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Review article

Prevalence of benzodiazepines and benzodiazepine-related drugs exposure before, during and after pregnancy: A systematic review and meta-analysis

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ABSTRACT

Background: Maternal use of benzodiazepines during pregnancy is common and has increased over the last decades. In this systematic review and meta-analysis, we studied the literature to estimate the worldwide use of benzodiazepines before, during and after pregnancy, which could help to estimate benzodiazepine exposure and to prioritize and guide future investigations.

Methods: We systematically searched Embase, Medline Ovid, Web of Science and Cochrane Central up until July 2019 for studies reporting on benzodiazepine use before (12 months), during and after pregnancy (12 months). Random effects meta-analysis was conducted to calculate pooled prevalence estimates, as well as stratified according to substantive variables.

Results: We identified 32 studies reporting on 28 countries, together reporting on 7,343,571 pregnancies. The worldwide prevalence of benzodiazepine use/prescriptions during pregnancy was 1.9% (95%CI 1.6%-2.2%; I^2 97.48%). Highest prevalence was found in the third trimester (3.1%; 95%CI 1.8%-4.5%; I^2 99.83%). Lorazepam was the most frequently used/prescribed benzodiazepine (1.5%; 95%CI 0.5%-2.5%; I^2 99.87%). Highest prevalence was found in Eastern Europe (14.0%; 95%CI 12.1%-15.9%; I^2 0.00%).

Limitations: All analyses revealed considerable heterogeneity.

Conclusions: Our meta-analysis confirmed that benzodiazepine use before, during and after pregnancy is prevalent. The relatively common use of benzodiazepines with possible risks for both mother and (unborn) child is worrying and calls for prescription guidelines for women, starting in the preconception period. Given the substantial proportion of children exposed to benzodiazepines in utero, future research should continue to study the short- and long-term safety of maternal benzodiazepine use during pregnancy and to explore non-pharmacological alternative treatments.

1. Introduction

Maternal use of prescription drugs during pregnancy is approached with caution by both pregnant women and their health care professionals, considering the potential harmful fetal effects during pregnancy on one hand, while considering maternal health on the other hand. Nonetheless, prescribed medication use is common during pregnancy, with estimations of 27–93% of pregnant women filling at least one prescription drug during pregnancy (e.g. anti-infectives, antihypertensive agents and psychotropic drugs), with a wide range between countries (Daw et al., 2011). In addition, the use of these medications during pregnancy has increased in the past decades (Bjorn et al., 2011; Mitchell et al., 2011; Smolina et al., 2015), including the use of benzodiazepines (Martin et al., 2015) and

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benzodiazepine-related drugs (Askaa et al., 2014).

Benzodiazepines and benzodiazepine-related drugs are generally prescribed for the treatment of sleep problems and anxiety disorders (Brunton et al., 2011; Shyken et al., 2019). These drugs have anxiolytic, hypnotic, muscle relaxant and anticonvulsant properties and may relieve symptoms in the short-term (Donoghue and Lader, 2010; Shyken et al., 2019). However, they are highly addictive and guidelines advise against long-term use (Ashton, 1994; Nelson and Chouinard, 1999), which is associated with pharmacological tolerance (Gravielle, 2016), physiological and psychological dependence and withdrawal (Shyken et al., 2019). When used during pregnancy, benzodiazepines and benzodiazepine-related drugs pass readily through the placenta, with a greater placental transfer in late pregnancy, compared to early pregnancy (Kanto, 1982). Associations with a range of adverse birth outcomes have been observed, such as higher risk of spontaneous abortion (odds ratio (OR) 2.39, 95% confidence interval (CI) 2.10–2.73) (Sheehy et al., 2019) and preterm birth (OR 2.03, 95% CI 1.11–3.69) (Ogawa et al., 2018). Moreover, maternal use of these drugs in the third trimester is associated with floppy infant syndrome, including symptoms of hypothermia, lethargy and respiratory problems (Bulletins–Obstetrics, 2008), which is also seen in the association between maternal use and the need for neonatal ventilatory support (OR 1.81, 95% CI 1.39–2.37) (Yonkers et al., 2017) and neonatal intensive care unit admissions (OR 2.02, 95% CI 1.11–3.66) (Freeman et al., 2018). On top of that, withdrawal symptoms may persist for several months in the neonate (Bulletins–Obstetrics, 2008). However, a meta-analysis in one million pregnancies did not find increased teratogenic risks, such as cardiovascular malformations and oral cleft, yielding an OR of 1.07 (95% CI 0.91–1.25) for cohort studies and of 1.27 (95% CI 0.69–2.32) for case-control studies (Enato et al., 2011). Unfortunately, in studies regarding the effects of benzodiazepine and benzodiazepine-related drug use during pregnancy on fetal development and birth outcomes, information on whether use is intermittent or chronic is often lacking. These studies on the use during pregnancy remain therefore inconclusive, especially the long-term effects are not entirely clear at this point (El Marroun et al., 2014).

Unfortunately, to date, clear data on the use of benzodiazepines and benzodiazepine-related drugs related to pregnancy remains unknown. In light of the considerable increase of prescribed medication during pregnancy in general, and with the potential harmful (fetal) effects of these drugs in particular, we assessed worldwide benzodiazepine and benzodiazepine-related drug use during the peripartum period. This could help to estimate exposure and to prioritize and guide future investigations.

We expect that prevalences drop during pregnancy, compared to the preconception period, for pregnant women have a strong preference for non-pharmacological treatment, because of possible harm for their unborn infant (Battle et al., 2013; Kothari et al., 2019). We expect an increase in the postpartum period again, for the high prevalence of sleep problems in postpartum women (Lee et al., 2000).

2. Objectives

This systematic review and meta-analysis aims at providing data on the prevalence of benzodiazepines and benzodiazepine-related drugs in the peripartum period. We studied the use of these prescription drugs before, during and after pregnancy, in the different trimesters, in various countries and we examined prevalence rates over time.

3. Methods

This meta-analysis was registered in PROSPERO under number CRD42018117197.

3.1. Literature search

A medical information specialist conducted the systematic electronic literature search on August 13th 2018. The search was conducted in Embase, Medline Ovid, Web of Science and Cochrane Central from inception onwards, using search terms describing the types of drugs (e.g. benzodiazepines, oxazepam), the target population (e.g. maternal, pregnancy) and the type of study (e.g. epidemiology, prevalence). A complete overview of the different search terms is shown in the Supplementary Material. The search was updated by a medical information specialist on July 2nd 2019.

3.2. Study criteria

PRISMA guidelines were followed for the reporting of the selection of the studies (Liberati et al., 2009). Studies were eligible for inclusion if they were peer-reviewed and written in English. We included observational studies that described any population of women using benzodiazepines or benzodiazepine-related drugs in the peripartum period, which we defined as: 12 months before pregnancy, during pregnancy and 12 months following pregnancy. We included studies that reported on use during pregnancy in general, in a specific trimester or at certain time points (e.g. first antenatal visit). We included benzodiazepines (Anatomical Therapeutic Chemical (ATC) codes N05BA and N05CD) and benzodiazepine-related drugs (ATC codes N05CF). Observational studies reporting a prevalence rate including the cohort size or reporting a numerator and denominator were included. Studies reporting on use without specifying the specific peripartum phase (before, during or after pregnancy) were excluded. We excluded conference abstracts, case-control studies, case reports, case series and reviews. Studies providing data in all countries were eligible for inclusion. No restrictions were set for year of publication.

3.3. Study selection and data collection

Duplicates were screened and removed with the citation manager EndNote. Two reviewers (BB, NM) independently screened the titles and abstracts and assessed the full text of the potential eligible studies. Mismatches between reviewers' selection were resolved by discussion until consensus was reached. When multiple papers reported on the same cohort, we included the publication with the highest level of detail (e.g. a study reporting on the prevalence before, during and after pregnancy was chosen over a study from the same cohort reporting on pregnancy only).

Two reviewers (BB, NM) extracted data using a data extraction form. Prevalence rate was extracted as outcome. As numerator, we used the number of pregnancies or the number of women using benzodiazepines or benzodiazepine-related drugs in a specific peripartum phase. As denominator, we used the total number of pregnancies or total number of women of the matching peripartum phase. Additionally, we extracted information regarding study period, type of study (retrospective or prospective), methods of recruitment of participants, geographic location, additional in- and exclusion criteria and definition of drug use (body sample, self-report and/or prescription records). We extracted whether cohorts included live births only and whether multiple pregnancies were included.

3.4. Quality assessment

The reviewers assessed the quality of the studies using the Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data (Munn et al., 2015). Potential bias was assessed with regard to the following design elements: sample frame, sampling method, sample size, detailed description of subjects and setting, measurement method, adequate response rate and sufficient coverage.

We considered a sample frame appropriate when the sample was a

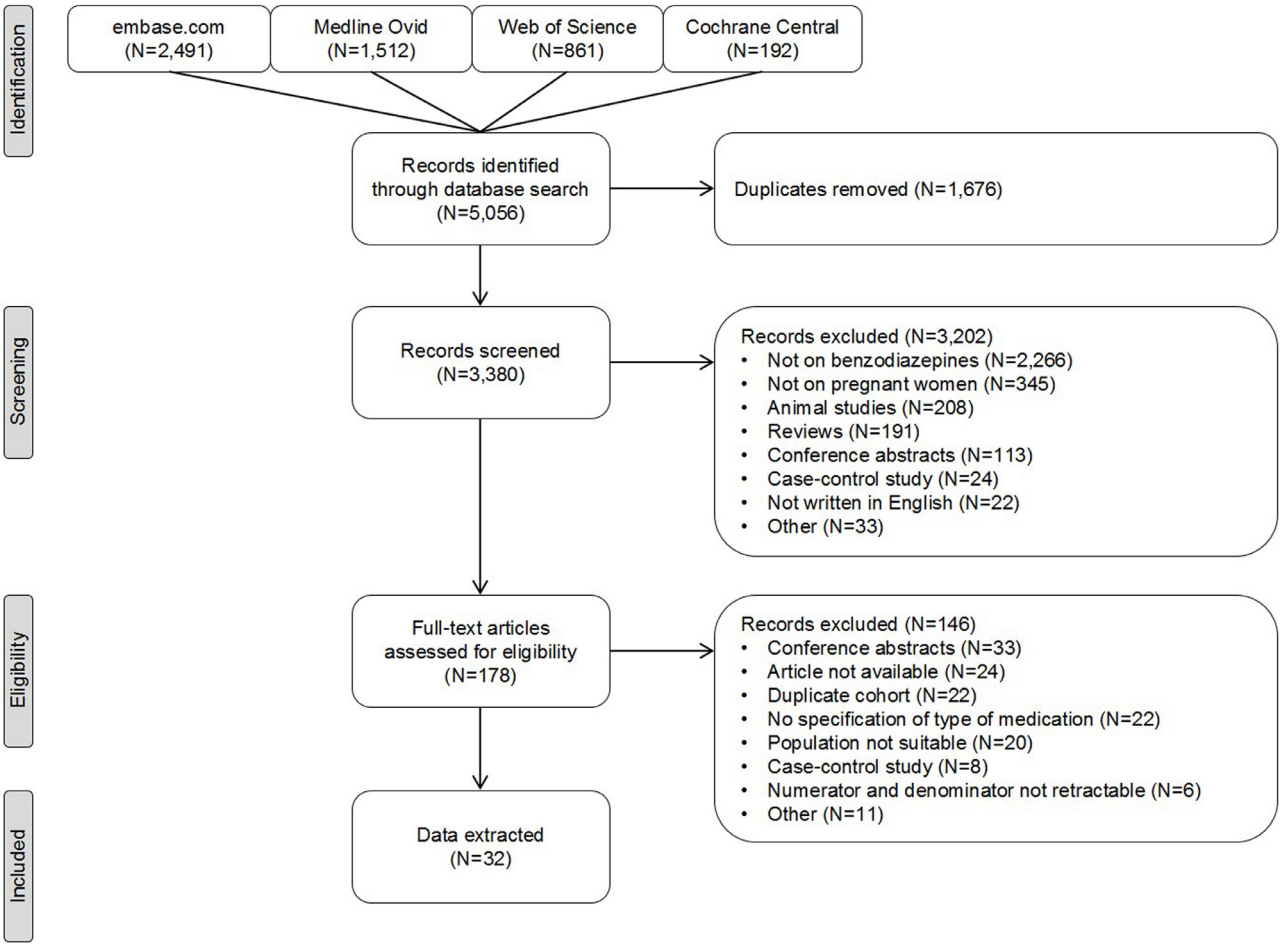

Fig. 1. Flow-chart of the article selection process in a meta-analysis of international use of benzodiazepine and benzodiazepine-related drugs in the peripartum period.

valid representation of the population of that country, such as information from national registers. A sampling method was considered appropriate when in- and exclusive criteria were not restrictive, for example not excluding women with a history of a mental disorder. Given the expected prevalence rate of overall benzodiazepine and benzodiazepine-related drug use, we considered sample sizes larger than 1000 women adequate. We considered all methods for outcome measurement valid (body samples such as urine and hair, (redemption of) prescriptions and self-reported use). Self-reported use was not considered as a standardized measurement method, all other methods (prescriptions and body samples, such as urine and hair) were regarded as standardized.

3.5. Statistical analysis

Data was analyzed using STATA (version 15, STATA Corporation, College Station, TX, USA) using *metaprop* procedures, which is able to perform meta-analyses of binomial data (Nyaga et al., 2014). We used random effects estimation and a 95% CI to calculate an overall prevalence. Subgroup differences were tested using the random effects model as well. Random effects was chosen over fixed effects as substantial heterogeneity was expected (Munn et al., 2015). We reported Cochrane's Q, I^2-statistics and significance levels. We conducted a meta-analysis when it was possible to pool data from two or more papers.

In our primary analysis, we studied the prevalence rates of benzodiazepines during pregnancy. Secondly, we studied the prevalence rates of benzodiazepines before and after pregnancy and benzodiazepine-related drugs before, during and after pregnancy. Next, to study benzodiazepine use during pregnancy into more detail, we studied the prevalence rates of benzodiazepines per trimester. We also studied prevalence rates of various specific benzodiazepines and benzodiazepine-related drugs during pregnancy. Then, we conducted our primary meta-analysis stratified by region, as important differences were expected. We identified 8 different regions: Northwestern Europe (Denmark, Finland, France, Germany, Iceland, Ireland, The Netherlands, Norway, Sweden, United Kingdom), Southern Europe (Italy, Malta, Monaco, Spain), Eastern Europe (Croatia, Czechoslovakia, Yugoslavia), North America (Canada, United States), Central and South America (Brazil, Costa Rica, Panama), Asia (India, Japan, Sri Lanka, Taiwan) and Africa (Ghana, Togo, Zimbabwe).

Due to limited information on prevalence rates per calendar year, we qualitatively reviewed the impact of time on prevalence rates first. In addition, the time trend was analyzed using random effects meta-regression analysis. For this analysis, we included articles for which the study period was made explicit. Regression coefficients and 95% CI are reported.

3.6. Sensitivity analyses

We stratified our primary analysis for substantive and methodological variables, the latter including quality criteria. For the prevalence by definition of medication use, we assessed self-report only, self-report + medical records versus prescription/dispensing, since only one study reported on self report + hair sample. We did not stratify for prevalence by live births only, since all studies included in the primary meta-analysis included all births. We used both random and fixed effect

calculation for our primary analyses to evaluate the impact of the estimation method for the use of benzodiazepines during pregnancy.

3.7. Small study effects

Funnel plots were used to visually assess the presence of small study effects, i.e. the tendency for the smaller studies in a meta-analysis to show larger outcomes. A funnel plot depicts the prevalence estimates against their standard error. In the bottom-right half, small studies with large prevalence estimates are shown. Studies in the bottom-left half are often omitted, since small studies reporting small non-significant effects are less likely to be published (Sterne and Egger, 2001). The presence of a small study effect was assessed formally by Egger's regression-based test (Egger et al., 1997). Small study effects are explored per pregnancy phase among studies reporting on benzodiazepine use.

4. Results

4.1. Selection of studies

The literature search produced 5056 papers, 3380 after de-duplication. Based on title and abstract, 3202 articles were excluded, 178 full-text articles were thus assessed for eligibility. After this assessment, 32 articles were included in this meta-analysis for further analyses. All studies reported on one database from one country, except for the study by Marchetti et al., who reported on 22 cohorts from 22 countries (Marchetti et al., 1993). Fig. 1 shows a flow-chart of the selection process. Interrater reliability was considered moderate to good (raw interrater agreement: 96%; kappa: 0.57, 95% CI 0.50–0.63) (Cohen, 1960).

4.2. Study characteristics

Prevalence data for benzodiazepine and benzodiazepine-related drug use in the peripartum period was analyzed for a total sample of 7343,571 pregnancies from 28 countries. Sample size per cohort ranged from 50 to 1886,825 pregnancies. Six studies focused on the year before pregnancy, all 32 studies focused on the pregnancy period itself (either on the complete pregnancy or on one or more trimesters) and four studies focused on the first year after pregnancy. Most studies included information on benzodiazepines in general (N = 23), while some studies focused on at least one specific benzodiazepine-related drug (N = 7). Nine studies focused on one or more specific benzodiazepines. Prevalence rates are reported across a 37-year period (from 1980 to 2017). Seventeen studies (53.1%) were retrospective cohorts. Detailed characteristics are provided in Supplementary Table 1 and 2.

4.3. Prevalence of medication in the peripartum period

Table 1 shows the pooled prevalence estimates for benzodiazepines before, during and after pregnancy and in the specific trimesters. One study reported on benzodiazepine-related drugs before, during and after pregnancy, with a prevalence of respectively 0.4%, 0.3% and 0.2% (Askaa et al., 2014). One study reported on the prevalence of benzodiazepines and benzodiazepine-related drugs combined before and during pregnancy, with a prevalence of respectively 3.6% and 3.9% (Hanley and Mintzes, 2014).

Benzodiazepine use increased from preconception to pregnancy (from 0.9% to 1.9%), with a subsequent decrease to postpartum (0.5%), which was statistically significant (Q-value = 392.63; df = 2; $p < .01$). Specifically, benzodiazepine prevalence was 0.5% in the first trimester, 0.3% in the second trimester and 3.1% in the third trimester, which differed statistically significant (Q-value = 21.78; df = 2; $p < .01$). Substantial heterogeneity was found between the different studies (>40% I^2).

Prevalence rates of benzodiazepines before, during and after pregnancy per individual cohort are shown in Supplementary Figures 1 to 3 in the online supplement.

4.4. Prevalence of specific drugs during pregnancy

Four studies reported specifically on the use of diazepam and lorazepam, three studies on temazepam and alprazolam, and two studies on oxazepam, zolpidem and clonazepam during pregnancy. All other benzodiazepines or benzodiazepine-related drugs were studied by one study only. Table 1 shows the pooled prevalence estimates of these specific benzodiazepines and benzodiazepine-related drugs. Considerable heterogeneity was found among the studies (>40% I^2). The highest prevalence rate was found for lorazepam (1.5%), followed by zolpidem (1.0%). The lowest prevalence rate was found for temazepam and alprazolam (both 0.1%). The difference between the specific benzodiazepines and benzodiazepine-related drugs was tested significant (Q-value = 1278.42; df = 6; $p < .01$).

4.5. Variation in prevalence estimates per region

Table 2 shows the pooled prevalence estimates of benzodiazepines during pregnancy per region. Analyses revealed substantial heterogeneity between the studies (>40% I^2). The highest prevalence estimate was found in Eastern Europe (14.0%), followed by Southern Europe (3.8%) and Central and Southern America (2.3%). Lowest prevalence estimates were found in Asia (0.9%) and Northwestern Europe (1.2%). Prevalence between regions differed significantly (Q-value = 187.18; df = 6; $p < .01$).

4.6. Prevalence rates over time

No cohorts reported prevalence rates (including numerator and denominator) over a series of subsequent calendar years. Two studies mentioned prevalence rates (in percentages, therefore unsuitable for meta-regression) in the first and last year of their cohort. Askaa et al. mentioned an increase in the prevalence of benzodiazepine-like drugs from 0.18% in 1997 to 0.23% in 2010 (Askaa et al., 2014). Martin et al. reported an increase in the prevalence of benzodiazepines from 0.3% in 2002 to 1.0% in 2009, with the highest prevalence in 2005 (1.2%) (Martin et al., 2015). Using meta-regression, we tried to quantify the development of the prevalence rates over time. Analyses were conducted including a subset of studies (N = 19) reporting on benzodiazepine use during pregnancy over a limited time frame (<5 years) (Azadi and Dildy, 2008; Bardy et al., 1994; Bergman et al., 1992; Bernard et al., 2019; Blotiere et al., 2019; Chaves et al., 2009; Daw et al., 2012; Hanley and Mintzes, 2014; Hurault-Delarue et al., 2016; Lendoiro et al., 2013; Leppee et al., 2010; Marchetti et al., 1993; Oga et al., 2018; Potchoo et al., 2009; Radojčić et al., 2017; Rausgaard et al., 2015; Sanaullah et al., 2006; Sherwood et al., 1999; Wang et al., 2010). Of four studies, the studied time frame was unknown or not clear, these were therefore excluded of these analyses (Bosio et al., 1997; Calderon-Margalit et al., 2009; McMillin et al., 2015; Sloan et al., 1992). Meta-regression did not show a significant increase of use over time during pregnancy (β = 0.001; 95% CI −0.003–0.01; p = .62).

4.7. Risk of bias

An overview of the quality assessment can be found in Supplementary Figures 4 and 5. Overall, most included studies had a low risk of bias on at least five out of seven quality criteria (87.5%). Four studies had a high risk of bias on three out of seven quality criteria (Chaves et al., 2009; Leppee et al., 2010; Marchetti et al., 1993; Rausgaard et al., 2015), three studies had a high risk on two quality criteria and an unclear risk on one quality criterion (Bosio et al., 1997; Calderon-Margalit et al., 2009; Potchoo et al., 2009). Most studies used

Table 1
Global random effects prevalence estimates of benzodiazepines in the peripartum period.

	Prevalence of benzodiazepines in the peripartum period							
	N of cohorts	N of pregnancies	N of countries	Random effects% prevalence	Forest plot of pooled random effect prevalence	95% CI	I^2 statistic (%)	Q statistic (df; p-value)
Benzodiazepines								
Year before pregnancy	2	357,317	2	0.9%		0.9%−0.9%	0.00	
During pregnancy	27	522,914	21	1.9%		1.6%−2.2%	97.48	
Year after pregnancy	2	346,218	2	0.5%		0.5%−0.6%	0.00	392.63 (2; <0.01)
Benzodiazepines								
First trimester	9	2163,124	6	0.5%		0.3%−0.7%	99.55	
Second trimester	2	357,317	2	0.3%		0.3%−0.3%	0.00	
Third trimester	5	448,680	3	3.1%		1.8%−4.5%	99.83	21.78 (2; <0.01)
Pregnancy								
Lorazepam	4	418,932	3	1.5%		0.5%−2.5%	99.87	
Zolpidem	2	225,016	2	1.0%		0.9%−1.0%	0.00	
Oxazepam	2	169,322	2	0.7%		0.7%−0.7%	0.00	
Diazepam	4	172,742	4	0.3%		0.0%−0.6%	95.45	
Clonazepam	2	165,875	2	0.3%		0.3%−0.3%	0.00	
Temazepam	3	1276,079	3	0.1%		0.1%−0.2%	96.72	
Alprazolam	3	172,115	3	0.1%		0.0%−0.1%	73.14	1278.42 (6; <0.01)
					0% 3% 6%			

Pooled prevalence rates calculated using random effect estimation. Analyses of trimesters and of specific benzodiazepines are not sub analyses of benzodiazepines during pregnancy.

Table 2
Global random effects prevalence estimates of benzodiazepines during pregnancy in different regions.

	Prevalence of benzodiazepines during pregnancy				Forest plot of pooled random effect prevalence	95% CI	I^2 statistic (%)	Q statistic (df; p-value)
	N of cohorts	N of pregnancies	N of countries	Random effects% prevalence				
Benzodiazepines								
Eastern Europe	2	1279	2	14.0%		12.1% – 15.9%	0.00	
Southern Europe	4	6853	3	3.8%		1.4% – 6.1%	93.07	
Central & South America	3	1274	2	2.3%		0.9% – 3.7%	55.10	
North America	3	118,746	2	1.8%		0.7% – 2.9%	99.93	
Africa	2	840	2	1.5%		0.7% – 2.3%	0.00	
Northwestern Europe	9	353,698	7	1.2%		0.8% – 1.5%	61.73	
Asia	4	44,660	3	0.9%		0.4% – 1.5%	83.88	187.18 (6; <0.01)
					0%	8%	16%	

Pooled prevalence rates calculated using random effect estimation.

a standardized measurement method (78.1%), provided detailed descriptions of subjects and settings (75%), had an adequate sample size (62.5%) and the sampling method was appropriate (62.5%). In most studies, the sample frame was considered inappropriate (65.6%). For example, Bergman et al. only included women who had Medicaid insurance (Bergman et al., 1992). Various studies, such as the study by Azadi et al. (Azadi and Dildy, 2008), Bosio et al. (1997), Chaves et al. (2009), Lendoiro et al. (2013) and Potchoo et al. (2009), included women who delivered at one specific hospital. Other studies, such as the study by Radojcic et al. (2017) and Calderon-Margalit et al. (2009) only included women who participated in a study. For all studies, risk of bias in coverage and response rate were considered low.

4.8. Sensitivity analyses

When assessing the impact of the estimation method, the overall prevalence estimates differed substantially between random and fixed effects calculations. The prevalence of benzodiazepines during pregnancy was 1.9% (95% CI 1.6% − 2.2%) using random effects and 1.0% (95% CI 1.0% − 1.0%) using fixed effects.

Table 3 shows the prevalence estimates of benzodiazepines during pregnancy, stratified by methodological variables and variables indicating risk of bias. When stratified by methodological variables, prospective studies reported a more than twice as higher prevalence (2.7%), compared to retrospective studies (1.2%; $p < .01$). Prevalence stratified by definition of benzodiazepine use also showed variation: exposure defined by self-report and/or hair sample in one study showed a prevalence of 11%, while exposure based on prescription or dispensing records showed a prevalence of 1.2% ($p < .01$). A significant difference was found between studies including singletons only (0.7%), compared to studies that did not (2.7%; $p < .01$).

Prevalence estimates stratified by the quality criteria all showed higher prevalences for high risk of bias, compared to low risk of bias. Studies with a standardized measurement method had a lower prevalence (1.4%), compared to studies that had unstandardized methods (3.1%; $p < .01$). Studies with a detailed description of subjects and settings had a lower prevalence rate (1.1%), compared to studies without (2.8%: $p < .01$). Studies with an adequate sample size had a lower prevalence (1.4%), compared to studies with an inadequate sample size (4.0%; $p < .01$). There were no studies with an inappropriate sampling method. Studies with an appropriate sampling method had a higher prevalence (2.5%), compared to studies with an unclear risk of bias (1.2%; $p < .01$). Prevalence estimates stratified by the quality assessment of an appropriate sample frame indicated lower prevalence rates in appropriate sample frames (0.9%), compared to inappropriate sample frames (2.4%; $p < .01$).

4.9. Small study bias

The funnel plot and the accompanying Egger's test regarding benzodiazepine use during pregnancy is reported in Supplementary Figure 6. There were only two observations in the preconception period and two observations in the postpartum period, precluding an Egger's test. The sample sizes of the studies during pregnancy ranged from small to (very) large. However, most studies were (very) large, depicted by the majority of the studies in the upper half of the plot. The asymmetric shape of the funnel plot further suggested the presence of reporting biases and/or heterogeneity between the studies. In the lower right half of the plot, we found a few cohorts from the study by Marchetti et al. (1993), indicative of a small studies effect. Egger's test reached significance for the included studies ($\beta = 2.40$; 95% CI −0.34–5.13; $p = .08$), suggesting publication bias.

Table 3
Global random effects prevalence estimates of benzodiazepines during pregnancy, stratified by substantive and methodological variables.

	Prevalence of benzodiazepines during pregnancy									
	N of cohorts	N of pregnancies	N of countries	Random effects% prevalence	Forest plot of pooled random effect prevalence	95% CI	I^2 statistic (%)		Q statistic (df; p-value)	
Methodological factors										
Prevalence by research design										
Prospective	23	30,568	21	2.7%		2.1% – 3.3%		94.85		
Retrospective	4	492,346	4	1.2%			0.6% – 1.8%	99.51		11.32 (1; 0.01)
Prevalence by definition medication use										
Self-report + hair sample	1	209	1	11%			–	–		
Self-report	19	14,448	19	3.1%			2.2% – 4.1%	94.85		
Self-report + records	4	16,157	4	1.5%			0.7% – 2.3%	94.49		
Prescription/dispensing	3	492,100	3	1.2%			0.5% – 1.8%	99.67	11.57 (2; < 0.01)	
Prevalence by singletons only										
No	24	128,275	22	2.7%			2.1% – 3.2%	95.37		
Yes	3	394,639	3	0.7%			0.5% – 1.0%	95.91	37.65 (1; < 0.01)	
Risk of bias criteria										
Standardized measurement method										
High risk of bias	20	14,694	19	3.1%			2.1% – 4.0%	95.64		
Low risk of bias	7	508,220	6	1.4%			1.0% – 1.9%	99.12	9.81 (1; .< 0.01)	
Detailed subjects and setting description										
High risk of bias	20	118,787	20	2.8%			2.1% – 3.5%	95.64		
Low risk of bias	7	404,127	7	1.1%			0.8% – 1.4%	94.92	19.58 (1; .< 0.01)	
Adequate sample size										
High risk of bias	18	7142	17	4.0%			2.6% – 5.4%	94.98		
Low risk of bias	9	516,102	8	1.4%			1.0% – 1.8%	98.84	11.76 (1; < 0.01)	
Sampling method appropriate										
Low risk of bias	23	161,300	20	2.5%			2.0% – 3.0%	97.51		
Unclear	4	361,614	4	1.2%			0.8% – 1.6%	94.41	13.45 (1; 0.01)	
Appropriate sample frame										
High risk of bias	25	170,333	20	2.4%			1.9% – 2.9%	97.38		
Low risk of bias	2	352,581	2	0.9%			0.9% – 0.9%	0.00	35.59 (1; < 0.01)	
					12%					
0%										
6%										

Pooled prevalence rates calculated using random effect estimation.

4.10. Comment

In this meta-analysis, we found a global prevalence of benzodiazepine use of 0.9% (95% CI 0.9% − 0.9%) before pregnancy, of 1.9% (95% CI 1.6% − 2.2%) during pregnancy and of 0.5% (95% CI 0.5% − 0.6%) after pregnancy. Our analyses showed that the prevalence is highly dependent on trimester, type of drug and region. Also, the prevalence was influenced to a great extent by characteristics of the study. Among the different studies, substantial heterogeneity was found.

4.11. Changes in prevalence in the postpartum period

In this meta-analysis, we observed that the prevalence during pregnancy was approximately four times higher compared to the postpartum period. However, the pooled prevalence in the postpartum period mainly originated from one large study (Riska et al., 2014), which may not be representative. This decrease in the postpartum period differs from the prevalence of other psychotropic medication, such as antidepressant medication, where prevalence generally increases from pregnancy to the postpartum period (Andrade et al., 2016; Cooper et al., 2007; Jimenez-Solem et al., 2013; Molenaar et al., 2019). Possibly, postpartum women do not want to use benzodiazepines or benzodiazepine-related drugs at night, for they want to stay alert for any nocturnal signals of their infant. Secondly, these drugs are transferred to breast milk (Kanto, 1982), which may drive the decrease in prevalence in the postpartum period.

Prevalence was highest in the third trimester (3.1%; CI 1.8% − 4.5%), followed by the first (0.5%; CI 0.3% − 0.7%) and second trimester (0.3%; CI 0.3% − 0.3%). A meta-analysis showed that during pregnancy sleep quality decreases from the second to the third trimester (Sedov et al., 2018), which may drive the increase in benzodiazepines in the third trimester. The decrease in sleep quality may be caused by increased sleeping problems as the third trimester progresses, when women have more difficulty finding a comfortable sleeping position (Mindell and Jacobson, 2000). Restless leg syndrome is common during pregnancy, with an increase to approximately 22% in the third trimester, which might also contribute to sleeping problems (Chen et al., 2018). Gastroesophageal reflux is most common in the third trimester (Ramu et al., 2011), which may be uncomfortable while laying down in bed, hence causing problems with sleep. Additionally, there is evidence suggesting that women experience more anxiety in the third trimester, which is also an indication for prescribing benzodiazepines or benzodiazepine-related drugs (Teixeira et al., 2009). Literature is not consistent in which trimester exposure would be more harmful for the fetus. On one hand, it is advised to avoid drug use during the first trimester, due to potential teratogenic risks (Iqbal et al., 2002), although these risks have thus far not been demonstrated by a meta-analysis (Enato et al., 2011). On the other hand, it is also mentioned that late third trimester use is associated with more risks for the fetus or neonate (McElhatton, 1994), including the risk of floppy infant syndrome, which could lead to hypoxia and even irreversible damage in the neonate (Bulletins–Obstetrics, 2008).

Of note, the high prevalence in the third trimester is mostly due to the study by Bardy et al. (1994), who reported a prevalence of 13.4% (95% CI 11.5% − 15.5). This study was conducted to study the use of analgesics during labor in obstetric practice, which could explain the high prevalence.

In a study from the United States, approximately 5.2% of the general population used benzodiazepines, with use being twice as prevalent among women compared to men (Olfson et al., 2015). Among women of childbearing age, prevalence ranged from 3.6% to 7.1% (Olfson et al., 2015). This prevalence is substantially higher, compared to the prevalence of 1.8% we found in the United States and the overall prevalence of 1.9%.

4.12. Types of drugs

The most often used or prescribed benzodiazepine or benzodiazepine-related drug was lorazepam, followed by zolpidem. The US Food and Drug Administration has categorized various drugs according to their risk during pregnancy and lactation (Howland, 2009). Most drugs, such as lorazepam, oxazepam and diazepam are categorized as D, indicating that there is evidence of human fetal risk (Okun et al., 2015). Zolpidem, the second most used or prescribed drug during pregnancy, is categorized as C, indicating that use is warranted (Okun et al., 2015), which might explain why this drug is second most used or prescribed during pregnancy. Underlying indications may explain the differences in prevalence. For example, in the United States, men are more likely to receive long-acting benzodiazepines, which are more preferred for anxiety, whereas women are more likely to receive short-acting benzodiazepines that are more preferred for insomnia (Mendelson, 1992). However, this should be studied in future research, since we do not have information on indications.

4.13. Variance among countries

We observed a substantial difference between prevalence rates based on region. The highest prevalence estimate was found in Eastern Europa, followed by Southern Europe and Central and South America. The lowest prevalence was found in Asia. International differences in use and prescriptions may reflect differences in the prevalence and/or severity of mental health problems (Steel et al., 2014), but could also be due to differences in prescribing behavior of physicians, beliefs about medication use in the population and available medical facilities. Other studies in psychotropic medication also found large variations among countries, both in youth and adults (Balter et al., 1984; Steinhausen, 2015; Zito et al., 2008, 2006). However, our findings must be approached with caution, since the three regions with the highest prevalence rates had a pooled sample size of 1279, 6853 and 1274, which could have biased the findings. In comparison, North America and Northwestern Europe had pooled sample sizes of 118,746 and 353,698 respectively, which may have produced more reliable findings.

4.14. Prescriptions versus use

We found different prevalence rates in our sensitivity analyses. Interestingly, when studies used prescription or dispensing records as a proxy for benzodiazepine use, the pooled prevalence was lower than when women reported their benzodiazepine use. This finding may be explained by women sporadically using medication from family members or friends. A study in the Netherlands showed that almost 13% of the general population acquired prescribed drugs through non-formal channels, with sleeping medication being one of the most frequently illegally obtained drugs (Koenraadt and De Haan, 2016). However, underestimation could still play a role here, when women are ashamed or feel guilty about medication use during pregnancy and do not admit to use medication during pregnancy (Hafferty et al., 2018). On the other hand, registry data may overestimate actual use due to non-compliance. Also, medications dispensed in the year preceding pregnancy, may actually be taken during pregnancy or even postpartum, which may under- and/or overestimate the prevalence in these peripartum phases. At this point, it is not entirely clear which method is more reliable in estimating the prevalence of benzodiazepine use. It is reported by one study that a high concordance between self-report and prescription data is indicated in a population of pregnant women, expect for medications used intermittently (Sarangarm et al., 2012). Since benzodiazepines and benzodiazepine-related drugs are usually used sporadically, on an “as needed” basis, it is possible that self-reported use may underestimate or overestimate prevalence rates in studies.

4.15. Rates over time

Lastly, we looked at prevalence rates over time. Only two studies reported on different years in their cohort, both finding an increase of benzodiazepines or benzodiazepine-related drugs in the past years (Askaa et al., 2014; Martin et al., 2015). Meta-regression did not show a significant change in benzodiazepine use over time during pregnancy. There were not enough studies to repeat these analyses in studies on the year preceding pregnancy or the year following pregnancy. Possibly, due to changing treatment guidelines in the treatment of anxiety disorder, where patients are more and more treated with antidepressants instead of benzodiazepines (Berney et al., 2008; Offidani et al., 2013), prevalence may decrease over time. However, due to the limited information, we cannot draw stringent conclusions on prevalence rates over time.

4.16. Limitations

Differences in study design, outcomes, time period and data collection made it difficult to pool all studies. For example, some studies only examined a specific trimester, whereas other studies reported the prevalence on the entire pregnancy. Various studies reported on benzodiazepine and benzodiazepine-related drug use during pregnancy, whereas other studies only reported on a specific drug. Additionally, all analyses revealed considerable heterogeneity. Despite using random-effects analyses, our results should therefore be interpreted with caution.

We have no information on dosing or the amount of prescriptions dispensed by women. Therefore, we have no information on intermittent and chronic users.

Only three studies had a low risk of bias on all seven quality criteria, indicating that the quality of most of the included studies is suboptimal. This is especially shown in the sample frame: approximately two third of the studies reported prevalence from an inappropriate sample frame. For future studies, it is important to conduct prospective longitudinal studies of high quality both on short-term and long-term effects, considering the high prevalence of in utero drug exposure. Moreover, it is important to learn which measurement method of benzodiazepine and benzodiazepine-related drug use is most reliable. Methodological sound studies may be helpful in supporting the development of evidence-based guidelines, which could offer guidance in the treatment of pregnant women and potentially lowering the amount of prescriptions and use of benzodiazepines and benzodiazepine-related drugs by pregnant women.

5. Conclusion

The use of benzodiazepines and benzodiazepine-related drugs during pregnancy is relatively common, in particular during the third trimester. Considering most used or prescribed drugs are considered as high-risk by the Food and Drug Administration, with potentially severe adverse outcomes for the (unborn) child, this is a worrying finding. Women and their prescribing physicians should be better informed about potential adverse outcomes, particularly as self-treatment and stigmatization are common. Also, the found high prevalence of benzodiazepine use in particular regions, such as Eastern Europe, is of concern. Given the substantial proportion of children exposed to these drugs in utero, future research should continue to study the short- and long-term safety of maternal use during pregnancy and to explore non-pharmacological alternative treatments.

CRediT authorship contribution statement

Babette Bais: Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Nina M. Molenaar:** Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Hilmar H. Bijma:** Conceptualization, Visualization, Writing - review & editing. **Witte J.G. Hoogendijk:** Project administration, Supervision, Writing - review & editing. **Cornelis L. Mulder:** Supervision, Writing - review & editing. **Annemarie I. Luik:** Conceptualization, Visualization, Writing - review & editing. **Mijke P. Lambregtse-van den Berg:** Project administration, Conceptualization, Supervision, Writing - review & editing. **Astrid M. Kamperman:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

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