre-pregnancy use only	174 / 9743	76873	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	174 / 10273	84178	0.88 (0.71-1.09)	0.93 (0.75-1.17)	0.88 (0.70-1.10)
No use before or during pregnancy	30815 / 3134152	27377539	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Pre-pregnancy use	174 / 9743	76873	2.08 (1.79-2.41)	2.18 (1.87-2.53)	1.40 (1.19-1.63)
No use before or during pregnancy without psychotic or bipolar disorders	30716 / 3128500	27341143	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
No use before or during pregnancy with psychotic or bipolar disorders	99 / 5652	36395	2.70 (2.22-3.29)	2.43 (1.99-2.96)	1.89 (1.54-2.30)
Maternal psychiatric disorder (secondary analyses)					
Psychotic and bipolar disorders					
Pre-pregnancy use only	18 / 1354	9058	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	68 / 2684	18831	1.80 (1.07-3.01)	1.72 (1.01-2.92)	1.67 (0.99-2.81)
Other psychiatric disorders					
Pre-pregnancy use only	80 / 4673	32892	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	58 / 3784	27221	0.84 (0.60-1.19)	0.83 (0.59-1.17)	0.84 (0.59-1.20)
No recorded psychiatric conditions					
Pre-pregnancy use only	76 / 3716	34923	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Use in pregnancy	48 / 3805	38126	0.57 (0.40-0.82)	0.63 (0.41-0.97)	0.62 (0.40-0.96)
Sibling analysis					
Unexposed	115 / 304	3042	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	82 / 186	1504	1.38 (0.94-2.03)	1.20 (0.74-1.95)	1.34 (0.75-2.39)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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

eTable 9. Hazard ratios and 95% confidence intervals (CIs) comparing the risk for ASD in exposed and unexposed children, with antipsychotic exposure defined as ≥2 filled prescriptions

			Hazard ratio (95% CI)		
Antipsychotic exposure	**No. with ASD / N**	**Person-years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Unexposed	38538 / 4315656	42043861	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	136 / 8430	69864	2.30 (1.94-2.73)	2.35 (1.99-2.78)	1.08 (0.89-1.30)
Type of antipsychotic exposure					
Typical antipsychotics only	52 / 2797	32779	1.71 (1.30-2.25)	1.85 (1.41-2.42)	1.02 (0.77-1.34)
Atypical antipsychotics only	69 / 4815	30046	3.09 (2.44-3.93)	2.99 (2.36-3.79)	1.23 (0.95-1.59)
Maternal psychiatric disorder					
Psychotic or bipolar disorders					
Unexposed	181 / 9468	66314	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	73 / 3273	25370	1.11 (0.83-1.47)	1.30 (0.97-1.73)	1.30 (0.95-1.77)
Other psychiatric disorders					
Unexposed	4471 / 418725	828608	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	49 / 2910	21318	1.51 (1.11-2.05)	1.52 (1.11-2.07)	1.10 (0.80-1.51)
No recorded psychiatric conditions					
Unexposed	41684 / 3887463	38832132	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	27 / 2247	23152	1.43 (0.97-2.10)	1.54 (1.05-2.26)	1.23 (0.84-1.82)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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

eTable 10. Hazard ratios and 95% confidence intervals (CIs) comparing the risk for ASD in exposed and unexposed children, with Norwegian cohort restricted to births after 2008

			Hazard Ratio (95% CI)		
Antipsychotic exposure	**No. with ASD / N**	**Person-Years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Unexposed	36808 / 4087582	39414709	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	233 / 14037	114109	2.35 (2.06-2.67)	2.28 (2.01-2.60)	1.18 (1.02-1.36)
Timing of exposure					
First trimester only	101 / 5633	46394	2.52 (2.07-3.06)	2.14 (1.77-2.61)	1.24 (1.01-1.52)
Second/third trimester only	47 / 3046	25176	2.19 (1.65-2.91)	2.35 (1.76-3.13)	1.19 (0.88-1.59)
First trimester and second/third trimester	85 / 5358	42537	2.34 (1.89-2.91)	2.46 (1.99-3.05)	1.05 (0.83-1.34)
Type of antipsychotic exposure					
Typical antipsychotics only	109 / 5659	61090	1.86 (1.54-2.25)	1.84 (1.52-2.22)	1.14 (0.94-1.39)
Atypical antipsychotics only	109 / 7600	46451	3.12 (2.58-3.77)	2.98 (2.47-3.59)	1.26 (1.02-1.55)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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

eTable 11. Hazard ratios and 95% confidence intervals (CIs) comparing the risk for ADHD and ASD in exposed and unexposed children in the sub-sample with at least one sibling with discordant antipsychotic exposure and outcome in the pooled data from Finland, Iceland, Norway, and Sweden (from 4533 clusters)

ADHD	No. with ADHD / N	Person-Years at risk	Crude	Model 1[a]	Model 2[b]
Standard analysis[c]					
Unexposed	290/674	6875	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	150/392	3068	1.45 (1.17-1.80)	1.21 (0.96-1.52)	1.15 (0.90-1.46)
Sibling analysis[d]					
Unexposed	290/674	6875	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	150/392	3068	1.21 (0.90-1.63)	1.12 (0.78-1.61)	1.10 (0.73-1.65)
ASD	**No. with ASD/ N**	**Person-Years at risk**	**Crude**	**Model 1[a]**	**Model 2[b]**
Standard analysis[c]					
Unexposed	84/236	2278	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	65/142	1126	1.70 (1.16-2.48)	1.19 (0.79-1.78)	1.17 (0.76-1.79)
Sibling analysis[d]					
Unexposed	84/236	2278	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Exposed anytime during pregnancy	65/142	1126	1.41 (0.92-2.17)	1.34 (0.79-2.28)	1.62 (0.83-3.16)

[a]Adjusted for source country, birth year, sex of child, maternal age, and parity

[b]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 (missing indicator rather than 2-stage calibration for this sensitivity analysis)

[c]Cox proportional hazards regression models and robust standard errors accounting for the clustering of siblings

[d]Cox proportional hazards regression models with stratification on sibling cluster

eTable 12. Distribution of exposures and outcomes among the siblings discordant on exposure and outcome or exposure only in the pooled data from Finland, Iceland, Norway, and Sweden

	ADHD				ASD			
Birth order	**1**	**2**	**3**	**4+**	**1**	**2**	**3**	**4+**
Discordant exposure and outcome within the sibling cluster								
Exposed, %	31.9	37.5	44.5	38.7	43.7	35.2	37.3	18.5
Outcome, %	69.2	33.1	17.5	6.5	62.0	32.4	16.4	14.8
Number of children	392	392	189	93	142	142	67	27
Discordant exposure only within the sibling cluster								
Exposed, %	45.2	38.0	37.3	31.0	45.2	38.0	37.3	31.0
Outcome, %	6.0	2.9	2.2	0.8	2.0	1.0	0.8	0.6
Number of children	4533	4533	1488	677	4533	4533	1488	677

We conducted a post-hoc sensitivity analysis to explore whether differences in point estimates from the primary analysis and the sibling analysis arose because the sibling analysis was performed in a selected population, i.e., children with at least one sibling with discordant antipsychotic exposure. In this sensitivity analysis, we compared estimates from a standard analysis and a sibling analysis both performed within the subgroup of children included in the sibling analysis in the pooled data from Finland, Iceland, Norway, and Sweden (N=4533 clusters). We restricted the cohort further to sibling clusters with both discordant exposures and outcomes, as these were the children that are informative in the sibling analysis.

Standard analysis: Cox proportional hazards regression models and robust standard errors accounting for the clustering of siblings (one baseline hazard for all subjects, standard errors accounted for the fact that siblings were expected to have more similar outcomes than unrelated individuals).

Sibling analysis: Cox proportional hazards regression models with stratification on sibling cluster (separate baseline hazards for each family, accounting for the differences between families attributed to factors that remain stable within the family, some of which were measured, e.g., mother's country of birth, and some unmeasured, e.g., genetic factors).

For ADHD, the estimates from the sibling analysis were slightly closer to the null than the standard analysis but very similar (eTable 11). For ASD, only the crude estimates were closer to the null. After adjusting for additional confounders, the sibling estimate was stronger, but with a wider confidence interval. For both ADHD and ASD, the fully adjusted HR from the analysis done in the standard way was close to the estimate from the primary adjusted analysis, suggesting that while the sibling sample was highly selected, it did not necessarily introduce selection bias once we controlled for measured confounders. Comparing the estimates from the sibling analysis to the standard analysis suggested that residual confounding by unmeasured familial factors was unsubstantial once we accounted for all measured confounders.

Hálfdánarson Ó, *et al*. *Evid Based Ment Health* 2021;0:1–9. doi: 10.1136/ebmental-2021-300311