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Review article

The international prevalence of antidepressant use before, during, and after pregnancy: A systematic review and meta-analysis of timing, type of prescriptions and geographical variability

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ABSTRACT

Background: Antidepressant use during pregnancy has increased over the last decades, while safety has been under debate. Our aim was to measure the international prevalence of antidepressant use before, during, and after pregnancy and examine timing, type of prescriptions and geographic variability.

Methods: We searched Embase, Medline Ovid, Web of Science, Cochrane Central and Google Scholar from their inception until February 19, 2019. We determined pooled prevalence estimates of antidepressants before, during, and after pregnancy, as well as stratified according to substantive variables.

Results: We identified 40 cohorts from 15 countries, together reporting on 14,072,251 pregnancies. Included studies had a low risk of bias, often reporting on large representative cohorts. Selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants during pregnancy, with an international prevalence estimate of 3.0% (95%CI 2.3;3.7). While Europe and Australasia had pooled prevalence estimates of 1.6% and 1.3% respectively, Northern America had a prevalence estimate of 5.5% (Q-value = 126.19; df = 2; p-value < 0.01). Highest SSRI prevalence rates were found for sertraline (1.10%), followed by citalopram and fluoxetine (0.77% and 0.76% respectively) (Q-value = 121.25; df = 5; p-value < 0.01). Qualitative analysis indicated an increase in antidepressant use over subsequent calendar years.

Limitations: Substantial heterogeneity remained unaccounted for throughout the analyses, even after accounting for hypothetical contributors.

Conclusions: This meta-analysis revealed substantial regional differences in antidepressant use around pregnancy, which could be due to variability in prescription behavior, healthcare seeking behavior and organization of healthcare. There is an urgent need for evidence on effectiveness, benefit, and harm of antidepressants during pregnancy to guide clinical practice.

1. Introduction

Prescribed medication use during pregnancy is common, with overall estimates in developed countries ranging from 27% to 93%, excluding vitamins and minerals (Daw et al., 2011). Over the last decades, this use of prescription medication during pregnancy has increased by more than 60% (Mitchell et al., 2011), and antidepressants greatly contribute to this increase (Andrade et al., 2016; Charlton et al., 2015; Cooper et al., 2007). In the general population, antidepressants are now among the top three most commonly prescribed therapeutic drug classes in the United States (Pratt et al., 2017). Antidepressants showed the largest increase in prescriptions during pregnancy over time, compared to other drugs associated with potential harmful neonatal effects (van Gelder et al., 2014).

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The use of antidepressants during pregnancy has been under debate, because evidence on adverse fetal and child outcomes is inconclusive (Simoncelli et al., 2010). Studies have found associations of maternal antidepressant use with increased risks for cardiovascular malformations (Grigoriadis et al., 2013b), persistent pulmonary hypertension of the neonate (Kieler et al., 2012), poor neonatal adaptation (Grigoriadis et al., 2013a), preterm delivery and lower birth weight (Ross et al., 2013), altered fetal brain development (Lugo-Candelas et al., 2018), and psychiatric disorders in the offspring such as mood disorders, autism spectrum disorders and behavioral disorders including ADHD (Liu et al., 2017). Other studies failed to find these increased risks or observed only modest effects (Furu et al., 2015; Huybrechts et al., 2015; Hviid et al., 2013). Since studies on antidepressants in pregnancy are not typically randomized, it is often difficult to determine if reported adverse outcomes associated with antidepressants are related to the medication itself, the underlying maternal mental illness, genetic risk differences between women with and without mental illness, other confounding exposures such as alcohol, smoking, substance abuse, nutrition, and other medications, or socioeconomic differences between cohorts. As a result, the risk of these medications is not definitively established. Coupled with the lack of robust data on alternative therapies while discontinuing antidepressants in pregnancy, both women and clinicians lack clear guidance whether they should continue antidepressants during pregnancy or not. Consequently, 50% of women decide to discontinue their antidepressants, either before or during pregnancy (Charlton et al., 2015; Hanley and Mintzes, 2014; Molenaar et al., 2019).

Limited data suggest that prescription rates and antidepressants use vary by country and study setting (Charlton et al., 2015). We performed a systematic review and meta-analysis to examine international prevalence rates and patterns of antidepressant use before, during, and after pregnancy. We explored use in the different trimesters, examined geographical differences in prescription patterns and examined prevalence trends over time.

2. Methods

2.1. Literature search

This systematic review and meta-analysis was conducted and reported in line with the PRISMA guidelines (Liberati et al., 2009). The protocol was registered in PROSPERO (CRD42018116978). All large databases, including embase.com, Medline Ovid, Web of Science, Cochrane Central and Google Scholar were searched by a medical information specialist from inception to February 19, 2019, using search terms describing types of antidepressants, the target population and type of study (full search strategy available in the Online Resource).

2.2. Eligibility criteria

Studies were eligible if they were peer-reviewed, written in English, and if they described a population of women using antidepressants either the year before pregnancy, during pregnancy, or the first postpartum year. The following groups of antidepressants were included: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other antidepressants (e.g. tetracyclics). To avoid unreliable comparisons, studies that did not specify on which groups of antidepressants they reported were excluded, as underreporting could not be ruled out (e.g. a study reporting on 'antidepressants' could be a study only including TCAs, thereby leading to a gross underreporting of the prevalence of antidepressants in the perinatal period). All observational studies reporting the antidepressant prevalence in a certain time period with a known cohort size or reporting a numerator and denominator were included. We excluded case-control studies, case reports, case series, reviews, conference abstracts, and studies reporting on antidepressant use without specifying the country or perinatal phase. We also excluded studies focused on specific subpopulations (population not suitable) instead of general prevalence of antidepressant use (e.g. antidepressant use in pregnant women suffering from a major depressive disorder, or antidepressant use in a population of women with birth defects in the offspring), as we were interested in the population-based prevalence rates.

2.3. Study selection and data extraction

Duplicates were screened and removed with the citation manager EndNote. Two reviewers (NMM, BB) independently screened the titles and abstracts and assessed the full text of potential eligible studies. When multiple papers reported on the same cohort, the paper with highest level of detail was included (e.g. a paper reporting on multiple antidepressant subgroups). Two reviewers (NMM, BB) independently extracted data using a standardized data extraction form. We extracted the number of pregnancies aided by antidepressant use specified to type of antidepressant and perinatal phase (numerator) and the total number of pregnancies in the corresponding perinatal phase (denominator) for the entire cohort and, when available, per subsequent calendar years for time trend analysis. We report whether the outcome describes all pregnancies or life births only and whether multiple pregnancies and consecutive pregnancies were included. Additionally, data was extracted regarding the study period, geographic location, type of study (prospective, retrospective), in- and exclusion criteria, and definition of antidepressant use (dispensing, prescription, self-report). Disagreements between reviewers were reconciled among NMM, BB and AMK.

2.4. Quality assessment

The quality of the studies related to antidepressant prevalence was assessed informed by the Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data (Munn et al., 2015, 2014). Potential bias with regard to the following quality criteria was assessed: 1) was the sample frame appropriate to address the target population, 2) were study participants sampled in an appropriate way, 3) was the sample size adequate, 4) were study subjects and setting described in detail, and 5) was the response rate adequate. The sample frame was deemed appropriate when the sample was a valid representation of the general population of the country where the study was performed (e.g. birth registers covering the entire country are appropriate, while a cohort from a single general hospital is not). There was an appropriate sampling method when in- and exclusion criteria were not restrictive. Sample size was considered adequate when larger than 2000 participants (Naing et al., 2006).

2.5. Procedure for meta-analyses

Data analysis was carried out in STATA (version 15, STATA Corporation, College Station, TX, USA) using *metaprop* procedures (Nyaga et al., 2014). Overall pooled estimates were calculated with inverse-variance weights obtained from the random-effects model using the method of DerSimonian and Laird. Confidence intervals of the unique studies were computed with the exact method. We calculated an overall prevalence and 95% Confidence Interval (CI) per antidepressant, per perinatal phase (before, during, after), and per geographic region. Subgroup differences were tested using the random-effects model. Random-effects was chosen over fixed-effects analysis as substantial heterogeneity was expected (Munn et al., 2015). We reported Cochran's Q-, I^2-statistics and significance levels. We also decided to calculate 95% prediction intervals using the method suggested by Higgins et al. given the substantial heterogeneity found (Higgins et al., 2009). We qualitatively reviewed the impact of time on

prevalence rates due to limited reported prevalence rates per calendar year. Additional time trend analysis using random-effects meta-regression analysis can be found in the Online Resource.

Sensitivity analysis were used to assess the robustness of our findings and to explore potential sources of heterogeneity. Per type of antidepressant we estimated the overall prevalence using both random- and fixed-effect calculation to evaluate the impact of the estimation method. We then examined prevalence rates of SSRIs during pregnancy in more detail, as that was the most frequently studied and most commonly used type of antidepressant. We estimated the impact of methodological factors, study quality and bias on the prevalence of SSRI use during pregnancy. We reported Cochran's *Q* and significance levels.

We used funnel plots to visually assess the presence of small-study effects per pregnancy phase among studies reporting on SSRI use, and Egger's regression-based test for formal assessment (results in Online Resource).

3. Results

3.1. Selection of studies

The literature search produced a set of 6618 articles after de-duplication, which were then reviewed based on titles and abstracts by two independent reviewers, resulting in an initial selection of 354 articles. After full-text assessment of the 354 articles, 39 articles, reporting on 40 cohorts (Charlton et al. reports on two separate Italian cohorts) (Charlton et al., 2015), were included (Fig. 1). Interrater reliability with respect to selected articles was considered good (inter-rater agreement: 96%, kappa: 0.66 (95%CI: 0.62–0.70).

3.2. Study characteristics

Prevalence data for antidepressant use in the perinatal period was provided for a total sample of 14,072,251 pregnancies from 15 high-income countries. Sample size per cohort ranged between 436 and 1,895,519 pregnancies. Thirty-five cohorts (87.5%) were retrospective in nature. Fifteen cohorts included data on the year before conception, all 40 cohorts focused on the pregnancy period itself (either on the complete pregnancy or on one or more trimesters) and eight cohorts included data from the first postpartum year. Most cohorts included information on SSRIs (k = 39), while some also focused on SRNIs (k = 12), TCAs (k = 15), MAOi (k = 4) or other forms of antidepressants (k = 12). Prevalence rates were reported across a 26-year period (from 1989 to 2015). Detailed characteristics of all cohorts are provided in Supplementary Table 1 and 2 in the Online Resource.

3.3. Prevalence estimates per perinatal phase for all major antidepressant groups

Fig. 2 presents the international random-effects prevalence estimates for all major antidepressant groups before, during, and after pregnancy. SSRIs were most often prescribed and examined (prevalence ranging from 3.01% to 4.66%), followed by SNRIs (prevalence ranging from 0.55% to 0.73%) and TCAs (prevalence ranging from 0.38% to 0.62%). Only two cohorts reported on MAOIs. SSRIs showed a small decrease in prevalence from preconception to pregnancy (from 3.50% to 3.01%) with a subsequent increase from pregnancy to the postpartum period (3.01%–4.66%). These fluctuations did not reach statistical significance (Q-value = 4.60; df = 2; p-value = 0.10). Forest plots of SSRI prevalence per perinatal phase can be found in the Online Resource (Supplementary Figs. 1–3). Prediction intervals were wide due to substantial heterogeneity.

3.4. Prevalence estimates of SSRIs during pregnancy

Fig. 3 presents the international random-effects prevalence estimates of SSRIs during pregnancy stratified by substantive variables. Out of the 40 cohorts, 22 cohorts reported on the prevalence of SSRI use for a specific trimester. Prevalence rates slightly decreased, albeit non-significantly so, from 2.46% in the first trimester to 1.59% in the second trimester, increasing to 1.84% in the third trimester (Q-value = 4.34; df = 2; p-value = 0.11). The observed prevalence estimates per trimester tend to be lower than the overall prevalence estimate during complete pregnancy (3.01%). Women may discontinue or initiate SSRIs during any given trimester and are therefore not always represented in each separate trimester. Ten cohorts reported on prevalence rates per specific SSRI. Highest SSRI prevalence rates were found for sertraline (1.10%), followed by citalopram and fluoxetine (0.77% and 0.76% respectively; Q-value = 121.25; df = 5; p-value $<$0.01).

3.5. Variation in prevalence estimates per geographical region

Fig. 4 represents the random-effects prevalence estimates of SSRIs during pregnancy per geographical region. Prevalence rates were lowest in Australasia, with an overall estimate of 1.35% (95%CI 0.20;2.50, prevalence interval 0.00;6.98). Three out of four Australasian cohorts reported a rate equal to or lower than 0.65%. In Europe, the overall estimate was slightly higher with 1.64% (95%CI 1.42;1.85, prevalence interval 0.79;2.48). Nine cohorts reported on prevalence rates in Northern America, coming to an overall estimate of 5.46% (95%CI 4.83;6.10, prevalence interval 3.05;7.87). The study by Cooper et al. (2007), reporting the prevalence in a cohort from 1999 to 2003, had the largest prevalence with 10.20%. The study by Figueroa (2010), reporting on a cohort from 1997 to 2002, had the lowest prevalence with 2.41%. Both of these studies had a high risk of bias regarding their sample frame (Supplementary Fig. 4 in the Online Resource). Differences between geographical regions were statistically significant (Q-value = 126.19; df = 2; p-value $<$0.01).

3.6. Prevalence rates over time

Of all 40 cohorts, only two reported prevalence rates (including numerator and denominator) over a series of subsequent calendar years (Huybrechts et al., 2015; Molenaar et al., 2019). Twelve cohorts from six countries mentioned prevalence rates in the first and last year of their cohort (in percentages, without numerator and denominator, therefore unsuitable for meta-regression). These prevalence rates are presented in Table 1. The majority of cohorts (90%) with a start date from 1992 to 2001 showed an increase in antidepressant use during pregnancy over time. Andrade et al. (Andrade et al., 2016), studying a cohort of 1,895,519 deliveries between 2001 and 2013, observed the largest increase over time. In this cohort, the SSRI prevalence during pregnancy increased from 1.7% in 2001 to 14.9% in 2010. In contrast, cohorts with a start date from 2004 to 2010 either showed stabilization or a slight decrease in antidepressant use during pregnancy over time. Quantitative analysis using meta-regression can be found in the Online Resource.

3.7. Risk of bias of the studies

Overall, included studies had a low risk of bias, often reporting on large representative cohorts. The sample frame was considered inappropriate in 51.3% of the included studies. For example, Boukhris et al. (2016) and Brown et al. (2017) predominantly included women of lower socio-economic status, while Wichman et al. (2009) only included women from a single hospital in one state. Sampling method was a potential risk in 33.3% of the studies. For example, Figueroa (2010) only included women with a hospitalized delivery. The gross majority of the studies were considered low risk of bias with

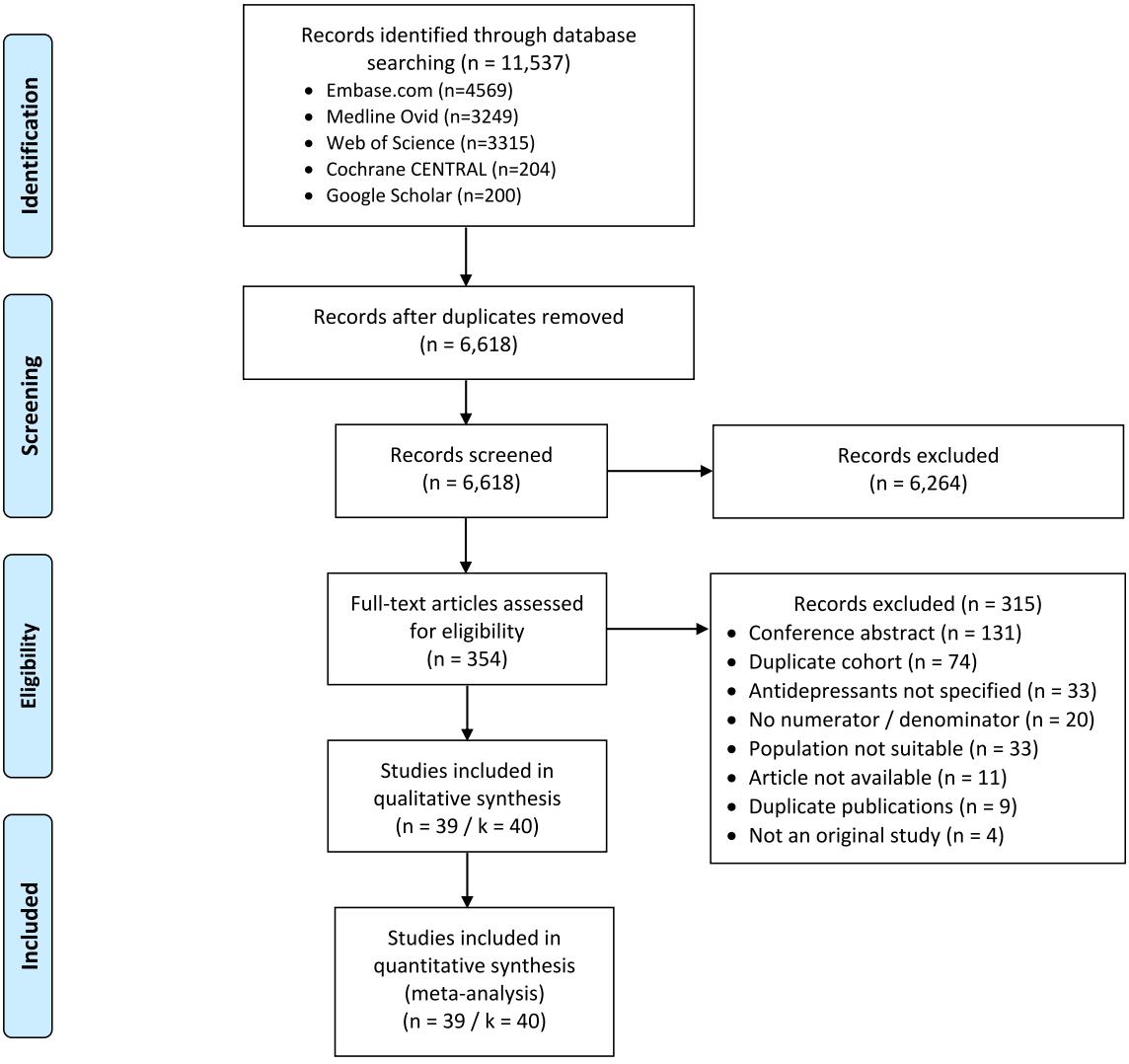

Fig. 1. PRISMA flow diagram of study inclusion

	Prevalence of antidepressants in the perinatal period								
	No. of cohorts	Pooled sample size	No. of countries	Pooled prevalence %	Forest plot of pooled random effect prevalence	95%CI	Prediction interval	I_2 statistic (%)	Q statistic (df; *p*-value)
SSRIs									
Year before pregnancy	14	4,783,284	7	3·50		(2·40;4·60)	(0·00;8·23)	99·97	
During pregnancy	24	8,135,384	13	3·01		(2·29;3·74)	(0·00;6·84)	99·98	
Year after pregnancy	7	1,394,101	4	4·66		(3·34;5·98)	(0·00;9·54)	99·93	4·60 (2; 0·10)
SNRIs									
Year before pregnancy	3	921,356	2	0·68		(0·43;0·94)	*NA*[b]	99·49	
During pregnancy	8	2,597,070	5	0·73		(0·54;0·92)	(0·02;1·44)	99·83	
Year after pregnancy	1	488,887	1	0·55		(0·53;0·57)	*NA*	*NA*	0·09 (1; 0·77)
TCAs									
Year before pregnancy	5	1,321,633	3	0·52		(0·26;0·79)	(0·00;1·55)	99·81	
During pregnancy	9	2,892,610	5	0·38		(0·29;0·46)	(0·06;0·69)	99·61	
Year after pregnancy	3	914,939	2	0·62		(0·01;1·22)	*NA*	99·91	1·63 (2; 0·44)
MAOi									
Year before pregnancy	*NA*	*NA*	*NA*	*NA*		*NA*	*NA*	*NA*	
During pregnancy	2	233,934	2	0·00		(0·00;0·00)	*NA*	*NA*	
Year after pregnancy	*NA*	*NA*	*NA*	*NA*		*NA*	*NA*	*NA*	*NA*
					0% 3% 6%				

Fig. 2. Global prevalence estimates per perinatal phase[a].

[a] Pooled prevalence rates and Q statistics calculated using random effect estimation. The I^2 statistic could not be calculated for pooled estimates of two cohorts or less. The *Q* statistic only reflects tested differences between categories with $n > 1$. [b] *NA* = Not Applicable

	Prevalence of selective serotonin reuptake inhibitors during pregnancy								
	No. of cohorts	Pooled sample size	No. of countries	Pooled prevalence %	Forest plot of pooled random effect prevalence	95%CI	Prediction interval	I_2 statistic (%)	Q statistic (df; *p*-value)
Overall pooled prevalence	24	8,135,384	13	3·01		(2·29;3·74)	(0·00;6·84)	99·98	
Prevalence by trimester									
First trimester	22	7,566,490	11	2·46		(1·82;3·10)	(0·00;5·73)	99·98	
Second trimester	18	6,625,968	9	1·59		(1·07;2·11)	(0·00;4·04)	99·97	
Third trimester	20	11,272,913	10	1·84		(1·32;2·36)	(0·00;4·39)	99·98	4·34 (2; 0·11)
Prevalence by individual SSRI									
Citalopram	11	4,009,196	5	0·77		(0·45;1·08)	(0·00;2·04)	99·94	
Escitalopram	9	3,876,322	4	0·47		(0·18;0·77)	(0·00;1·59)	99·96	
Fluoxetine	12	4,072,591	7	0·76		(0·44;1·08)	(0·00;2·07)	99·94	
Fluvoxamine	6	2,315,809	5	0·01		(0·00;0·02)	(0·00;0·04)	96·07	
Paroxetine	11	3,729,292	6	0·56		(0·41;0·71)	(0·00;1·15)	99·79	
Sertraline	12	4,072,591	6	1·10		(0·60;1·60)	0·00;3·14)	99·97	121·25 (5; <0·01)
					0% 3% 6%				

Fig. 3. Global random effects prevalence estimates of SSRIs during pregnancy stratified by substantive variables[a].
[a] Pooled prevalence rates and Q statistics calculated using random effect estimation.

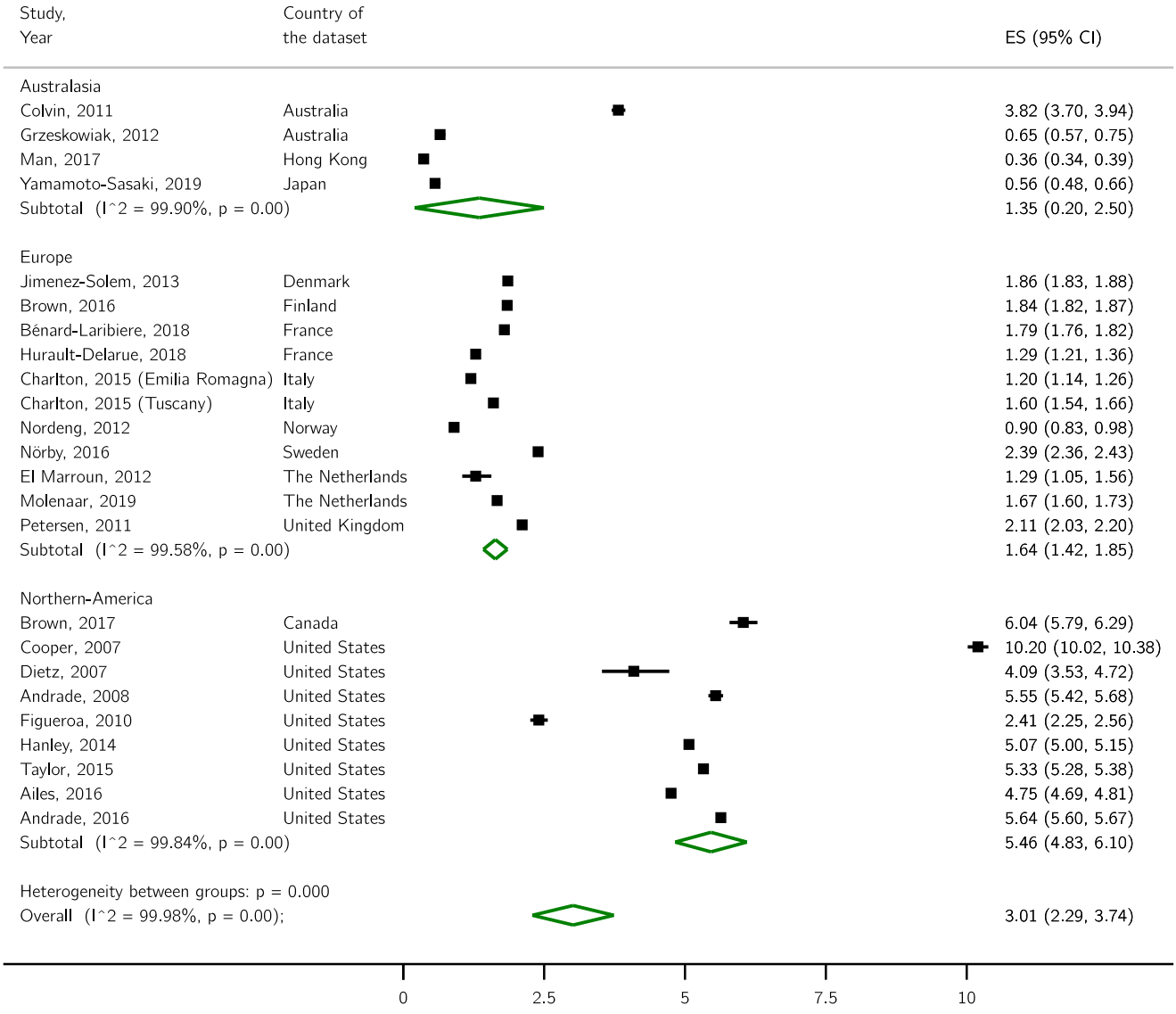

Fig. 4. Prevalence estimates of SSRIs during pregnancy stratified by region.

regards to sample size, description of subjects and setting, and response rate (Supplementary Figs. 4 and 5 in the Online Resource).

3.8. Sensitivity analysis

The overall prevalence estimates per type of antidepressant differed substantially between random- and fixed-effect calculations. The prevalence estimate for SSRIs during pregnancy was 2.33% (95%CI

Table 1
Studies reporting prevalence rates of antidepressants during pregnancy over time.

Study	Start	%	End	%		Country	AD type
Petersen (2011)	1992	0.8	2006	3.3	↑	United Kingdom	Overall
Andrade (2008)	1996	2.0	2005	7.6	↑	USA	Overall
	1996	1.5	2005	6.2	↑		SSRIs
Jimenez-Solem (2013)	1997	0.2	2009	3.2	↑	Denmark	Overall
Cooper (2007)	1999	5.7	2003	13.4	↑	USA	Overall
	1999	2.9	2003	10.2	↑		SSRIs
Molenaar (2019)	1999	0.8	2014	2.1	↑	The Netherlands	SSRIs
Huybrechts (2015)	2000	2.3	2010	2.6	→	USA	SSRIs
Andrade (2016)	2001	1.7	2010	14.9	↑	USA	SSRIs
Charlton (2015)	2004	1.4	2009	1.8	→	Italy (Tuscany)	SSRIs
Charlton (2015)	2004	1.4	2009	1.3	→	Italy (Emilia Romagna)	SSRIs
Taylor (2015)	2005	7.7	2013	6.3	↓	USA	Overall
Hurault-Delarue (2018)	2005	2.0	2014	1.7	→	France	Overall
Hanley (2014)	2010	6.7	2011	6.4	→	USA	Overall
Andrade (2016)	2010	14.9	2013	10.8	↓	USA	SSRIs

Narratively reported prevalence rates in the start year and end year of the cohort. Studies are sorted on start date of reported cohort. Arrows indicate an increase (green), stabilization (yellow) or decrease (red) of prevalence rates. A difference <0.5% is regarded as stabilization.

2.32;2.34) using fixed-effects and 3.01% (95%CI 2.29;3.74) using random-effects calculations. For SNRIs, this was 0.35% (95%CI 0.34;0.36) and 0.73% (95%CI 0.54;0.92), and for TCAs 0.16% (95%CI 0.16;0.17) and 0.38% (95%CI 0.29;0.46) respectively.

The results of the sensitivity analysis for SSRI use during pregnancy are presented in Supplementary Figure 6 (Online Resource). Retrospective studies reported an almost four times higher prevalence (3.19%) than prospective studies (0.93%; *p*-value <0.01). Exposure defined by prescription/dispensing records showed an overall prevalence of 3.23%, while exposure based on self-report had a prevalence rate of 1.53% (*p*-value = 0.02). No significant differences were seen in prevalence between studies including livebirths only, singletons only, or inclusion of consecutive pregnancies (*p*-values between 0.21 and 0.48). Prevalence estimates stratified by the quality assessment of an appropriate sample frame indicated lower prevalence rates in appropriate sample frames (2.20%) compared to non-appropriate sample frames (3.85%; *p*-value <0.01). Studies with a detailed description of subjects and setting had a lower prevalence rate (3.02%) compared to studies without (4.20%; *p*-value <0.01), although only two studies in this analysis lacked a detailed description (Taylor et al., 2015; Yamamoto-Sasaki et al., 2019).

Results of small-study assessment can be found in the Online Resource (Supplementary Fig. 7).

4. Discussion

Our findings demonstrate that the international use of antidepressants in the perinatal period depends on geographical region, type of antidepressant and certain methodological factors. SSRIs were the most commonly used antidepressant during pregnancy, with an international prevalence estimate of 3.0% (95% CI 2.3;3.7) across a 26-year period (from 1989 to 2015). A qualitative increase in prevalence of antidepressants during pregnancy was noted. The most striking difference in prevalence estimates arose when stratifying by geographical region. While the countries in Europe and Australasia had pooled prevalence estimates of 1.6% and 1.3% respectively, Northern America had a prevalence estimate of 5.5%. Unfortunately, no studies were available from Eastern European countries, or from developing geographical regions such as the Middle East, Central Asia and the African continent, perhaps as a result of the absence of central birth registers, linking pharmacy to birth records.

The observed differences in prevalence estimates for antidepressant use during pregnancy by geographical region may reflect differences in the prevalence and/or severity of underlying mental disorders leading to medication use. However, previous studies have demonstrated similar lifetime prevalence rates in English-speaking high-income countries and European high-income countries (Steel et al., 2014). It is more plausible that the geographical variations are due to local prescribing behavior of medication in general as well as prescribing behaviors specific to antidepressants. In addition, help-seeking behavior of the population and the organization of health care likely contribute to geographic variation in antidepressant use. For example, in the United States psychotherapy is often associated with out of pocket expenses. Moreover, people in the US use mental health services less than in other developed countries, while these services are consistently more expensive in the US than in comparably wealthy OECD countries (Sawyer and Sroczynski, 2016). The US has a lower number of psychologists (0.93) and psychiatrists (7.79) per 100,000 population than most comparable countries (31 psychologists and 18 psychiatrists per 100,000 on average) (Sawyer and Sroczynski, 2016). The bulk of mental health services for people with depression are therefore provided in primary care settings, who prescribe 79% of antidepressant medications (Barkil-Oteo, 2013). A survey amongst primary care physicians showed that two-thirds reported that they could not get outpatient mental health services for patients due to provider shortages, health plan barriers and lack of coverage, thereby affecting offered treatment methods (Cunningham, 2009).

Studies with detailed information on type of SSRI observed that sertraline was most frequently prescribed during pregnancy, followed by citalopram and fluoxetine. Sertraline is recommended for use during pregnancy by multiple guidelines due to its favorable profile during lactation (Pinheiro et al., 2015). Fluoxetine is not recommended as first choice due to its long half-life and presence in breastmilk. Use of paroxetine has been associated to an increased risk of congenital cardiovascular malformation, but this is not confirmed (Grigoriadis et al., 2013b). In general, guidelines discourage switching during pregnancy, even when using a non-preferred SSRI (Molenaar et al., 2018b).

When we stratified by definition of SSRI use, we found a higher prevalence estimate for studies using pharmacy records (prescription/dispensing data) compared to studies relying on self-report. There is some evidence that self-reported psychiatric medication use is less accurate (Haapea et al., 2010; Van den Brandt et al., 1991), as a result of social desirability bias or self-stigmatization (Cotterchio et al., 1999; Nielsen et al., 2008; Rauma et al., 2013), but a recent large population-based study showed the opposite: a very good agreement between antidepressant self-report and prescription data (Hafferty et al., 2018). The observed difference might therefore rather reflect a difference in included study population.

There was a trend for a decrease in prevalence for both SSRIs and TCAs from preconception to pregnancy, persisting into the second trimester. Many women are reluctant to continue antidepressants during pregnancy, because of potential negative consequences for the fetus, and express a preference for non-pharmacological treatment (Battle et al., 2013). Additionally, providers may counsel women to discontinue antidepressants in pregnancy due to fears of fetal exposure, sometimes unfortunately at the expense of maternal health and safety (Molenaar et al., 2018a). Approximately 50% of women therefore decides to discontinue their medication, either shortly before pregnancy or during their first trimester (Molenaar et al., 2019). Since antidepressants are often not initiated during pregnancy, this results in lower prevalence rates in the second and third trimesters. But discontinuation patterns have changed over time, with fewer women discontinuing their antidepressants in the more recent calendar years (Molenaar et al., 2019). It is unclear whether this trend to continue more often is initiated by clinicians or pregnant women themselves.

Current guidelines do not give clear recommendations regarding the continuation or discontinuation of antidepressant maintenance treatment throughout pregnancy (Molenaar et al., 2018a, 2018b), which is remarkable given the high prevalence of antidepressant use. Multiple recent studies in the general (non-pregnant) population showed equal efficacy of psychotherapy to antidepressant continuation in remitted patients (Bockting et al., 2018; Fava et al., 2004; Kuyken et al., 2015, 2008; Segal et al., 2010).

Lastly, we looked at prevalence rates over time. We used qualitative trend analysis from twelve cohorts since the included studies had limited quantitative information on prevalence rates per subsequent calendar year. While substantial increases in prevalence rates were observed in cohorts with a start date between 1992 and 2001, cohorts with a start date from 2004 onwards showed a stabilization or even small decrease in prevalence rates. This may indicate saturation of the market or reflect public opinion on the safety and efficacy of antidepressants during pregnancy. In contrast, prevalence rates in the general population were still rising in these later time periods (Hafferty et al., 2019; Pratt et al., 2017). The latter may, however, result both from an increased longer-term use by regular antidepressant users driving much of the increased reported prevalence, and from an increase in the aging population, who in general have a higher prevalence of antidepressant use (Pratt et al., 2017). Future studies are encouraged to quantitatively assess prevalence rates of antidepressants during pregnancy over time to adequately map longitudinal evolution of prescribing behavior in an international setting.

Our study has several limitations. We restricted our inclusion to articles written in English, and did not search grey literature, which may have contributed to the absence of data from low- and middle-income countries. We did not contact authors of excluded articles. In the estimation of prevalence rates per trimester, some women might have contributed information to multiple subgroups (when they continued medication throughout several trimesters), which underestimates the variation between groups. Furthermore, we found that substantial heterogeneity remained unaccounted for throughout the analyses, even after accounting for hypothetical contributors. Prevalence intervals were wide, predicting high variability in future studies.

The results of this meta-analysis indicate that antidepressant use during pregnancy is prevalent, with substantial variability based on geographical region and study population. Driving factors for geographical differences, such as health care service barriers and prescribing behavior, have to be identified in order to improve treatment management. Special emphasis should be placed on research examining the effectiveness of antidepressant maintenance treatment during the perinatal period to determine the justifiable prevalence rate of antidepressants. Furthermore, risks of discontinuation and use of other treatment and preventive options such as psychological interventions should be examined in rigorous trials. Only after we have an accurate estimate of the risks and benefits to both the fetus and the mother with continuation and discontinuation of antidepressants, as well as alternative therapies when discontinuing antidepressants, can we begin to develop evidence-based clinical guidelines for women with mental health illnesses and their providers.

CRediT authorship contribution statement

Nina M. Molenaar: Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Babette Bais:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Mijke P. Lambregtse-van den Berg:** Writing - review & editing. **Cornelis L. Mulder:** Writing - review & editing. **Elizabeth A. Howell:** Writing - review & editing. **Nathan S. Fox:** Writing - review & editing. **Anna-Sophie Rommel:** Writing - review & editing. **Veerle Bergink:** Writing - review & editing. **Astrid M. Kamperman:** Conceptualization, Data curation, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interests.

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Supplementary materials

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