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Antipsychotic drug use in pregnancy: A multinational study from ten countries

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ABSTRACT

Aim: To compare the prevalence and trends of antipsychotic drug use during pregnancy between countries across four continents.
Methods: Individually linked health data in Denmark (2000−2012), Finland (2005–2014), Iceland (2004–2017), Norway (2005–2015), Sweden (2006–2015), Germany (2006–2015), Australia (New South Wales, 2004–2012), Hong Kong (2001–2015), UK (2006–2016), and the US (Medicaid, 2000–2013, and IBM MarketScan, 2012–2015) were used. Using a uniformed approach, we estimated the prevalence of antipsychotic use as the proportion of pregnancies where a woman filled at least one antipsychotic prescription within three months before pregnancy until birth. For the Nordic countries, data were meta-analyzed to investigate maternal characteristics associated with the use of antipsychotics.
Results: We included 8,394,343 pregnancies. Typical antipsychotic use was highest in the UK (4.4%) whereas atypical antipsychotic use was highest in the US Medicaid (1.5%). Atypical antipsychotic use increased over time in most populations, reaching 2% in Australia (2012) and US Medicaid (2013). In most countries, prochlorperazine was the most commonly used typical antipsychotic and quetiapine the most commonly used atypical antipsychotic. Use of antipsychotics decreased across the trimesters of pregnancy in all populations except Finland. Antipsychotic use was elevated among smokers and those with parity ≥4 in the Nordic countries.
Conclusion: Antipsychotic use during pregnancy varied considerably between populations, partly explained by varying use of the typical antipsychotic prochlorperazine, which is often used for nausea and vomiting in early pregnancy. Increasing usage of atypical antipsychotics among pregnant women reflects the pattern that was previously reported for the general population.

1. Introduction

Antipsychotic drugs are often prescribed as the standard of care for schizophrenia, other psychotic disorders and bipolar disorder. They

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are also prescribed, but to a lesser degree, for depression, anxiety, insomnia, autism, as well as for nausea and vomiting in early pregnancy (Halfdanarson et al., 2017; Minami et al., 2019; Toh et al., 2013). The mechanism of action and indications differ to a varying degree between typical (first generation) antipsychotics and the more recently introduced atypical (second generation) antipsychotics. In general, atypical antipsychotics have a stronger serotonin receptor antagonism, and are used to treat mood disorders to a larger extent.

Discontinuation of antipsychotic treatment during pregnancy may increase the risk of recurrence of mental disorders including bipolar disorder (Viguera et al., 2007) and psychosis (Tosato et al., 2017). On the other hand, potential risks associated with antipsychotic use during pregnancy include metabolic disturbances, abnormal fetal growth (Boden et al., 2012b), preterm birth (Lin et al., 2010), as well as congenital anomalies (Huybrechts et al., 2016). However, findings to date are not consistent and some increased risks for adverse outcomes may be illness-rather than drug-related (Boden et al., 2012a). Thus, women treated with antipsychotics and their clinicians, are faced with the complex challenge of balancing the benefits and potential risks of antipsychotic drug treatment during pregnancy.

Since the introduction of the first antipsychotic, chlorpromazine, in the 1950s, various antipsychotics have been developed, and studies have found increasing use of antipsychotics in the general population in recent years (Halfdanarson et al., 2017; Olfson et al., 2012). At the same time, a widening of both on- and off-label antipsychotic indications has been observed (Halfdanarson et al., 2017; Hojlund et al., 2019). However, little is known about the worldwide patterns of antipsychotic use among pregnant women.

To enable international comparisons and to inform future studies investigating the benefits and risks associated with antipsychotic use in pregnancy, our aim was to describe antipsychotic drug use during pregnancy and the three months before by type of antipsychotic, trends in prevalence and the characteristics of users in ten countries: Australia, Denmark, Finland, Germany, Hong Kong, Iceland, Norway, Sweden, the United Kingdom (UK), and the United States (US).

2. Methods

2.1. Study population

The study included pregnancies from 11 populations in 10 countries with pregnancies ending in live births or stillbirths. The full population is included in the Nordic countries data registries, while the datasets from the other countries are selected samples. However, the German and UK data sources are considered representative of their respective populations, and the databases from Hong Kong, Australia, and the two US databases combined, include the majority of the women giving birth in their respective regions. The data sources are described in Panel 1 and below.

From the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) we used population-based birth and dispensed prescription drug registers which were individually-linked using the civil personal registration number, uniquely assigned to each resident at birth or immigration (Furu et al., 2010; Langhoff-Roos et al., 2014).

From New South Wales (NSW), the most populous state in Australia, we used population-based birth data and dispensed pharmaceutical claims data which were probabilistically linked using identifiers including name, address, and date of birth (Tran et al., 2017). The study population was restricted to pregnancies among concessional beneficiaries, eligible for reduced co-payments due to low income, chronic illness, or disability, representing 20.3% of births in NSW, 2006–2012, for whom complete dispensing data are recorded.

From Germany, we used the German Pharmacoepidemiological Research Database (GePaRD) which is based on claims data from four statutory health insurance providers, currently including information on about 25 million persons from all geographical regions of Germany, representative of all persons with a statutory health insurance in Germany, which is about 90% of the population. We identified pregnancies from this database using an algorithm based on diagnostic and health care codes (Wentzell et al., 2018).

From Hong Kong, we used the pregnancy cohort nested in the electronic health records of the Clinical Data Analysis and Reporting System (CDARS), which covers health care services available to all residents in Hong Kong (Lao et al., 2017). CDARS contains deterministic linkage of the records of all in-patient, out-patient, and emergency room admissions in hospital ambulatory clinics, drug prescription and dispensing, through a unique patient identification number (Man et al., 2017).

From the UK, we used data from The Health Improvement Network (THIN), a large primary care database that includes longitudinal clinical and prescribing records from general practice and includes data from about 6% of the UK population. Over 98% of the UK population is registered with a general practitioner, and the register is broadly representative of the UK population (Petersen et al., 2017).

From the US, we included a pregnancy cohort nested within the Medicaid Analytic eXtract (MAX) database which includes inpatient and outpatient claims, as well as outpatient prescriptions dispensed for publicly-insured individuals from 46 US states and the District of Columbia (Palmsten et al., 2013). We also included a pregnancy cohort nested within the IBM MarketScan© Commercial Claims and Encounters Database, which includes similar healthcare claims from privately-insured individuals from all regions of the US (MacDonald et al., 2019).

2.2. Drug exposure

Antipsychotic drugs were defined using the World Health Organization Anatomical Therapeutic Chemical (ATC) classification codes starting with N05A. Lithium (N05AN01) was excluded because it has a different mechanism of action. Prochlorperazine (N05AB04) was not captured in the data from Australia and Finland and was not approved in Germany and Hong Kong. Typical and atypical antipsychotic drugs were classified according to Supplementary Table 1.

Use of Antipsychotics any time during the pregnancy period was defined by at least one filled prescription for an antipsychotic drug from 90 days before the first day of the last menstrual period (LMP) until birth. We also classified use according to trimester including the three-month pre-pregnancy period (up to 90 days before LMP), first trimester (T1 = 0–97 days of gestation), second trimester (T2 = 98–202 days of gestation), and third trimester (T3 = 203

days of gestation to birth). The trimester definitions used in the Finnish data were as follows: T1 = 0–84, T2 = 85–182, and T3 = 183 days of gestation to birth.

2.3. Data analysis

The prevalence of antipsychotic use (any, typical, atypical) was calculated as the proportion of pregnancies in each population where the woman had filled at least one prescription for an antipsychotic drug from 90 days before the first day of LMP and throughout the whole pregnancy period. We described prevalence by maternal age category and by trimester. To assess the relative change in use of antipsychotics across calendar years, we calculated the prevalence ratios with 95% confidence intervals (CI) between the first and last year of available data for each population by antipsychotic class, with the first year as the reference. In addition, linear time trends in prevalence were calculated using linear regression models. The resulting linear regression estimate (β) can be interpreted as the average percentage point change in prevalence per year.

Further, among each population we identified the five most commonly dispensed antipsychotics in the first and last year of available data. As prochlorperazine is almost exclusively used as an antiemetic during pregnancy (Fiaschi et al., 2019), we performed sub-analyses

Panel 1
Study populations and data source characteristics.

Country and years of coverage	Data sources and study populations	Pregnancies included	Drug information available
Australia, New South Wales (NSW) 2004–2012	a) NSW Perinatal Data Collection (state-wide birth register) b) Pharmaceutical Benefits Scheme (national claims data) Publicly insured	All pregnancies resulting in live birth or stillbirth from 20 weeks of gestation or birthweight of at least 400 g Only pregnancies among women who were concessional beneficiaries (eligible for increased subsidy for prescription drugs) were included	All dispensed, subsidised prescription drugs in outpatient care and private hospitals
Denmark 2000–2012	a) Medical Birth Register b) National Prescription Registry (National health registers) Publicly insured	All pregnancies resulting in live birth or stillbirth from 22 weeks of gestation	All dispensed prescription drugs in outpatient care
Finland 2005–2014	a) Medical Birth Register b) Register of Reimbursed Drug Purchases and Register of Medical Special Reimbursements (National health registers) Publicly insured	All pregnancies resulting in live birth or stillbirth from 22 weeks of gestation	All dispensed, reimbursed prescription drugs in outpatient care
Germany 2006–2015	German Pharmacoepidemiological Research Database (GePaRD) (Healthcare claims database) Publicly insured	All pregnancies resulting in live birth or stillbirth (>500 g)	All dispensed, reimbursed prescription drugs in outpatient care
Hong Kong 2001–2015	Clinical Data Analysis and Reporting System (CDARS)	All pregnancies in public hospitals resulting in live birth or stillbirth are directly identified in the database.	All dispensed prescription drugs in public in- and outpatient care
Iceland 2004–2017	a) Medical Birth Register b) National Medicine Registry (National health registers) Publicly insured	All pregnancies resulting in live birth or stillbirth from 22 weeks of gestation	All dispensed prescription drugs in outpatient care
Norway 2005–2015	a) Medical Birth Registry of Norway b) Norwegian Prescription Database (National health registers) Publicly insured	All pregnancies resulting in a live birth or stillbirth from 12 weeks of gestation	All dispensed prescription drugs in outpatient care
Sweden 2006–2015	a) Medical Birth Register b) Prescribed Drug Register (National health registers) Publicly insured	All pregnancies resulting in a live birth or stillbirth from 22 weeks of gestation	All dispensed prescription drugs in outpatient care
UK 2001–2015	The Health Improvement Network (THIN) database (Primary care database) Publicly insured	All pregnancies identified based on the recorded birth date, the last menstrual period and the estimated birth dates	All drugs prescribed in general practice
US MarketScan 2012–2015	IBM MarketScan® Commercial Claims and Encounters (MarketScan) database (Healthcare claims database) Privately insured	All pregnancies in women continuously enrolled in their health plan from before pregnancy until birth, identified with an ICD-9-based algorithm to identify live births and stillbirths	All dispensed, reimbursed prescription drugs in outpatient care
US MAX 2000–2013	Medicaid Analytic eXtract (MAX) database (Healthcare claims database) Publicly insured	All pregnancies in women continuously enrolled in a state Medicaid program from before pregnancy until birth, identified with an ICD-9-based algorithm to identify live births	All dispensed, reimbursed prescription drugs in outpatient care

excluding users of prochlorperazine from the estimated prevalence of typical antipsychotics. We also analyzed the prevalence and trends of prochlorperazine use separately.

For the Nordic countries, where data sources are similar, we further present the use of antipsychotics by women's parity, smoking status, and cohabitation. To this end, we meta-analyzed the prevalence estimated from each Nordic country by weighting each population by the inverse of the variance of the prevalence in the population (Barendregt et al., 2013).

2.4. Ethical approvals

The study was approved by the following country specific institutional review boards. Australia: The NSW Population and Health Services Research Ethics Committee (2012/06/397) and the Australian Institute of Health and Welfare Ethics Committee (2012/2/22).

Denmark: The Data Protection Agency (Record No. 2013-41-2569).

Finland: The Finnish Institute for Health and Welfare (THL/1551/6.02.00/2018), The Social Insurance Institution of Finland (Kela 148/52/2018) and Statistics Finland (TK-53-1870-18).

Germany: Studies based on GePaRD are exempt from institutional review board review.

Hong Kong: The institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW15-619)

Iceland: The National Bioethics Committee (VSN-18-123).

Norway: The Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics (REC-South East).

Sweden: The regional ethics review board in Stockholm, Sweden (N 2015/1826–31/2).

UK: The Health Improvement Network Scientific Review Committee (18THIN072).

US: The institutional review board of Brigham and Women's Hospital for the Medicaid data and Harvard TH Chan School of Public Health for the MarketScan data.

In the remaining participating countries, according to their respective regulations, no ethical approval was necessary for this study.

3. Results

The study included 8,394,343 pregnancies. Table 1 shows the prevalence of antipsychotic use in pregnancy by population, maternal age, and antipsychotic class. The overall prevalence of antipsychotic use during pregnancy ranged from 0.28% in Germany to 4.64% in the UK. The use of typical and atypical antipsychotics was lowest in Germany (0.12%) and Denmark (0.16%), respectively. The use of typical antipsychotics was highest in the UK (4.42%), whereas the use of atypical antipsychotics was highest in the US Max population (1.53%). Young women (≤24 years) had the highest use of typical antipsychotics in six

Table 1
Antipsychotic drug use during the pregnancy period by country and maternal age.

	Total number of pregnancies	Pregnancies with at least 1 filled prescription of:		
		Any antipsychotic	Typical antipsychotic	Atypical antipsychotic
	N	N (%)	N (%)	N (%)
Australia, NSW 2004–2012				
All ages	148,462	2355 (1.59)	497 (0.33)	2020 (1.36)
≤24 years	50,573	635 (1.26)	110 (0.22)	559 (1.11)
25–34 years	73,399	1195 (1.63)	269 (0.37)	1017 (1.39)
≥35 years	24,480	523 (2.14)	119 (0.49)	443 (1.81)
Denmark 2000–2012				
All ages	813,360	2858 (0.35)	1844 (0.23)	1269 (0.16)
≤24 years	87,014	458 (0.53)	307 (0.35)	211 (0.24)
25–34 years	485,356	1240 (0.26)	864 (0.18)	487 (0.10)
≥35 years	125,804	565 (0.45)	382 (0.30)	218 (0.17)
Finland 2005–2014				
All ages	584,139	4374 (0.75)	977 (0.17)	3741 (0.64)
≤24 years	103,690	1114 (1.07)	166 (0.16)	1014 (0.98)
25–34 years	370,232	2372 (0.64)	549 (0.15)	2021 (0.55)
≥35 years	110,217	888 (0.81)	262 (0.24)	706 (0.64)
Germany 2006–2015				
All ages	999,105	2842 (0.28)	1193 (0.12)	1912 (0.19)
≤24 years	80,050	369 (0.46)	165 (0.21)	241 (0.30)
25–34 years	616,444	1442 (0.23)	613 (0.10)	960 (0.16)
≥35 years	302,611	1031 (0.34)	415 (0.14)	711 (0.23)
Hong Kong 2001–2015				
All ages	416,494	1408 (0.34)	910 (0.22)	705 (0.17)
≤24 years	43,205	187 (0.43)	113 (0.26)	110 (0.25)
25–34 years	269,014	744 (0.28)	490 (0.18)	357 (0.13)
≥35 years	104,274	477 (0.46)	307 (0.29)	238 (0.23)
Iceland 2004–2017				
All ages	60,477	881 (1.46)	504 (0.83)	435 (0.55)
≤ 24 years	10,738	239 (2.23)	110 (1.02)	145 (1.05)
25–34 years	37,237	487 (1.31)	304 (0.82)	216 (0.41)
≥35 years	12,502	155 (1.24)	90 (0.72)	32 (0.41)
Norway 2005–2015				
All ages	645,459	7492 (1.16)	6162 (0.95)	1539 (0.24)
≤ 24 years	103,305	1560 (1.51)	1236 (1.20)	378 (0.37)
25–34 years	418,034	4472 (1.07)	3772 (0.90)	809 (0.19)
≥35 years	124,120	1460 (1.18)	1154 (0.93)	352 (0.28)
Sweden 2006–2015				
All ages	1,028,732	3929 (0.38)	2079 (0.20)	2097 (0.20)
≤24 years	148,042	731 (0.49)	367 (0.25)	423 (0.29)
25–34 years	654,477	2249 (0.34)	1243 (0.19)	1136 (0.17)
≥35 years	226,190	949 (0.42)	538 (0.24)	469 (0.21)
UK 2006–2016				
All ages	767,251	35,577 (4.64)	33,884 (4.42)	2115 (0.28)
≤24 years	232,391	8427 (3.63)	8093 (3.48)	431 (0.19)
25–34 years	374,185	20,053 (5.36)	19,187 (5.13)	1096 (0.29)
≥35 years	160,675	7097 (4.42)	6604 (4.11)	588 (0.37)
US, MarketScan 2012–2015				
All ages	859,505	6761 (0.79)	3371 (0.39)	3514 (0.41)
≤24 years	134,218	1905 (1.42)	688 (0.51)	1261 (0.94)
25–34 years	532,887	3485 (0.65)	2007 (0.38)	1534 (0.29)
≥35 years	192,400	1371 (0.71)	676 (0.35)	719 (0.37)
US, MAX 2000–2013				
All ages	2,071,359	66,820 (3.23)	37,200 (1.80)	31,712 (1.53)
≤24 years	1,180,493	34,530 (2.93)	19,626 (1.66)	15,741 (1.33)
25–34 years	752,111	27,241 (3.62)	15,151 (2.01)	13,109 (1.74)
≥35 years	138,755	5049 (3.64)	2423 (1.75)	2862 (2.06)

Note: The pregnancy period is defined as 90 days before the date of the last menstrual period to the date of birth.

of the eleven populations (Denmark, Germany, Iceland, Norway, Sweden, and US MarketScan) and of atypical antipsychotics in eight populations (Denmark, Finland, Germany, Hong Kong, Iceland, Norway, Sweden, and US MarketScan).

Fig. 1 a,b, and c show the trends in antipsychotic use in pregnancy by calendar year and population and Supplementary Table 2 shows the accompanying prevalence ratios and CIs. When comparing the first and last year of available data, overall antipsychotic use increased in six populations (Australia, Denmark, Finland, Germany, Iceland, and UK), with the largest increase in Finland (3.63-fold from 2005 to 2014) and Australia (2.34-fold from 2004 to 2012) (Suppl. Table 2). Overall antipsychotic use decreased in three populations (Norway, Sweden, and US Max).

The prevalence of typical antipsychotic use increased in the UK, was stable in three populations (Australia, Denmark, Iceland), and decreased in the other seven populations (Suppl. Table 2). Atypical antipsychotic use increased in all populations except in Iceland and US MarketScan (Fig. 1c: Suppl. Table 2).

Fig. 2a to e present the prevalence of antipsychotic drug use in the pre-pregnancy period and by trimester in each population. The overall use of antipsychotics was highest in the pre-pregnancy period in six populations and in the first trimester in the remaining five populations (Fig. 2a). For typical antipsychotics, a slightly higher use in the pre-pregnancy period was found in four populations (Australia, Denmark, Germany, and Hong Kong), whereas the use was markedly higher in the first trimester in six populations (Iceland, Norway, Sweden, UK, US MarketScan, and US MAX) (Fig. 2b). The use of typical antipsychotics declined from the first to the third trimester in all populations except for Finland, where prochlorperazine was not captured (Fig. 2b). For atypical antipsychotics, the use was highest 90 days before pregnancy in all populations, and thereafter decreased throughout pregnancy.

Prochlorperazine was approved and captured in seven populations (Denmark, Iceland, Norway, Sweden, UK, US MarketScan, and US MAX). In these, its use decreased over time except in UK where its use nearly doubled (Suppl. Table 2, Suppl. Fig. 1a). When the prochlorperazine users were excluded, a decreasing trend for typical antipsychotics was seen in six out of the eleven populations (Finland, Germany, Hong Kong, Norway, Sweden, and US MarketScan; Suppl. Table 2, Suppl. Fig. 1b). Prochlorperazine use accounted for a large proportion of the use of typical antipsychotics in five populations (Iceland, Norway, UK, US MarketScan, and US MAX) (Fig. 2b and e), but the pattern of declining use over the trimesters remained after excluding the prochlorperazine users (Fig. 2e).

Table 2 presents the five most commonly dispensed antipsychotics in the pregnancy period in the first and last year of available data by population. Atypical antipsychotics dominated in the most recent year in all populations, except that prochlorperazine continued to be the most commonly used antipsychotic in Norway, UK, and US. In the most recent year, quetiapine was the most commonly used atypical antipsychotic drug in all populations, followed by olanzapine in six populations and by aripiprazole in five populations. The proportion of pregnancies exposed to atypical antipsychotics increased markedly over time in all populations with quetiapine reaching 1.35% in Australia and 0.94% in Finland at the end of the study period.

Table 3 presents the prevalence of antipsychotic use among pregnant women in the Nordic countries by demographic and pregnancy-related characteristics. Antipsychotic use was more prevalent among women with higher parity, reaching 0.92% for any antipsychotic among women with parity of four or more. Furthermore, the prevalence of antipsychotic use was 1.46% in smokers versus 0.43% among non-smokers during pregnancy, and both typical and atypical antipsychotic use was higher in smokers.

4. Discussion

4.1. Key results

In our study of over eight million pregnancies with data from 2000 to 2017 in ten countries (eleven populations), applying a

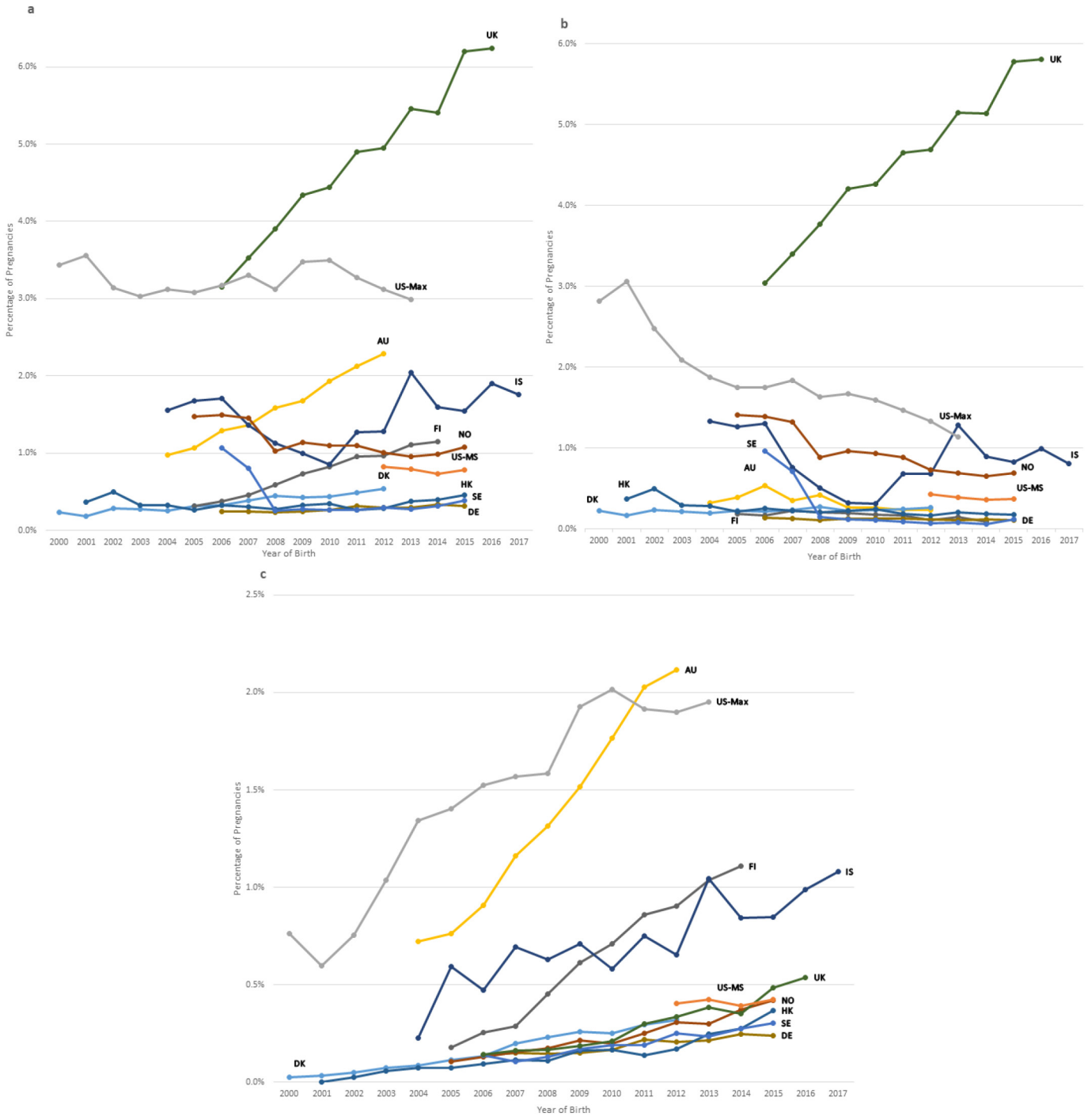

Fig. 1. a–c Trends in antipsychotic drug use during the pregnancy period by population per year. The pregnancy period is defined as 90 days before the date of the last menstrual period to the date of birth. Fig. 1a Any antipsychotic drug use by population. Fig. 1b Typical antipsychotic drug use by population. Fig. 1c Atypical antipsychotic drug use by population. Abbreviations: AU = New South Wales, Australia; DK = Denmark; FI = Finland; DE = Germany; HK = Hong Kong; IS = Iceland; NO = Norway; SE = Sweden; GB = United Kingdom; US-MS = US MarketScan; US-MAX = US MAX. The y-axis scales for each country are different, and the trends in antipsychotic drug use should be interpreted accordingly.

uniform approach for data analysis, the use of antipsychotics during the pregnancy period varied considerably between countries. The highest prevalence of typical antipsychotics was observed in the UK (4.42%, driven by the use of prochlorperazine) and of atypical antipsychotics in the US Max population (1.53%). In most populations, the use of typical antipsychotics decreased or was stable, whereas atypical antipsychotic use increased over time. Use of antipsychotics decreased with each trimester of pregnancy in most populations.

4.2. Interpretation & comparison with other studies

Factors which may explain differences in antipsychotic use between the countries include varying clinical practices reflecting different guidelines (Graham et al., 2018), pricing policies and reimbursement practices which may influence physicians' prescribing patterns. There may also be differences in what proportion of the actual antipsychotic medication is distributed from outpatient pharmacies as opposed to directly from psychiatric or other clinics. Furthermore, the prevalence of

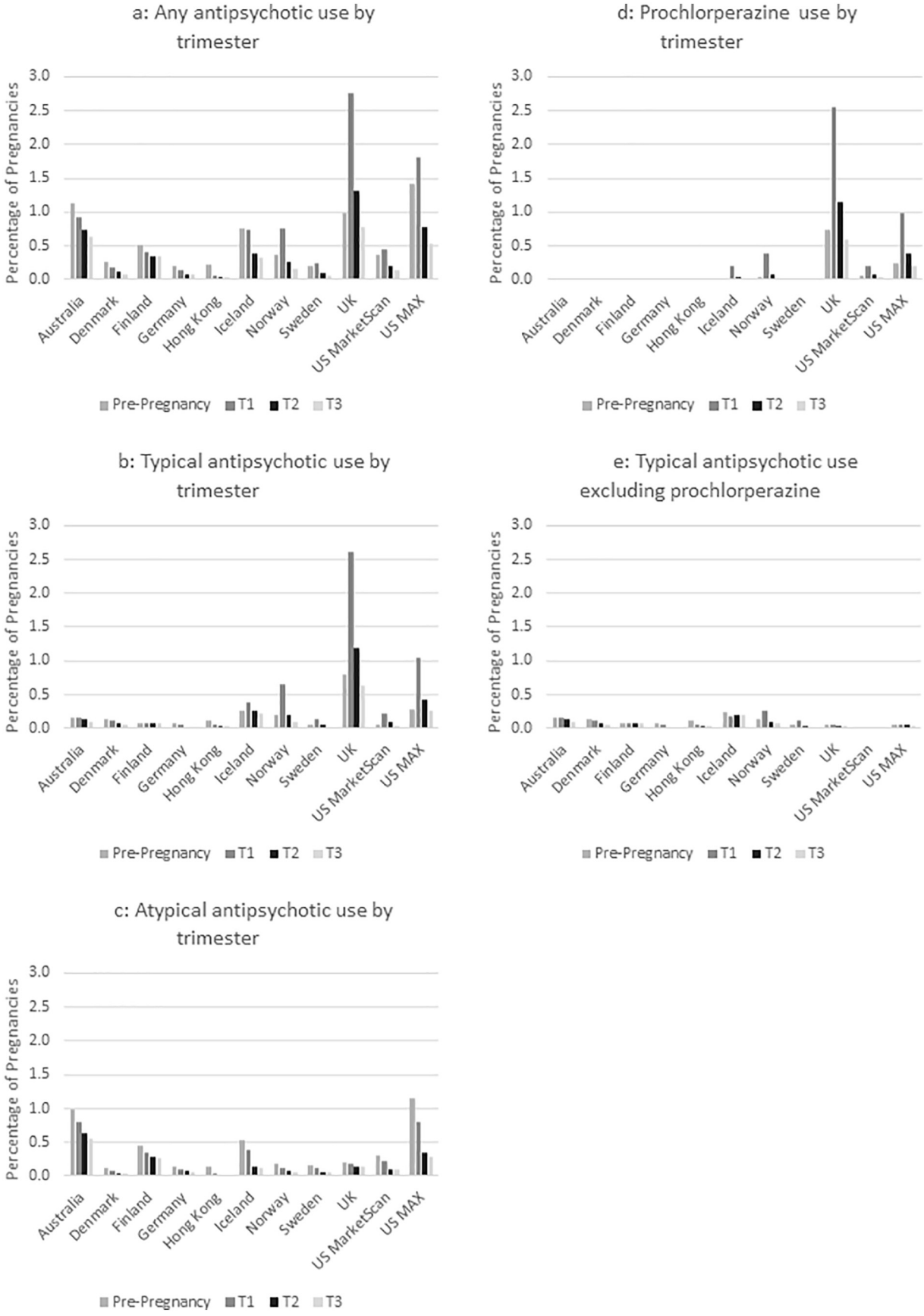

Fig. 2. a–e Prevalence of antipsychotic drug use during the pregnancy period by trimester and population. The pregnancy period is defined as 90 days before the date of the last menstrual period to the date of birth.

Table 2
Five most commonly dispensed antipsychotic drugs during the pregnancy period in the first and last year of available data by population.

Rank	Antipsychotic	% of all AP[a] users	% of all pregnancies	Rank	Antipsychotic	% of all AP[a] users	% of all pregnancies
Australia	***2004***				***2012***		
1	Olanzapine	36.94	0.36	**1**	Quetiapine	59.02	1.35
2	Risperidone	20.38	0.20	**2**	Olanzapine	24.59	0.56
3	Quetiapine	17.83	0.17	**3**	Risperidone	9.84	0.22
4	Chlorpromazine	13.38	0.13	**4**	Aripiprazole	5.46	0.12
5	Haloperidol	10.19	0.10	**5**	Chlorpromazine	3.83	0.09
Denmark	***2006***				***2013***		
1	Flupentixol	18.47	0.04	**1**	Quetiapine	39.87	0.21
2	Zuclopenthixol	17.83	0.04	**2**	Chlorprothixene	24.12	0.13
3	Levomepromazine	15.29	0.04	**3**	Perphenazine	17.04	0.09
4	Chlorprothixene	10.83	0.03	**4**	Aripiprazole	8.04	0.04
5	Perphenazine	9.55	0.02	**5**	Olanzapine	7.40	0.04
Finland	***2005***				***2014***		
1	Quetiapine	23.89	0.08	**1**	Quetiapine	81.37	0.94
2	Olanzapine	18.89	0.06	**2**	Olanzapine	9.92	0.11
3	Perphenazine	16.67	0.05	**3**	Aripiprazole	6.41	0.07
4	Risperidone	11.67	0.04	**4**	Risperidone	4.43	0.05
5	Chlorprothixene	8.89	0.03	**5**	Perphenazine	3.05	0.04
Germany	***2006***				***2015***		
1	Olanzapine	18.89	0.05	**1**	Quetiapine	47.86	0.15
2	Fluspirilene	17.97	0.04	**2**	Aripiprazole	12.03	0.04
3	Quetiapine	10.14	0.03	**3**	Pipamperone	9.36	0.03
4	Perazine	9.22	0.02	**4**	Olanzapine	8.56	0.03
5	Risperidone	9.22	0.02	**5**	Risperidone	8.02	0.03
Hong Kong	***2001***				***2015***		
1	Haloperidol	25.00	0.09	**1**	Quetiapine	38.20	0.17
2	Chlorpromazine	50.00	0.18	**2**	Haloperidol	20.22	0.09
3	Trifluoperazine	25.00	0.09	**3**	Olanzapine	16.85	0.08
4	Thiridazine	25.00	0.09	**4**	Risperidone	16.85	0.08
5	-	-	-	**5**	Trifluoperazine	16.29	0.07
Iceland	***2004***				***2017***		
1	Prochlorperazine	70.97	1.10	**1**	Quetiapine	50.00	0.88
2	Quetiapine	8.06	0.13	**2**	Perphenazine	32.86	0.58
3	Chlorpromazine	8.06	0.13	**3**	Olanzapine	11.43	0.20
4	Levomepromazine	4.84	0.08	**4**	Levomepromazine	7.14	0.13
5	Risperidone	3.23	0.05	**5**	Flupentixol	4.29	0.08
Norway	***2005***				***2015***		
1	Prochlorperazine	48.97	0.72	**1**	Prochlorperazine	41.53	0.45
2	Chlorpromazine	19.15	0.28	**2**	Quetiapine	27.32	0.29
3	Levomepromazine	13.82	0.20	**3**	Levomepromazine	10.86	0.12
4	Dixyrazine	8.97	0.13	**4**	Olanzapine	7.51	0.08
5	Chlorprothixene	5.21	0.08	**5**	Chlorprothixene	5.43	0.06
Sweden	***2006***				***2015***		
1	Dixyrazine	72.52	0.77	**1**	Quetiapine	45.06	0.18
2	Prochlorperazine	9.54	0.02	**2**	Olanzapine	22.99	0.09
3	Olanzapine	6.30	0.01	**3**	Aripiprazole	12.87	0.05
4	Risperidone	4.01	0.01	**4**	Prochlorperazine	10.80	0.04
5	Levomepromazine	3.05	0.01	**5**	Levomepromazine	8.74	0.03
UK	***2006***				***2016***		
1	Prochlorperazine	92.88	2.93	**1**	Prochlorperazine	91.39	5.71
2	Olanzapine	1.86	0.06	**2**	Quetiapine	5.68	0.35
3	Chlorpromazine	1.82	0.06	**3**	Aripiprazole	1.69	0.11
4	Quetiapine	1.61	0.05	**4**	Olanzapine	1.48	0.09
5	Flupentixol	1.40	0.04	**5**	Chlorpromazine	0.91	0.06
US MarketScan	***2012***				***2015***		
1	Prochlorperazine	48.66	0.40	**1**	Prochlorperazine	44.91	0.35
2	Aripiprazole	20.49	0.17	**2**	Quetiapine	22.66	0.18
3	Quetiapine	19.90	0.16	**3**	Aripiprazole	17.36	0.14
4	Risperidone	5.60	0.05	**4**	Lurasidone	6.44	0.05
5	Olanzapine	3.27	0.03	**5**	Risperidone	5.93	0.05
US MAX	***2000***				***2013***		
1	Prochlorperazine	80.93	2.88	**1**	Prochlorperazine	37.89	1.18
2	Olanzapine	7.97	0.28	**2**	Quetiapine	23.70	0.74
3	Risperidone	6.19	0.22	**3**	Aripiprazole	20.93	0.65
4	Quetiapine	3.65	0.13	**4**	Risperidone	11.71	0.37
5	Haloperidol	1.86	0.07	**5**	Olanzapine	4.67	0.15

Note: The pregnancy period is defined as 90 days before the date of the last menstrual period to the date of birth.
Annotation: Antipsychotic names in light gray = typical antipsychotic; white = atypical antipsychotic; dark gray = typical antipsychotic usually used as an antiemetic.
[a]AP = Antipsychotic.

Table 3
Pooled prevalence of antipsychotic drug use during the pregnancy period in the Nordic countries by maternal and pregnancy characteristics.

Country (weight %)	Total	Any antipsychotic		Typical antipsychotic		Atypical antipsychotic	
		N	Prevalence (95% CI)[a]	N	Prevalence (95% CI)[a]	N	Prevalence (95% CI)[a]
Pooled (100)	3,132,167	19,534	0.58 (0.58, 0.59)	11,566	0.32 (0.31, 0.33)	9081	0.27 (0.26, 0.27)
Denmark (26.0)	813,360	2858	0.35 (0.34, 0.36)	1844	0.23 (0.22, 0.24)	1269	0.16 (0.15, 0.16)
Iceland (1.9)	60,477	881	1.46 (1.36, 1.55)	504	0.83 (0.76, 0.91)	435	0.72 (0.65, 0.79)
Finland (18.7)	584,139	4374	0.75 (0.73, 0.77)	977	0.17 (0.16, 0.18)	3741	0.64 (0.62, 0.66)
Norway (20.6)	645,459	7492	1.16 (1.13, 1.19)	6162	0.95 (0.93, 0.98)	1539	0.24 (0.23, 0.25)
Sweden (32.8)	1,028,732	3929	0.38 (0.37, 0.39)	2079	0.20 (0.19, 0.21)	2097	0.20 (0.20, 0.21)
Parity							
1	1,299,079	7580	0.55 (0.54, 0.56)	4497	0.30 (0.29, 0.31)	3583	0.27 (0.26, 0.28)
2	1,004,582	5177	0.47 (0.45, 0.48)	3600	0.34 (0.33, 0.35)	1782	0.16 (0.16, 0.17)
3	381,385	2553	0.62 (0.60, 0.65)	1781	0.41 (0.39, 0.43)	895	0.22 (0.21, 0.24)
≥4	169,324	1604	0.92 (0.87, 0.96)	1053	0.57 (0.53, 0.60)	658	0.38 (0.36, 0.41)
Missing	277,797	2620	0.93 (0.90, 0.97)	635	0.21 (0.19, 0.23)	2163	0.21 (0.19, 0.23)
Smoking[b][c]							
No	2,551,171	11,892	0.43 (0.42, 0.44)	7411	0.24 (0.24, 0.25)	4953	0.18 (0.18, 0.19)
Yes	341,726	5123	1.46 (1.42, 1.50)	2448	0.68 (0.65, 0.71)	3198	0.86 (0.83, 0.89)
Missing	178,793	1638	0.88 (0.84, 0.92)	1203	0.62 (0.58, 0.65)	495	0.27 (0.24, 0.29)
Cohabitation[b]							
Cohabiting	1,876,289	8653	0.49 (0.48, 0.50)	3930	0.20 (0.20, 0.21)	5368	0.33 (0.32, 0.34)
Not cohabiting	516,888	2721	0.50 (0.48, 0.52)	1172	0.39 (0.38, 0.41)	1750	0.65 (0.63, 0.66)
Missing	93,531	668	0.70 (0.65, 0.75)	302	0.36 (0.32, 0.39)	424	1.06 (1.03, 1.08)
Multi-fetal pregnancy							
No	3,077,982	19,231	0.58 (0.58, 0.59)	11,392	0.34 (0.33, 0.35)	8939	0.27 (0.26, 0.27)
Yes	53,052	302	0.54 (0.48, 0.60)	174	0.31 (0.26, 0.36)	142	0.23 (0.19, 0.27)
Year of birth							
2000-2004[c]	323,511	852	0.26 (0.24, 0.27)	712	0.21 (0.20, 0.23)	179	0.23 (0.19, 0.27)
2005–2009	1,285,897	8695	0.64 (0.62, 0.65)	6457	0.44 (0.43, 0.45)	2730	0.20 (0.20, 0.21)
2010–2017	1,522,759	9987	0.61 (0.59, 0.62)	4397	0.23 (0.22, 0.24)	6172	0.37 (0.36, 0.38)

Note: The pregnancy period is defined as 90 days before the date of the last menstrual period to the date of birth.
[a] Prevalence per 100 pregnancies weighted by population and 95% confidence intervals (CI).
[b] Data on smoking available for Denmark, Finland, Norway, Sweden; Data on cohabitation available for Denmark, Iceland, Finland, Sweden; For Denmark' Cohabiting' reflects marital status.
[c] Only Denmark and Iceland included births occurring in 2000–2004.

mental disorders may differ between settings and countries. Within the US, there was a notably higher antipsychotic use among the publicly-insured (MAX) than the privately-insured (MarketScan) women. This may be because the publicly-insured US MAX population includes women with low economic resources, in whom psychiatric disorders are more prevalent (Kasper, 1986). This interpretation should also be applied to the Australian estimates. It may also be partly due to our inclusion of prochlorperazine, as lower rates reported previously from US MAX did not include that medication (Park et al., 2017). Perceptions and attitudes among the mentally ill and care providers regarding the value of antipsychotics (Morrison et al., 2015; Velligan et al., 2009) may also differ. Finally, some classification differences may apply. For example, in Australia, prochlorperazine is classified as an antiemetic (ATC A04AD) instead of as an antipsychotic and was therefore not included in the study data.

Previous reports regarding patterns of antipsychotic drug use among pregnant women come from a number of country-specific studies. A study of data from 11 different private health plans from 2001 to 2007 in the US, found a stable prevalence of 0.09% for typical antipsychotics but an increasing trend from 0.33% to 0.82% for atypical antipsychotics (Toh et al., 2013). Similar patterns were reported in both a Tennessee Medicaid study (Epstein et al., 2013), and a previous Medicaid MAX study covering 2001 to 2010, which partly overlap with our study (Park et al., 2017). Also spanning different time periods, data from some of the other data sources included in this study have also been reported in country-specific studies previously. Thus, in THIN data (UK) from 1995 to 2007, 0.29% of women were prescribed antipsychotics in the six months before they became pregnant and 0.19% of women after the first six weeks of pregnancy, with an overall time trend of increasing use of atypical antipsychotics whereas that of typical antipsychotics decreased (Petersen et al., 2014). In Hong Kong, from 2004 to 2014, the prevalence of antipsychotic use in pregnancy increased from 0.18% to 0.27% (Lao et al., 2017). Our data from the UK and Hong Kong cover more recent years, and for the US we include a broader population, yet these trends have persisted. In Denmark, a prevalence of antipsychotic use of 0.20% was reported among pregnant women from 1997 to 2012 (Ingstrup et al., 2018) and in Norway, 1% of pregnant women used antipsychotics (including lithium) from 2005 to 2015 (Engeland et al., 2018). Time trends were not reported in these studies, but our analyses of data for similar time periods found increasing use of atypical antipsychotics also in Denmark and Norway.

During the study period, new atypical antipsychotics were marketed and indications were expanded, which together with off-label use (Alexander et al., 2011; Maher and Theodore, 2012) and removal of some older typical antipsychotics (e.g. dixyrazine) from the market in certain countries, may explain the increase in use of atypical antipsychotics in our study populations. Atypical antipsychotics have increasingly been recommended as treatment for bipolar disorder and as add-on treatment for unipolar depression, especially with quetiapine, olanzapine, and aripiprazole (Kennedy et al., 2016). Further, atypical antipsychotics may be preferred because of safety concerns regarding antiepileptics as mood stabilizers in women with bipolar disorder during pregnancy (Petersen et al., 2017). Quetiapine was the most commonly dispensed atypical antipsychotic in all countries, possibly partly due to off-label use for indications such as insomnia (McKean and Monasterio, 2012), with a similar pattern of increasing use found for aripiprazole. Our findings for pregnant women mirror the trend of increasing use of atypical antipsychotics in the general population worldwide (Halfdanarson et al., 2017).

For typical antipsychotics, use was clearly most common in the first trimester, especially in countries where prochlorperazine use was captured. Prochlorperazine is almost exclusively used as an antiemetic (Fiaschi et al., 2019), and nausea and vomiting is usually most pronounced in the first trimester (Louik et al., 2006). Our

results further suggest that many women did not continue to refill their antipsychotic prescriptions, or physicians stopped prescribing, during the second and third trimester. This corroborates findings for antipsychotics in the UK in both the CPRD and THIN databases (Margulis et al., 2014; Petersen et al., 2014), Sweden in 2007 (Stephansson et al., 2011), and in the Sentinel system in the US (Illoh et al., 2018). Even after removing the women who were prescribed prochlorperazine, the pattern of decreased use remained as the pregnancies progressed. A similar pattern has also been observed for antidepressants (Illoh et al., 2018; Stephansson et al., 2011; Zoega et al., 2015). Discontinuation of psychotropic medication during pregnancy is common due to concerns that fetal exposure to these medication may have harmful effects for the child (Einarson et al., 2001), although the data regarding antipsychotics are not yet conclusive (Huybrechts et al., 2016). Some women who filled antipsychotic prescriptions in the first trimester may not yet have been aware that they were pregnant, and the pregnancy may have been unintended (Finer and Zolna, 2016). It could be speculated that stopping the use of antipsychotics during the latter part of pregnancy may decrease the risk of delayed neural development and pregnancy complications, including gestational diabetes. On the other hand, there is a high risk of relapse for those who discontinue medication for schizophrenia (Lin et al., 2010) and bipolar disorder (Viguera et al., 2007; Yonkers et al., 2004), and untreated psychiatric illness may confer health risks both for the mother and unborn child, as well as for the child after birth (Boden et al., 2012a; Gentile, 2017).

In the Nordic countries we found that pregnant women with four or more previous deliveries had the highest antipsychotic use, which was not explained by age; there was an inverse association between antipsychotic use and age. Pregnant women who smoked during pregnancy had a higher prevalence of typical and atypical antipsychotic use than non-smoking women, similar to findings reported for SSRIs and SNRIs (Zoega et al., 2015). This was expected since the rate of smoking is much higher among individuals with mental disorders (de Leon and Diaz, 2005; Jimenez-Solem et al., 2013). The finding may imply that women with mental disorders have a different pattern of risk factors of adverse outcomes, pointing to the need to control for such factors in future studies evaluating outcomes in relation to antipsychotic medication during pregnancy.

4.3. Limitations

Limitations that are inherent in the observational design include circumstances that may have led to overestimation of use because the analyses were based on prescriptions or dispensing of antipsychotic medication for which the adherence to treatment is not known. Underestimation of antipsychotic use may also have occurred since antipsychotic medication dispensed directly to the women by hospitals or other clinics were not captured, or because they were not reimbursed antipsychotics; the latter was the case for prochlorperazine in Australia and Finland. The underlying indication for the prescribed antipsychotics was not available in the study data. Further, the databases differ in their set up and collection of data, with the Nordic countries providing data for the whole population, whereas the data from the non-Nordic countries were selected samples to varying degrees but are still considered representative of their country's pregnant population (Panel 1). For Finland, the first trimester was shorter than for the other countries, which may have affected the proportion of use during T1; however, this is not expected to affect the overall conclusions of the study which are not related to the investigation of outcomes during a specific exposure period. Finally, a limitation of our study is that countries had different time periods of data availability for antipsychotic use during pregnancy, but we consider it unlikely that the main patterns and trends identified in this study would change in the countries with fewer years of follow-up.

5. Conclusion

In summary, this study found that the prevalence of antipsychotic drug use varied between populations, partly driven by variations in the capture of prochlorperazine mainly used for nausea in early pregnancy. The use of antipsychotics was highest pre-pregnancy and at the beginning of the pregnancy. Most countries showed an increasing trend for use of atypical antipsychotics. This reflects the pattern in the general population, and demonstrates the worldwide uptake of newer antipsychotic medication, also in pregnant women.

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Contributors

Authors JR, CC, JMC, HZ, and GB designed the study. Author JR managed the literature searches. Authors CC and LP undertook the statistical analysis, and author JR wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of the funding source

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Declaration of competing interest

JR, CC, LP, and GB, are employees of the Centre for Pharmacoepidemiology which receives funding from pharmaceutical companies and regulatory authorities for drug safety/utilization studies, unrelated to the submitted work. BTB has participated as an investigator on grants to the Brigham and Women's Hospital from Pfizer, GSK, Lilly, Baxalta, and Pacira, not related to the topic of the submitted work. SH-D has participated as investigator in projects funded by Pfizer, GSK, and Lilly; and consulted for Boehringer-Ingelheim, Roche and UCB as a methods advisor for pregnancy studies. KFH has participated as an investigator on grants to the Brigham and Women's Hospital from Boehringer Ingelheim, Pfizer, Lilly and GSK, not related to the topic of the submitted work. The other authors declare no personal conflict of interest.

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