Risks associated with antipsychotic treatment in pregnancy: Comparative cohort studies based on electronic health records

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Abstract

Background: Limited information is available on whether antipsychotics prescribed in pregnancy are associated with increased risks of adverse outcomes.

Methods: We used electronic health records from pregnant women and their children to examine risks of adverse maternal and child outcomes in three cohorts of women who: (A) received antipsychotic treatment in pregnancy (n = 416) (B) discontinued antipsychotic treatment before pregnancy (n = 670), and (C) had *no* records of antipsychotic treatment before or during pregnancy (n = 318,434). Absolute and risk ratios were estimated and adjusted for health and lifestyle and concomitant medications.

Results: Caesarean section was more common in cohort A (25%) than C (18%), but non-significant after adjustment for health and lifestyle factors (Risk Ratio (adj.) 1.09 (95% CI: 0.92, 1.30). Proportion of gestational diabetes was similar in cohort A (2.6%) and B (2.7%), but lower in A than B after adjustments (RRadj: 0.43 (0.20, 0.93). Premature birth/low birthweight were more common in cohort A (10%) than B (4.3%) and C (3.9%), A versus B (RRadj: 2.04 (1.13, 3,67), A versus C (RRadj: 1.43 (0.99, 2.05). Major congenital malformations were more common in A (3.4%), than B (2.2%) and C (2%). However no significant difference was observed (A versus B: RRadj: 1.79 (0.72, 4.47) A versus C RRadj: 1.59 (0.84, 3.00)). Risk estimates were similar for women prescribed atypical and typical antipsychotics.

Conclusions: Antipsychotic treatment in pregnancy carries limited risks of adverse pregnancy and birth outcomes once adjustments have been made for health and lifestyle factors.

1. Introduction

Antipsychotics are increasingly prescribed for schizophrenia, bipolar disorder and severe depression in women of child bearing potential (Hayes et al., 2011; Marston et al., 2014; Prah et al., 2012; Verdoux et al., 2010) as well as in pregnancy (Margulis et al., 2014; Petersen et al., 2014; Toh et al., 2013). However, no psychotropic medication has been licenced for use in pregnancy and the 2014 National Institute for Health and Care Excellence (NICE) guidelines on antenatal and postnatal mental health emphasised that there are limited data on the safety of the use of these drugs in pregnancy and the postnatal period.(National Institute for Health and Care Excellence (NICE), 2014) This leaves women and their health care professionals in a treatment dilemma as they strive to balance all aspects of the mother's health as well as that of the unborn child.

In this study we used electronic health records from United Kingdom to examine potential adverse effects of antipsychotic medication prescribed in pregnancy on maternal and child outcome before and after adjustment for a range of health and lifestyle factors as well as concomitant psychotropic medication. We compare women who received antipsychotic prescriptions in pregnancy against women who discontinued treatment before pregnancy as well as women not receiving antipsychotics.

2. Methods

We used data from two electronic health records data sources, The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD). These are large primary care databases that provide anonymised longitudinal general practice (family practice) data on patients' clinical and prescribing records and include data from around 10% of the United Kingdom population. Diagnoses and symptoms are recorded by practice staff using Read codes, which is a hierarchical coding system including more than 100,000 codes.(Chisholm, 1990; Davé and Petersen, 2009) The Read code system can be mapped to ICD-10, but in addition the Read codes include a number of symptoms and administrative codes.(Davé and Petersen, 2009) Information on weight, height, smoking habits, alcohol intake and illicit drug problems is also recorded as well as information on antenatal care and birth details, pregnancy outcomes and postnatal care. Prescriptions are issued electronically and directly recorded on the general practice computer systems. In addition, the databases holds individual patient level information about year of birth (month of birth for individuals below 15 years of age), date of registration, dates of death and transfer out of the practice. There is also a household identifier, which is the same for individuals who are registered with the same practice and live in the same household.

Over 98% of the UK population are registered with a general practitioner (GP, family doctor) (Lis and Mann, 1995) and the databases are broadly representative of the United Kingdom population.(Blak et al., 2011; Williams et al., 2012) However, Blak *et al.* demonstrated that THIN contained slightly more patients who lived in the most affluent areas.(Blak et al., 2011) While antenatal care is often shared between general practice staff and midwives, the GP remains responsible for women's general medical care during pregnancy including prescribing of medicines. Some women with psychosis also receive care from local National Health Service (NHS) mental health trusts, but most trusts have limited prescribing budgets and for most women prescribing of psychotropic medication remains with the GP during pregnancy and hence this information is available in THIN and CPRD.

During the late 1980's general practices started using computer systems for recording of consultations and patient managements and from the mid 1990's an increasing number became fully computerised. (Horsfall et al., 2013) In this study we utilised data from 1st January 1995 or when general practices met data quality standards.(Horsfall et al., 2013; Maguire et al., 2009; Williams et al., 2012)

Pregnancy and mother-child cohorts

We created a cohort of pregnant women using data from THIN for the period 1 January 1995 to 31 December 2012. We subsequently linked the pregnant women's clinical records to those of a child with the same household identifier if they were registered with the same general practice within six months after they were born. Our pregnancy cohort was based on the: recorded date of delivery of the women; antenatal records, postnatal care records; the first day of last menstrual period (LMP); the estimated delivery dates (EDD). A very small proportion (1%) of the pregnancy cohort was identified from LMP and antenatal records alone. In order to increase the sample sizes of the cohorts of women who were prescribed antipsychotics before and during pregnancy we combined records from THIN and CPRD. Some practices contributed data to both databases and therefore we de-duplicated the records as described by Cai *et al.*(Cai et al., 2010)

Cohorts

We defined three sub-cohorts based on antipsychotic prescriptions. **Cohort A** contained women with records of antipsychotic treatments two years before start of pregnancy *and* with records of antipsychotic treatment issued between 31 and 105 days (inclusive) after the start of pregnancy (covering the critical period for many major congenital malformations)). **Cohort B** contained women with records of antipsychotic treatment in the two years before start of pregnancy, but *no prescriptions issued after four weeks prior* to pregnancy start. **Cohort C** contained women with *no*

records of antipsychotic treatment in the two years before the start of pregnancy and through to the delivery date. Start of pregnancy was defined as the first day of LMP or 280 days before delivery if no records suggested a different duration of pregnancy.

To examine maternal outcomes we used the cohorts of pregnant women, while for the child outcomes we used the linked mother-child cohorts which were subsets of the pregnant cohorts including between 65 – 75% of the pregnancies. For *one* child outcome, *adverse birth outcome* (see below) we replaced cohort A with a cohort of 322 women who received antipsychotic prescriptions in the *last* trimester of pregnancy as this is a more relevant risk period for these outcomes. Of these, 274 met the criteria for the original cohort A.

Antipsychotics

We used all antipsychotics listed in British National Formulary (BNF) (https://www.medicinescomplete.com/about/publications.htm) chapter 4.2.1 except prochlorperazine which is primarily prescribed for 'morning sickness' in pregnancy. Appendix 1 includes the names of the relevant antipsychotics.

Outcomes

Following maternal outcomes were examined*:* pre-eclampsia, gestational hypertension, gestational diabetes, perinatal death, and caesarean section. These are all outcomes that have previously been examined in association with exposure to psychotropic medication in pregnancy (Coughlin et al., 2015; Reis and Källén, 2008). We included the following child outcomes: major congenital malformations, prematurity, low Apgar score (less than 7), low birth weight (less than 2500 g), , tremor, agitation, any breathing problems and problems with the infants' muscle tone. We combined prematurity and, low birth weight into one composite outcome which we refer to **premature/low birth weight outcome** and tremor, agitation, breathing and muscle tone problems, low Apgar score into a second composite outcome, which we refer to as **adverse birth outcomes**. This was done for several reasons. First, from a mother's (and health care professional's) perspective these outcomes are all signs of adverse birth outcomes and as they are all equally relevant, there is no obvious choice of one over the other as a primary outcome. Further, the clinical decision to stop psychotropic medication in pregnancy is often based on a general uncertainty about adverse effects rather than the risks of specific adverse outcomes.(Nordeng et al., 2010; Petersen et al., 2015) Finally, the use of composite outcomes reduces the number of statistical tests and may improve the statistical power of the study, albeit with the potential disadvantage that results relate to a cluster of outcomes that make up the composite outcome, and cannot be extrapolated to the individual components.(Freemantle et al., 2003)

Covariates

We extracted information from the women's electronic health records on: age at delivery, calendar year of delivery, obesity (body mass index of 30 or above recorded in the year before LMP, but not in pregnancy), illicit drug use, alcohol problem, smoking status, pre-existing medical conditions (depression, epilepsy, psychosis, hypertension, diabetes), prescriptions of concomitant medication listed in the BNF chapter 4 including antidepressants, anxiolytics, hypnotics, anticonvulsant mood stabilisers and lithium. As our data are clinical data and records of illicit drug use, alcohol problems and smoking status are not entered on regular basis we considered records made up to three years before LMP or in pregnancy.

Data analysis

We tabulated characteristics of the women and the outcomes for each of the cohorts A, B and C and where there were more than five events we tabulated the numbers, absolute risks and risk difference with 95% confidence intervals. We estimated relative risk ratios using Poisson regression. Comparisons were made between cohort A (women who had continued antipsychotic medication in the first part of pregnancy) and cohort B (women who had discontinued treatment before pregnancy) using the latter as reference category. Likewise, comparisons were made between cohort A and cohort C (women who had *not* been treated with antipsychotic medication) using the latter as reference category. In addition we stratified the cohorts on typical and atypical antipsychotics and estimated the absolute risks and risk differences, but as number of events for several outcomes were small we did not estimate relative risks.

Ethics

The scheme for THIN to obtain and provide anonymous patient data was approved by the National Health Service South-East Multicenter Research Ethics Committee (MREC) in 2002 and the CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies. Scientific approval for this study was obtained from CSD Medical Research's Scientific Review Committee and scientific approval for use of CPRD data was obtained from ISAC (protocol number 14_087R).

3. Results

In total, 319,520 women were included in the study. Of these, 416 received antipsychotic treatment in pregnancy and 670 received antipsychotics treatment before, but not in pregnancy (Table 1). The mean age of women who were prescribed antipsychotics in pregnancy (Cohort A) was 32 years compared to 30 years cohort B and C (Table 1). A higher proportion of women who continued antipsychotics in pregnancy (Cohort A) as well as those who discontinued (Cohort B) had records of

illicit drug use, alcohol problems, smoking and obesity than women not on treatment (Cohort C). Hence, of the women in Cohort A 14% and 8% in Cohort B had a previous record of illicit drug use in contrast to 0.6% of women in Cohort C. For obesity the figures were 17% in cohort A and 12% in cohort B versus 6.5% in cohort C (Table 1). More than 1 in 5 women who continued atypical antipsychotics in pregnancy were obese, far more than women on typical antipsychotics (Table 1).

Many women who continued antipsychotics in pregnancy were also prescribed other medications listed in BNF chapter 4. Thus, 57% also received antidepressant and 11% anticonvulsant treatment. In contrast less than 2% of the women in cohort C received antidepressants and less than 0.5% received anticonvulsant mood stabilisers.

The characteristics of women in the mother-child cohorts varied slightly from the distribution in the pregnancy cohorts (Table 2). More girls (54.5%) than boys (45.5%) were born to women in cohort A compared to cohort B and C (Table 2).

Women in cohort A were more likely to deliver by caesarean section (25% (104/416)) than women in cohort C (18% (58,532/318,434)) (Table 3a), but after adjustment for medication use and health and lifestyle factors there were no significant difference (Risk Ratio (adj.) 1.09 (95% CI 0.92 to 1.30) (Table 4). There was no difference in the risk of delivering by caesarean section between cohort A and B (table 4) and after adjustments, women in cohort A were at *lower* risk of developing gestational diabetes than women in cohort B (Risk Ratio (adj.): 0.43 (95% CI 0.20 to 0.93) (Table 4). Notably in this analysis, obesity was strongly associated with gestational diabetes (Risk Ratio (adj.) 5.49 (95% CI 2.67 to 11.2) (Table 4).

Ten out of 290 (3.4%) women prescribed antipsychotics in pregnancy (cohort A) gave birth to a child with a major congenital malformations in comparison to 2.2% in cohort B, and 2.1% in cohort C (Table 3a), but the associations were not statistically significant (A vs B, Risk Ratio (adj) 1.79 (95% CI 0.72 to 4.47); A vs C, Risk Ratio (adj) 1.59 95% CI 0.84 to 3.00)). Children of women prescribed antipsychotics in pregnancy (cohort A) were more than twice as likely to experience premature birth/low birth weight than children of women in both cohort B and C (Table 3a and 5). The risk attenuated after adjustments, but there remained a significant difference between cohort A and B (Risk Ratio adj 2.04 (95% CI 1.13 to 3,67) and borderline difference between cohort A and C (Risk Ratio adj 1.43 (95% CI 0.99 to 2.05) (Table 5).

Fourteen out of 233 (6%) women prescribed antipsychotics in the third trimester of pregnancy (cohort A) gave birth to a child which experienced an adverse birth outcome (tremor, agitation, breathing and muscle tone problems, low Apgar score) in comparison 4.7% in cohort B and 2.5% in

cohort C. However, after adjustments for concomitant medication use and health and lifestyle factors there were no statistically significant difference (Table 5).

There were no marked differences in the absolute risks and risk differences for women who received typical or atypical antipsychotics (Table 3b and 3c).

4. Discussion

Women prescribed antipsychotics in pregnancy (cohort A) were at higher risks of giving birth by caesarean section and to experience adverse birth outcomes than women *not* prescribed antipsychotics (cohort C). The effects attenuated after adjustment for health and lifestyle factors and concomitant medication and were no longer statistically significant. Children of women prescribed antipsychotics in pregnancy (cohort A) were more than twice as likely to experience premature birth/low birth weight compared to children of women in both cohort B and C. This risk attenuated, but remained elevated after adjustments.

The prevalence of gestational diabetes was similar among women from cohort A and B. However, there was a 3 to 5-fold increased risk among obese women irrespectively of antipsychotic treatment in pregnancy. Once adjustments were made for obesity, women who continued treatment in pregnancy (cohort A) had less of a risk of gestational diabetes than women who discontinued treatment before pregnancy (cohort B).

A major strength of our study is the comparative cohort design allowing for examination of a range of outcomes in women of different exposure status. A limitation of our study is that exposure status was based on prescription data, hence it is possible that some women would not have taken antipsychotic treatment in pregnancy although they were prescribed the medication, this would lead to a bias towards the null.

Previous research on antipsychotic treatment in pregnancy includes pharmacovigilance studies from drug companies' safety databases (Brunner et al., 2013; Goldstein et al., 2000) as well as cohort studies based on various data sources.(Boden et al., 2012; Diav-Citrin et al., 2005; Habermann et al., 2013; Kallen et al., 2013; Kulkarni et al., 2014; Lin et al., 2010; McKenna et al., 2005; Munk et al., 2005; Newham et al., 2008; Sadowski et al., 2013) A review published in 2009 on the use and safety of individual antipsychotics prescribed in pregnancy found no definite associations between antipsychotic use during pregnancy and adverse perinatal outcomes.(Einarson and Boskovic, 2009) The review highlighted, however, the occurrence of weight gain in women on atypical antipsychotics; a risk factor for both hypertension and diabetes which in turn exert their own risk on pregnancy outcomes.(Anderson et al., 2005; Henderson, 2007) Our findings suggest that the risks

of gestational diabetes may operate via obesity in women treated with antipsychotics both before and during pregnancy, but our study was not designed to evaluate whether antipsychotics have a direct impact on weight gain during pregnancy.

A recent review suggested that women requiring antipsychotic treatment during pregnancy have a higher risk of adverse birth outcomes although most studies in the review made limited adjustment for potential confounding.(Coughlin et al., 2015) A Canadian study sought to account for confounding by matching treated and un-treated women on a range of factors and as a result found no differences .(Vigod et al., 2015)

Our study results are similar to a Swedish birth register study on women who reported antipsychotics use in early pregnancy. (Reis and Källén, 2008) Thus, the Swedish study reported an elevated risk of preterm birth (Odds Ratios: 1.73 (95% CI 1.31 to 2.29) and low birth weight (OR: 1.67 (95% CI 1.21–2.29)). Initially the study also found a significant association between antipsychotic exposure in pregnancy and severe congenital malformations (OR 1.52 (95% CI 1.05 to 2.19)) mainly due to cardiovascular defects (atrium or ventricular septum defects), but after exclusion of women exposed to concomitant anticonvulsant medication, the odds ratio attenuated and was no longer statistically significant.(Reis and Källén, 2008)

Risks of extrapyramidal and withdrawal syndromes associated with third trimester exposure of first generation antipsychotics have long been recognised (Falterman and Richardson, 1980) and the US Food and Drug Administration (FDA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) updated their advice on the risks of extrapyramidal and withdrawal syndromes in 2011.("Antipsychotics: risk of extrapyramidal effects or withdrawal symptoms in newborns Drug Safety Update - GOV.UK," n.d.) Our estimates of adverse pregnancy outcomes attenuated substantially after adjustment for concomitant medication, health and life style factors. Likewise, Vigod *et al.* observed a seven-fold increased risk for neonatal adaptation syndrome, but this was reduced to a small non-significant relative risk in a matched cohort analysis, suggesting that the observed patterns may be due to confounding by concomitant medication use as well as other factors such as alcohol and substance misuse.(Vigod et al., 2015) Like others we also observed a high prevalence of smokers and individuals with illicit drug problems as well as other factors that may have an inverse impact on pregnancy outcomes.(Taylor et al., 2015)

5. Conclusions

Women receiving antipsychotic treatment in pregnancy are of higher risk of a range of adverse pregnancy outcomes. Except from low birth weight/premature birth, our results suggest that rather

than being specific associations/effects with antipsychotics, these increased risks may be associated with other health and lifestyle factors which are more common in this group of women. These include greater levels of obesity, smoking, alcohol problems, concomitant medication and illicit drug use. It may therefore be counterproductive to discontinue antipsychotic treatment in pregnancy where such treatment is judged to carry important benefits for the mental health of the mother.

6. Disclosures and acknowledgements

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PJC has in the last three years been a paid member of an advisory boards of Lundbeck. CJS has received funding for research from Novartis Vaccines and Diagnostics. IP supervises a PhD student who is sponsored by Novo Nordisk. IN is currently member of the NIHR HTA commissioning board.

Table 1 Characteristics of women prescribed antipsychotics in pregnancy (Cohort A) versus women who discontinued (Cohort B) and women not prescribed antipsychotics (Cohort C)

	Typical antipsychotics				Atypical antipsychotics				All antipsychotics				No antipsychotics	
Cohort	A	(%)	B	(%)	A	(%)	B	(%)	A	(%)	B	(%)	C	(%)
Total	157	(100)	406	(100)	280	(100)	302	(100)	416	(100)	670	(100)	318,434	(100)
Age (years)														
Mean (SD)	*32*	*(5.8)*	*30*	*(5.7)*	*32*	*(5.7)*	*30*	*(6.1)*	*32*	*(5.8)*	*30*	*(5.9)*	*30*	*(5.9)*
12-19	0	(0)	10	(2.5)	0	(0)	12	(4)	0	(0)	21	(3.1)	14,004	(4.4)
20(29	49	(31.2)	185	(45.6)	91	(32.5)	128	(42.4)	136	(32.7)	291	(43.4)	123,704	(38.8)
30(39	91	(58)	196	(48.3)	163	(58.2)	144	(47.7)	238	(57.2)	326	(48.7)	165,353	(51.9)
40(49	17	(10.8)	15	(3.7)	26	(9.3)	18	(6	42	(10.1)	32	(4.8)	15,373	(4.8)
Year														
1995(1999	14	(8.9)	42	(10.3)	1	(0.4)	1	(0.3)	14	(3.4)	42	(6.3)	46,548	(14.6)
2000(2004	49	(31.2)	161	(39.7)	19	(6.8)	31	(10.3)	63	(15.1)	184	(27.5)	80,542	(25.3)
2005(2009	50	(31.8)	132	(32.5)	78	(27.9)	115	(38.1)	120	(28.8)	232	(34.6)	99,765	(31.3)
2010(2012	44	(28)	71	(17.5)	182	(65)	155	(51.3)	219	(52.6)	212	(31.6)	91,579	(28.8)
Lifestyle variables														
Smoker	66	(42)	164	(40.4)	141	(50.4)	110	(36.4)	195	(46.9)	254	(37.9)	62,746	(19.7)
Illicit drug use	21	(13.4)	39	(9.6)	37	(13.2)	23	(7.6)	56	(13.5)	56	(8.4)	2,002	(0.6)
Alcohol problems	12	(7.6)	21	(5.2)	19	(6.8)	21	(7)	29	(7)	37	(5.5)	1,624	(0.5)
Obesity	18	(11.5)	40	(9.9)	60	(21.4)	46	(15.2)	72	(17.3)	77	(11.5)	20,554	(6.5)
BMI														
Mean (SD)	*28*	*(7.3)*	*27*	*(6.7)*	*29*	*(6.2)*	*28*	*(6.8)*	*28*	*(6.5)*	*27*	*(6.8)*	*26*	*(6.3)*
Missing	105	(66.9)	276	(68)	146	(52.1)	187	(61.9)	241	(57.9)	443	(66.1)	232,039	(72.9)
Use of psychiatric drugs during exposure period A														
Anticonvulsant mood stabilisers	14	(8.9)	9	(2.2)	32	(11.4)	9	(3)	44	(10.6)	15	(2.2)	1,305	(0.4)
Lithium	2	(1.3)	2	(0.5)	12	(4.3)	2	(0.7)	13	(3.1)	4	(0.6)	11	(0)
Antipsychotics	157	(100)	0	0	280	(100)	0	(0)	416	(100)	0	(1)	0	(0)
Antidepressants	90	(57.3)	82	(20.2)	163	(58.2)	79	(26.2)	238	(57.2)	150	(22.4)	5942	(1.9)
Anxiolytics	17	(10.8)	23	(5.7)	34	(12.1)	13	(4.3)	48	(11.5)	33	(4.9)	805	(0.3)
Hypnotics	29	(18.5)	20	(4.9)	41	(14.6)	17	(5.6)	63	(15.1)	32	(4.8)	598	(0.2)
Pre(existing medical conditions														
Depression	39	(24.8)	134	(33	69	(24.6)	97	(32.1)	105	(25.2)	217	(32.4)	20,374	(6.4)
Epilepsy	10	(6.4)	21	(5.2)	21	(7.5)	10	(3.3)	31	(7.5)	30	(4.5)	4,846	(1.5)
SMI	85	(54.1)	87	(21.4)	183	(65.4)	137	(45.4)	250	(60.1)	204	(30.4)	1,480	(0.5)
Pre(existing hypertension	28	(17.8)	42	(10.3)	34	(12.1)	28	(9.3)	57	(13.7)	66	(9.9)	26,232	(8.2)
Pre(existing diabetes	3	(1.9)	7	(1.7)	7	(2.5)	3	(1)	9	(2.2)	9	(1.3)	2,762	(0.9)

Table 2 Characteristics of women in the *mother-child cohort* prescribed antipsychotics in pregnancy (Cohort A) versus women who discontinued (Cohort B) and women not prescribed antipsychotics (Cohort C)

	Typical antipsychotics				**Atypical antipsychotics**				**All antipsychotics**				**No antipsychotics**	
Cohort	**A**	**(%)**	**B**	**(%)**	**A**	**(%)**	**B**	**(%)**	**A**	**(%)**	**B**	**(%)**	**C**	**(%)**
Total	102		292		203		230		290		492		210,966	
Age (years)														
Mean (SD)	*32*	*(5.8)*	*30*	*(5.5)*	*32*	*(5.5)*	*30*	*(6.1)*	*32*	*(5.6)*	*30*	*(5.7)*	*30*	*(5.9)*
12-19	0	(0)	5	(1.7)	0	(0)	8	(3.5)	0	(0)	12	(2.4)	8,955	(4.2)
20(29	32	(31.4)	140	(47.9)	63	(31)	99	(43)	92	(31.7)	222	(45.1)	80,491	(38.2)
30(39	59	(57.8)	138	(47.3)	119	(58.6)	110	(47.8)	166	(57.2)	236	(48)	110,839	(52.5)
40(49	11	(10.8)	9	(3.1)	21	(10.3)	13	(5.7)	32	(11)	22	(4.5)	10,681	(5.1)
Year														
1995(1999	9	(8.8)	25	(8.6)	1	(0.5)	0	(0)	9	(3.1)	25	(5.1)	13,339	(6.3)
2000(2004	30	(29.4)	119	(40.8)	13	(6.4)	22	(9.6)	40	(13.8)	134	(27.2)	46,707	(22.1)
2005(2009	32	(31.4)	99	(33.9)	57	(28.1)	85	(37)	82	(28.3)	173	(35.2)	77,626	(36.8)
2010(2012	31	(30.4)	49	(16.8)	132	(65)	123	(53.5)	159	(54.8)	160	(32.5)	73,294	(34.7)
Lifestyle variables														
Smoker	51	(50)	120	(41.1)	99	(48.8)	77	(33.5)	139	(47.9)	183	(37.2)	42,502	(20.1)
Illicit drug use	15	(14.7)	27	(9.2)	24	(11.8)	17	(7.4)	37	(12.8)	40	(8.1)	1,354	(0.6)
Alcohol problems	10	(9.8)	16	(5.5)	15	(7.4)	17	(7.4)	23	(7.9)	28	(5.7)	1,124	(0.5)
Obesity	11	(10.8)	31	(10.6)	45	(22.2)	38	(16.5)	53	(18.3)	62	(12.6)	15,363	(7.3)
BMI														
Mean (SD)	*28*	*(7.6)*	*27*	*(6.9)*	*29*	*(6.3)*	*28*	*(6.7)*	*28*	*(6.7)*	*27*	*(6.8)*	*26*	*(6.4)*
Missing	67	(65.7)	192	(65.8)	105	(51.7)	139	(60.4)	164	(56.6)	315	(64)	148,897	(70.6)
Use of psychiatric drugs during exposure period A														
Antiepileptics	8	(7.8)	8	(2.7)	21	(10.3)	9	(3.9)	27	(9.3)	14	(2.8)	887	(0.4)
Lithium	1	(1)	1	(0.3)	10	(4.9)	1	(0.4)	11	(3.8)	2	(0.4)	7	(0)
Antipsychotics	102	(100)	0	(0)	203	(100)	0	(0)	290	(100)	0	(0)	0	(0)
Antidepressants	61	(59.8)	61	(20.9)	118	(58.1)	73	(31.7)	169	(58.3)	124	(25.2)	4351	(2.1)
Anxiolytics	12	(11.8)	14	(4.8)	21	(10.3)	13	(5.7)	31	(10.7)	24	(4.9)	523	(0.2)
Hypnotics	19	(18.6)	16	(5.5)	26	(12.8)	17	(7.4)	41	(14.1)	28	(5.7)	423	(0.2)
Pre(existing medical conditions														
Depression	30	(29.4)	94	(32.2)	52	(25.6)	68	(29.6)	79	(27.2)	152	(30.9)	14,626	(6.9)
Epilepsy	7	(6.9)	16	(5.5)	10	(4.9)	7	(3)	17	(5.9)	22	(4.5)	3,254	(1.5)
SMI	57	(55.9)	63	(21.6)	135	(66.5)	96	(41.7)	180	(62.1)	144	(29.3)	882	(0.4)
Pre(existing hypertension	20	(19.6)	28	(9.6)	25	(12.3)	22	(9.6)	42	(14.5)	47	(9.6)	19,570	(9.3)
Pre(existing diabetes	2	(2)	5	(1.7)	6	(3)	2	(0.9)	7	(2.4)	6	(1.2)	2,005	(1)
Child characteristics														
Males	52	(51)	143	(49)	90	(44.3)	121	(52.6)	132	(45.5)	253	(51.4)	107,979	(51.2)
Females	50	(49)	149	(51)	113	(55.7)	109	(47.4)	158	(54.5)	293	(48.6)	102,987	(48.8)

Days of child follow up, median(Inter Quartile Range)	909	(490, 1595)	1,102	(392, 1979)	551	(245, 882)	638	(303, 1408)	657	(286, 1351)	834	(353, 1758)	738	(349, 1416)
Days to Major Congenital Malformations record, median(IQR)	110	(90, 333)	169	(54, 934)	43	(8, 7)	48	(1, 1167)	85	(21, 110)	136	(33,1167)	50	(10, 120)

Table 3a. Absolute risks and risk differences of adverse maternal and child outcomes associated with antipsychotic treatment in pregnancy

	Absolute risk (%)						Risk Difference (95% CI)			
	A		B		C		A vs B		A vs C	
Maternal outcomes										
Total # in cohort	416	(100)	670	(100)	318,434	(100)	-	-	-	-
Pre-eclampsia	18	(4.3)	28	(4.2)	9355	(2.9)	0.1	(-2.3, 2.6)	1.4	(-0.6, 3.3)
Gestational diabetes	11	(2.6)	18	(2.7)	5227	(1.6)	<0.1	(-2, 1.9)	1.0	(-0.5, 2.5)
Caesarean section	104	(25)	145	(21.6)	58532	(18.4)	3.4	(-1.8, 8.6)	**6.6**	**(2.5, 10.8)**
Perinatal death	<5		<5		931	(0.3)	-	-	-	-
Child outcomes										
Total # in cohort	290	(100)	492	(100)	210966	(100)	-	-	-	-
Major congenital malformations	10	(3.4)	11	(2.2)	4162	(2)	1.2	(-1.3, 3.7)	1.5	(-0.6, 3.6)
Premature/low birth weight outcome	29	(10)	21	(4.3)	8319	(3.9)	**5.7**	**(1.8, 9.6)**	**6.1**	**(2.6, 9.5)**
Adverse birth outcome**	14	(6)	23	(4.7)	5290	(2.5)	1.3	(-2.2, 4.9)	3.5	(0.4, 6.6)

* Cohort A: Women prescribed antipsychotics in pregnancy, B: Women who discontinued antipsychotics before pregnancy, C: Women who were not on antipsychotic treatment.

**For this outcome cohort A comprises women prescribed antipsychotics in third trimester (N = 233)

Table 3b Absolute risks and risk differences of adverse maternal and child outcomes associated with ***typical*** antipsychotic treatment in pregnancy

	Absolute risk (%)						Risk Difference (95% CI)			
	A		B		C		A vs B		A vs C	
Maternal outcomes										
Total # in cohort	157	(100)	406	(100)	318434	(100)				
Pre-eclampsia	8	(5.1)	17	(4.2)	9355	(2.9)	0.9	(-3, 4.9)	2.2	(-1.3, 5.6)
Gestational diabetes	<5		8	(2)	5227	(1.6)	-	-	-	-
Caesarean section	42	(26.8)	85	(20.9)	58532	(18.4)	5.8	(-2.2, 13.8)	**8.4**	**(1.4, 15.3)**
Perinatal death	<5		<5		931	(0.3)	-	-	-	-
Child outcomes										
Total # in cohort	102	(100)	292	(100)	210,966	(100)				
MCM	<5		8	(2.7)	4162	(2)	-	-	-	-
Premature/low birth weight outcome	12	(11.8)	14	(4.8)	8319	(3.9)	**7**	**(0.3, 13.7)**	**7.8**	**(1.6, 14.1)**
Adverse birth outcome**	5	(6.1)	14	(4.8)	5290	(2.5)	1.3	(-4.4, 7)	3.6	(-1.6, 8.8)

* Cohort A: Women prescribed typical antipsychotics in pregnancy, B: Women who discontinued typical antipsychotics before pregnancy, C: Women who were not on antipsychotic treatment.

**For this outcome cohort A comprises women prescribed typical antipsychotics in third trimester

Table 3c Absolute risks and risk differences of adverse maternal and child outcomes associated with ***atypical*** antipsychotic treatment in pregnancy

	Absolute risk (%)						Risk Difference (95% confidence interval)			
	A		B		C		A vs B		A vs C	
Maternal outcomes										
Total # in cohort	280	(100)	302	(100)	318,434	(100)				
Pre-eclampsia	12	(4.3)	14	(4.6)	9355	(2.9)	-0.4	(-3.7, 3)	1.3	(-1, 3.7)
Gestational diabetes	9	(3.2)	11	(3.6)	5227	(1.6)	-0.4	(-3.4, 2.5)	1.6	(-0.5, 3.6)
Caesarean section	69	(24.6)	67	(22.2)	58532	(18.4)	2.5	(-4.4, 9.3)	**6.3**	**(1.2, 11.3)**
Perinatal death	<5		<5		931	(0.3)	-	-	-	-
Child outcomes										
Total # in cohort	203	(100)	230	(100)	210,966	(100)				
MCM	7	(3.4)	<5		4162	(2)	-	-	1.5	(-1, 4)
Premature/low birth weight outcome	17	(8.4)	9	(3.9)	8319	(3.9)	4.5	(-0.1, 9)	**4.4**	**(0.6, 8.2)**
Adverse birth outcome**	9	(5.7)	9	(3.9)	5290	(2.5)	1.8	(-2.6, 6.2)	3.2	(-0.4, 6.9)

* Cohort A: Women prescribed atypical antipsychotics in pregnancy, B: Women who discontinued atypical antipsychotics before pregnancy, C: Women who were not on antipsychotic treatment.

**For this outcome cohort A comprises women prescribed atypical antipsychotics in third trimester

Table 4 Relative risks of adverse pregnancy outcomes associated with antipsychotic treatment in pregnancy. Results from crude and adjusted Poisson regression models

	Relative risk ratios (95% CI)		P values	Relative risk ratios (95% CI)		P values
Cohort comparisons	A vs. B			A vs. C		
Pre-eclampsia	1.03	(0.57, 1.87)	0.908	1.47	(0.92, 2.33)	0.100
Pre-eclampsia (adjusted)	0.69	(0.37, 1.29)	0.248	1.24	(0.79, 1.96)	0.342
Age (tertiles**)**						
1	1			1		
2	1.11	(0.54, 2.30)		0.99	(0.94, 1.04)	
3	1.17	(0.55, 2.47)		**1.19**	**(1.13, 1.24)**	
Obesity	**2.37**	**(1.27, 4.41)**		**1.92**	**(1.80, 2.06)**	
Alcohol problems	1.27	(0.43, 3.74)		0.77	(0.56, 1.07)	
Smoker	0.92	(0.52, 1.63)		0.83	(0.78, .880)	
Illicit drug use	1.49	(0.68, 3.28)		0.94	(0.72, 1.22)	
Antidepressants	**2.26**	**(1.19, 4.29)**		**1.20**	**(1.05, 1.37)**	
Anticonvulsants	1.02	(0.35, 2.98)		1.13	(0.85, 1.51)	
Gestational diabetes	0.98	(0.46, 2.08)	0.966	1.61	(0.89, 2.91)	0.114
Gestational diabetes (adjusted)	**0.43**	**(0.20, 0.93)**	**0.032**	0.95	(0.53, 1.69)	0.867
Age (tertiles**)**						
1	1			1		
2	2.17	(0.71, 6.61)		**1.59**	**(1.48, 1.71)**	
3	**3.17**	**(1.01, 9.90)**		**2.46**	**(2.30, 2.64)**	
Obesity	**5.49**	**(2.67, 11.2)**		**3.32**	**(3.08, 3.57)**	
Alcohol problems	0.50	(0.07, 3.56)		0.92	(0.61, 1.37)	
Smoker	1.39	(0.64, 3.02)		0.86	(0.80, .930)	
Illicit drug use	-	-		1.21	(0.87, 1.67)	
Antidepressants	**3.73**	**(1.75, 7.96)**		**1.51**	**(1.29, 1.75)**	
Anticonvulsants	1.54	(0.53, 4.45)		0.96	(0.65, 1.42)	
Caesarean section	1.15	(0.89, 1.48)	0.261	**1.36**	**(1.12, 1.64)**	**0.001**
Caesarean section (adjusted)	1.05	(0.82, 1.34)	0.671	1.09	(0.92, 1.30)	0.278
Age (tertiles**)**						
1	1			1		
2	1.23	(0.89, 1.68)		**1.32**	**(1.29, 1.34)**	
3	**1.79**	**(1.34, 2.40)**		**1.67**	**(1.64, 1.70)**	
Obesity	**1.45**	**(1.10, 1.90)**		**1.55**	**(1.51, 1.59)**	
Alcohol problems	0.97	(0.61, 1.54)		0.98	(0.88, 1.09)	
Smoker	0.99	(0.78, 1.25)		0.98	(0.96, 1.00)	
Illicit drug use	1.21	(0.85, 1.72)		0.98	(0.89, 1.08)	
Antidepressants	0.95	(0.74, 1.22)		**1.16**	**(1.10, 1.21)**	
Anticonvulsants	1.02	(0.64, 1.62)		**1.17**	**(1.06, 1.29)**	

The adjusted models includes adjustment for age, obesity, alcohol problems, smoking, illicit drug use, and antidepressant prescribing and nticonvulsant mood stabilisers

Table 5 Relative risks of adverse child outcomes associated with antipsychotic treatment in pregnancy. Results from crude and adjusted Poisson regression models.

Cohort comparisons	Relative risk ratios (95% CI) A vs. B		P values	Relative risk ratios (95% CI) A vs. C		P values
Major Congenital Malformations	1.54	(0.65, 3.63)	0.321	1.74	(0.93, 3.25)	0.077
Major Congenital Malformations (adjusted)	1.79	(0.72, 4.47)	0.207	1.59	(0.84, 3.00)	0.148
Age (tertiles)						
1	1			1		
2	1.33	(0.42, 4.16)		0.92	(0.86, 1.00)	
3	1.28	(0.65, 3.63)		1.01	(0.94, 1.09)	
Obesity	0.57	(0.72, 4.47)		0.99	(0.87, 1.12)	
Alcohol problems	-	-		1.10	(0.75, 1.62)	
Smoker	0.14	(0.03,0.62)		1.03	(0.95, 1.11)	
Illicit drug use	-	-		1.03	(0.72, 1.48)	
Antidepressants	0.89	(0.37, 2.17)		1.01	(0.82, 1.24)	
Anticonvulsants	-	-		**1.68**	**(1.18, 2.40)**	
Premature/low birth weight outcome	**2.34**	**(1.33, 4.10)**	**0.003**	**2.53**	**(1.76, 3.65)**	**<0.001**
Premature/low birth weight outcome (adjusted)	**2.04**	**(1.13, 3.67)**	**0.017**	1.43	(0.99, 2.05)	0.052
Age (tertiles)						
1	1			1		
2	0.98	(0.49, 1.95)		0.95	(0.90, 1.00)	
3	1.01	(0.52, 1.98)		1.03	(0.98, 1.09)	
Obesity	0.89	(0.42, 1.84)		**1.13**	**(1.04, 1.23)**	
Alcohol problems	0.41	(0.10, 1.59)		1.21	(0.97, 1.51)	
Smoker	0.99	(0.56, 1.74)		**1.39**	**(1.33, 1.46)**	
Illicit drug use	1.78	(0.89, 3.54)		**1.94**	**(1.64, 2.29)**	
Antidepressants	1.44	(0.81, 2.56)		**1.55**	**(1.38, 1.73)**	
Anticonvulsants	1.13	(0.43, 2.91)		**1.37**	**(1.06, 1.76)**	
Adverse birth outcome**	1.28	(0.66, 2.49)	0.459	**2.39**	**(1.41, 4.04)**	**0.001**
Adverse birth outcome (adjusted)**	1.03	(0.50, 2.12)	0.927	1.46	(0.87, 2.46)	0.151
Age (tertiles)						
1	1			1		
2	1.79	(0.80, 4.01)		0.85	(0.80, .915)	
3	1.41	(0.59, 3.36)		0.95	(0.89, 1.01)	
Obesity	1.45	(0.67, 3.11)		**1.38**	**(1.25, 1.51)**	
Alcohol problems	1.49	(0.45, 4.91)		**1.41**	**(1.07, 1.86)**	
Smoker	1.52	(0.80, 2.90)		**1.24**	**(1.16, 1.32)**	
Illicit drug use	1.01	(0.37, 2.74)		**1.61**	**(1.26, 2.04)**	
Antidepressants	0.77	(0.39, 1.54)		**1.55**	**(1.32, 1.84)**	
Anticonvulsants	**4.11**	**(1.66, 10.1)**		**1.56**	**(1.15, 2.13)**	

adjusted models includes adjustment for age, obesity, alcohol problems, smoking, illicit drug use, and antidepressant prescribing and anticonvulsant mood stabilisers. **For this outcome cohort A comprises women prescribed antipsychotics in third trimester

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