



Prescription patterns of benzodiazepine and benzodiazepine-related drugs in the peripartum period: A population-based study

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ABSTRACT

Using prescription drugs during pregnancy is challenging and approached with caution. In this study, we present population-based information on prescription patterns of benzodiazepines and benzodiazepine-related drugs in the peripartum period. A population-based study of 1,154,817 pregnancies between 1997 and 2015 in Denmark, of which 205,406 (17.8%) pregnancies in women with a psychiatric history. Prescription drugs starting with Anatomical Therapeutic Chemical codes N05BA, N05CD, and N05CF from 12 months before pregnancy to 12 months following pregnancy were identified. We used generalised estimating equations to estimate the adjusted 5 year risk difference in the proportion of women redeeming benzodiazepines from 1 year to 5 years after. Logistic regression was used to analyze the association between characteristics and discontinuation of benzodiazepines during pregnancy. The prevalence of benzodiazepine prescriptions was 1.9% before pregnancy, 0.6% during pregnancy, and 1.3% after pregnancy. In women with a psychiatric history, the prevalence was 5–6 times higher. A significant decrease in prescriptions to women with a psychiatric history was observed, which was less profound among women with no psychiatric history. Approximately 90% of women discontinue benzodiazepines during pregnancy, with a higher percentage of women discontinuing from 1997 to 2015. The observed decrease is likely explained by changing treatment guidelines.

1. Introduction

The use of prescription drugs during pregnancy is approached with caution by both pregnant women and their health care professionals, weighting both fetal and maternal health. Despite this caution, prescribed medication use is common during pregnancy, with estimations of 27–93% of pregnant women using prescription drugs (Daw et al., 2011), including benzodiazepines. Benzodiazepines are prescribed for the treatment of anxiety disorders and also sleep problems (Brunton et al., 2011). The effects of benzodiazepines are mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (D'Hulst et al., 2009). Benzodiazepines have anxiolytic, hypnotic, anticonvulsant, and muscle relaxant properties, which can relieve symptoms in the short term (D'Hulst et al., 2009; Donoghue and Lader, 2010). However, benzodiazepines are highly addictive and guidelines advice against long term use (Ashton, 1994; Nelson and Chouinard, 1999).

Studies on maternal use of benzodiazepines during pregnancy mainly focused on adverse birth outcomes. A recent study showed an increased risk of spontaneous abortion with an odds ratio (OR) of 1.85 (95% confidence interval (CI) 1.61–2.12) (Sheehy et al., 2019). An increased risk was also found for preterm birth (OR 2.03; 95% CI 1.11–3.69) (Ogawa et al., 2018), cesarian delivery (OR 2.45; 95% CI

1.36–4.40), low birth weight (OR 3.41; 95% CI 1.61–7.26), and use of neonatal ventilatory support (OR 2.85; 95% CI 1.20 – 6.90) (Yonkers et al., 2017). Children exposed to benzodiazepines in utero have a higher chance to be admitted to a neonatal intensive care unit (OR 2.02; 95% CI 1.11 – 3.66) and to have small head circumferences (OR 3.89; 95% CI 1.25 – 12.03) (Freeman et al., 2018). Most studies adjusted for underlying maternal mental illness (Freeman et al., 2018; Sheehy et al., 2019; Yonkers et al., 2017), which are also associated with adverse birth outcomes (Grote et al., 2010; Jarde et al., 2016). A meta-analysis did not find increased teratogenic risks, 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).

Considering the potential risks of the use of benzodiazepines, it is important to have an overview of prescription patterns of benzodiazepines and benzodiazepine-related drugs in the peripartum period, which will be helpful in estimating the prevalence of benzodiazepine usage and to explore future research priorities. This is considered relevant, as the use of prescription medication during pregnancy has increased in the past decades (Bjorn et al., 2011; Ingstrup et al., 2018; Mitchell et al., 2011; Smolina et al., 2015). In the present study, we aimed to present population-based information on prescription patterns of benzodiazepines and benzodiazepine-related drugs in the peripartum

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period over 19 years in Denmark. We further studied whether prescription prevalence rates increased in accordance with trends observed in other prescription medications.

2. Method

2.1. Study population

We conducted a population-based cohort study using Danish national registers. All individuals in Denmark have a unique personal civil registration number that enables the individual-level linkage of information across nationwide registries. All pregnancies leading to live birth(s) in Denmark between 1 January 1997 and 31 December 2015 ($N = 1182,529$) were identified from the Danish Medical Birth Registry (Bliddal et al., 2018), since prescription data was available until 2016 and prevalence was studied until 12 months after delivery. The registry contains data on the mother and child, such as parity, date of birth, birth weight, length, sex, and gestational age of the offspring. We excluded 660 pregnancies by women aged <15 or >45 years. Furthermore, 27,052 pregnancies were excluded due to missing information in gestational age or if gestational age was recorded as <22 weeks or >45 weeks. Thus, 1154,817 pregnancies were included in the analyses.

2.2. Assessment of prescription for benzodiazepine and benzodiazepine-related drugs

Information on medication prescriptions in the peripartum period was obtained from the linkage of study subjects to the National Prescription Registry (Pottegård et al., 2017). The register contains individual-level data on all prescribed drugs dispensed at all pharmacies in Denmark since 1995. Registered information includes the type of drug, strength, quantity dispensed, and dispensing dates. The international Anatomical Therapeutic Chemical (ATC) classification system was used to code all medications. From April 1st, 2004 onwards, an indication variable was also added. The prescriber, e.g., a general practitioner or a hospital physician, may select an indication code from a drop-down menu containing a list of indications, or they can include the indication as free text, in which case no code is recorded (Denmark Statistics, 2013). Women were considered as user of benzodiazepines or benzodiazepine-related drugs (hereinafter referred to as benzodiazepines) if they claimed any drugs starting with ATC codes N05BA, N05CD, and N05CF from 12 months prior to the pregnancy to 12 months following the pregnancy. We defined pregnancy from the first day of the last menstrual period until delivery. We estimated the start of pregnancy by subtracting gestational age from the birth date. Since 1995, ultrasound measurements have been widely used to determine gestational age in nearly all pregnancies (Jorgensen, 1999).

2.3. Assessment of psychiatric history

In this study, we also focused on women with a psychiatric history, since treatment decisions are even more complex in this group (Ingstrup et al., 2018). We defined previous psychiatric history as at least one in- or outpatient treatment for psychiatric disorders or redeemed one prescription for psychotropic medications (ATC codes N05 and N06) at the time of 12 months before the index pregnancy. Information on psychiatric history before pregnancy was extracted from the Danish Psychiatric Central Research Register (Mors et al., 2011). It contains data on all inpatient contacts since 1969 and from 1995 also outpatient contacts. The International Classification of Diseases (ICD) codes, version 8 (ICD-8) was used from 1977 to 1993 and ICD-10 from 1994 and onwards. The following ICD codes were used to identify psychiatric disorders: ICD-8 codes 290–315; ICD-10 codes F00–F99.

2.4. Treatment indications of benzodiazepine prescriptions

We investigated the treatment indications of benzodiazepine prescriptions in a subset of women who gave birth to children from 2007 to 2015, due to substantial missing or unspecified indication codes during 2004–2005 in the Danish National Prescription Registry. Here, the number of prescriptions is counted, and overall, 27,094 prescriptions dispensed before pregnancy, 6820 during pregnancy and 16,574 after pregnancy were included. We excluded the prescriptions with missing or unspecified indications; 6898 (25.5%) before pregnancy, 2064 (30.3%) during pregnancy, and 3884 (23.4%) after pregnancy.

2.5. Ethics

Registries were linked, and personal data analyzed on Statistics Denmark, where data was made available with encrypted personal information. This ensures that no individuals can be identified. In Denmark, The Act on Processing of Personal Data does not require ethical permission or obtained written informed consent for anonymised retrospective registry studies. The present study has been approved by the Danish Data Protection Agency.

2.6. Statistical analysis

All data management and analyses were performed using Stata 15.0 (StataCorp, College Station, TX, USA). We analyzed dispensed benzodiazepine prescriptions in women during three periods: 12 months leading to pregnancy, during pregnancy, and 12 months after pregnancy. We first examined the overall prevalence of benzodiazepine prescriptions before, during, and after pregnancy. We allowed for exposure to benzodiazepines several times during the study period. For further explanation of the calculation of period prevalence, consider the following example: woman A redeemed three prescriptions from 12 months before pregnancy to 12 months after pregnancy, one before pregnancy, one during pregnancy, and another after pregnancy. She will consequently contribute information in the calculation of period prevalence before, during, and after pregnancy.

To determine whether patterns of prescribing of benzodiazepine drugs changed over time, we used generalised estimating equations with an identity link to estimate the adjusted 5-year risk difference (Hanley et al., 2003), i.e., the difference in the proportion of women redeeming benzodiazepines before, during, or after pregnancy from one year to five years after. We treated calendar year as a continuous variable (in years), and adjusted for age (<25 , 25–34 or ≥ 35 years), primiparity (yes/no), and socioeconomic status (lowest quartile, second quartile, third quartile, or highest quartile) at the time of delivery in the models. Since the pattern of benzodiazepine prescriptions may be influenced by previous psychiatric history, all the analyses were stratified by previous psychiatric history.

We defined the following seven mutually exclusive benzodiazepine groups: (1) prescriptions before pregnancy only; (2) prescriptions during pregnancy only; (3) prescriptions after pregnancy only; (4) prescriptions both before and during pregnancy; (5) prescriptions both before and after pregnancy; (6) prescriptions both during and after pregnancy; (7) prescriptions before, during, and after pregnancy. Note, the number of women with benzodiazepine prescriptions was counted for these analyses. In the analysis of the association between general characteristics and discontinuation of a benzodiazepine during pregnancy, only women receiving benzodiazepine prescriptions before pregnancy (i.e., group 1, 4, 5, and 7) were included, and binary logistic regression models were used. The following characteristics were included in the models: age at delivery, primiparity, socioeconomic status, previous psychiatric history, hospital contact for psychiatric disorders, and co-dispensing of other psychotropic medication (ATC codes N05 and N06 excluding N05BA, N05CD, and N05CF; yes or no) in the year before pregnancy, and calendar year at delivery (1997–2000,

Table 1
Characteristics of the study population.

Characteristics	Women with psychiatric history ^a		Women with no psychiatric history		Total (N = 1154,817)
	No prescription drug (N = 930,291)	With prescription drug (N = 19,120)	No prescription drug (N = 186,576)	With prescription drug (N = 18,830)	
Age at conception (years)					
15–24	22,084 (11.8)	1934 (10.3)	124,228 (13.4)	2930 (15.3)	151,176 (13.1)
25–34	119,776 (64.2)	11,525 (61.2)	651,921 (70.1)	12,796 (66.9)	796,018 (68.9)
35–45	44,716 (24.0)	5371 (28.5)	154,142 (16.6)	3394 (17.8)	207,623 (18.0)
Primiparous (%)	81,228 (43.5)	7872 (41.8)	420,794 (45.2)	8270 (43.3)	518,164 (44.9)
Socioeconomic status at conception					
Lowest quartile	31,246 (16.8)	4763 (25.3)	146,912 (15.8)	3500 (18.3)	186,421 (16.1)
2nd quartile	43,874 (23.5)	5102 (27.1)	181,002 (19.5)	4547 (23.8)	234,525 (20.3)
3rd quartile	44,718 (24.0)	4025 (21.4)	238,100 (25.6)	4738 (24.8)	291,581 (25.3)
Highest quartile	48,731 (26.1)	3888 (20.6)	310,342 (33.4)	5656 (29.6)	368,617 (31.9)
Unknown	18,007 (9.7)	1052 (5.6)	53,935 (5.8)	679 (3.6)	73,673 (6.4)
Other psychotropic medications in the year before pregnancy	32,984 (17.7)	7751 (41.2)	10,102 (1.1)	1872 (9.8)	52,709 (4.6)
Hospital contact for psychiatric disorders in the year before pregnancy	6120 (3.3)	2075 (11.0)	2983 (0.3)	632 (3.3)	11,810 (1.0)
Calendar year of childbirth					
1997–2000	15,446 (8.3)	3386 (18.0)	227,272 (24.4)	6397 (33.5)	252,501 (21.9)
2001–2005	40,023 (21.5)	5429 (28.8)	261,328 (28.1)	5793 (30.3)	312,573 (27.1)
2006–2010	61,612 (33.0)	5587 (29.7)	238,950 (25.7)	4244 (22.2)	310,393 (26.9)
2011–2015	69,495 (37.2)	4428 (23.5)	202,741 (21.8)	2686 (14.1)	279,350 (24.2)

^a Women with psychiatric history was defined as at least one hospital contact for psychiatric disorders or dispensing one psychotropic prescription before our study period, i.e., 12 months prior to the index pregnancy.

2001–2005, 2006–2010 or 2011–2015).

3. Results

Of 1154,817 pregnancies, 205,406 (17.8%) pregnancies were in women with a psychiatric history 12 months before pregnancy. Table 1 presents the characteristics of the study subjects. Women with a psychiatric history before pregnancy were older, were less often primiparous, and had lower socioeconomic status, compared to women with no psychiatric history. Women with a psychiatric history more often used other psychotropic medications and had more often hospital contacts for psychiatric disorders in the year before pregnancy, as expected.

The prevalence of women with benzodiazepine prescriptions was 1.9% before pregnancy, 0.6% during pregnancy, and 1.3% after pregnancy. Prevalence specifically during pregnancy was 0.5% in the first trimester, 0.3% in the second trimester, and 0.2% in the third trimester. Among 6806 women using benzodiazepines during pregnancy, 4446 (65.3%) women did not receive benzodiazepine prescriptions in the year preceding pregnancy (Table 2).

The most frequently prescribed drug was zopiclone before pregnancy, where this was oxazepam during and after pregnancy (Supplementary Table 1). Benzodiazepines were most often prescribed for sleeping problems (52.3%) in the peripartum period, followed by anxiety disorder (40.6%) and panic disorder (4.7%) (Supplementary Table 2). In women with a psychiatric history before pregnancy, the prevalence of women with benzodiazepine prescriptions in the

peripartum period was approximately 5 to 6 times higher, compared to women with no psychiatric history (Fig. 1).

Fig. 2 displays the percentage of women receiving benzodiazepine prescriptions by calendar year. From 1997 to 2015, a significant decrease in the percentage of benzodiazepines prescribed to women with a psychiatric history was observed before, during, and after pregnancy, with an adjusted 5 year risk difference of -2.3% (95% CI $-2.4 - 2.2\%$), -0.9% (95% CI $-1.0\% - 0.8\%$), and -1.5% (95% CI $-1.6\% - 1.4\%$), respectively. The decrease was less profound among women with no psychiatric history, where the risk difference was -0.2% (95% CI $-0.2\% - 0.2\%$) before pregnancy, -0.1% (95% CI $-0.1\% - 0.1\%$) during pregnancy, and -0.2% (95% CI $-0.2\% - 0.2\%$) after pregnancy.

Among 22,043 women who were prescribed benzodiazepines before pregnancy, 19,683 (89.3%) women discontinued this during pregnancy (Table 2). This percentage was lower in women with a psychiatric history (83.1%), compared to women with no psychiatric history (97.1%). A higher percentage of women discontinuing benzodiazepines during pregnancy was observed from 1997 to 2015. This increase was more profound among women with a psychiatric history (Fig. 3).

Various characteristics were associated with benzodiazepine discontinuation (Fig. 4). Primiparity, higher socioeconomic status, and a later calendar year of childbirth were associated with higher odds for discontinuation during pregnancy. A higher age, a previous psychiatric history, the use of other psychotropic medications, and hospital contacts for psychiatric disorders in the year before pregnancy were associated with lower odds for discontinuation during pregnancy.

Table 2
Prevalence of women with benzodiazepine prescriptions before, during, and after pregnancy.

Benzodiazepine prescriptions during perinatal period	With psychiatric history (N = 205,406)	With no psychiatric history (N = 949,411)
Before pregnancy only	8895 (4.3)	9087 (1.0)
During pregnancy only	1578 (0.8)	2425 (0.3)
After pregnancy only	4665 (2.3)	6796 (0.7)
Both before and during pregnancy	822 (0.4)	187 (<0.1)
Both before and after pregnancy	1337 (0.7)	364 (<0.1)
Both during and after pregnancy	280 (0.1)	163 (<0.1)
Both before, during, and after pregnancy	1253 (0.6)	98 (<0.1)

Figures are numbers of women (%).

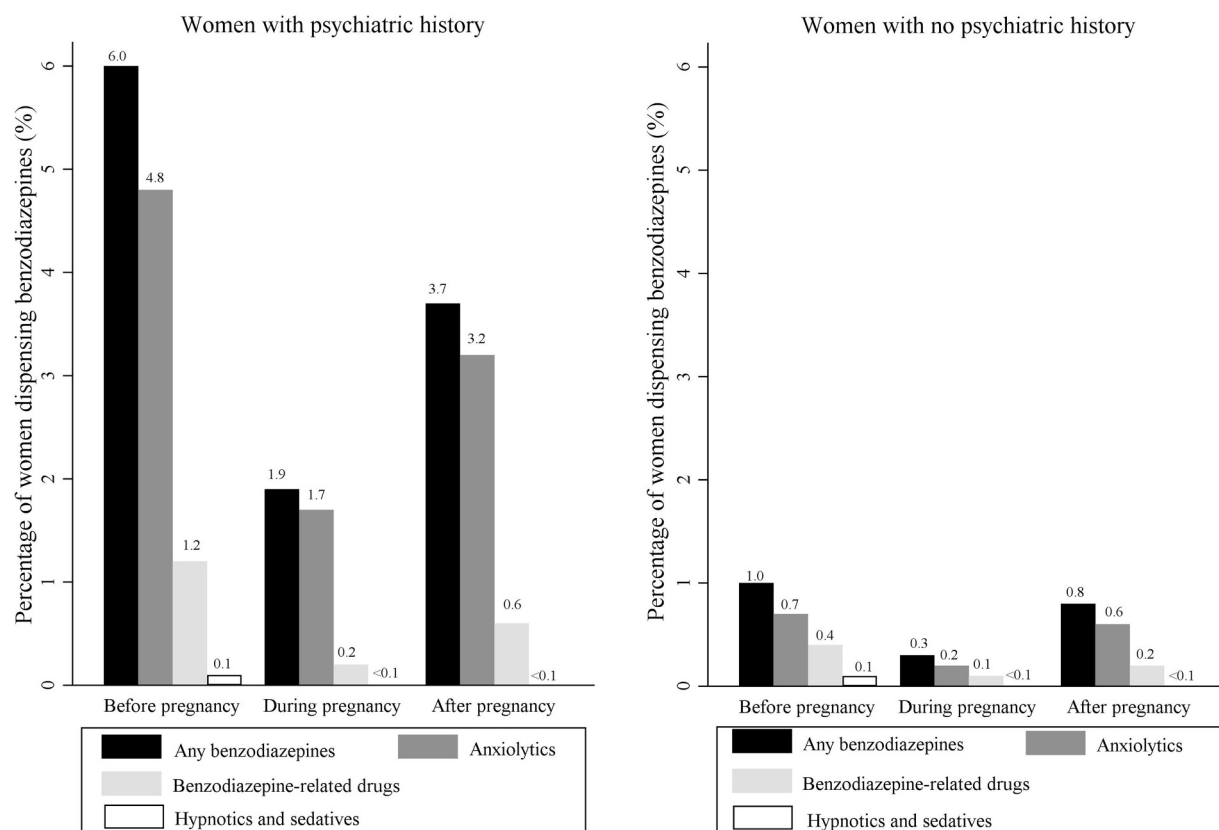


Fig. 1. The use of anxiolytics, hypnotics and sedatives, and benzodiazepine-related drugs in the year before, during pregnancy, or in the year following pregnancy.

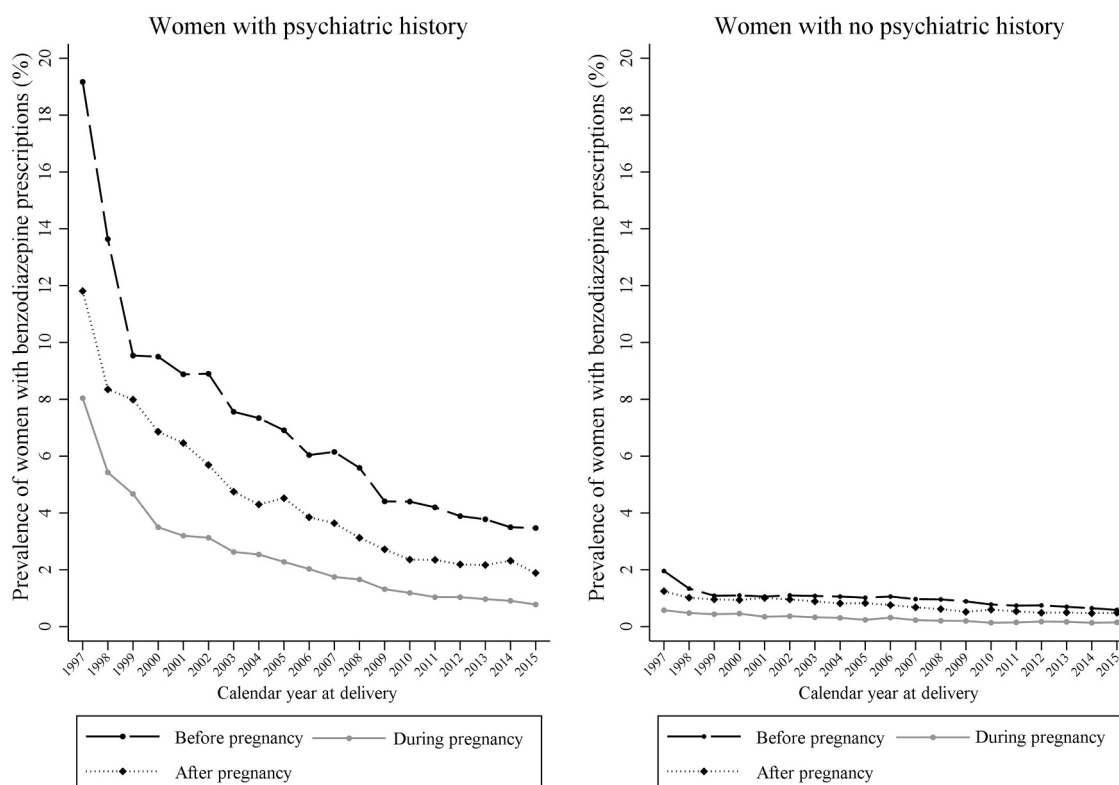


Fig. 2. Number of deliveries in which the women received a dispensing for benzodiazepine and benzodiazepine-related drugs in the year before, during pregnancy or in the year following pregnancy.

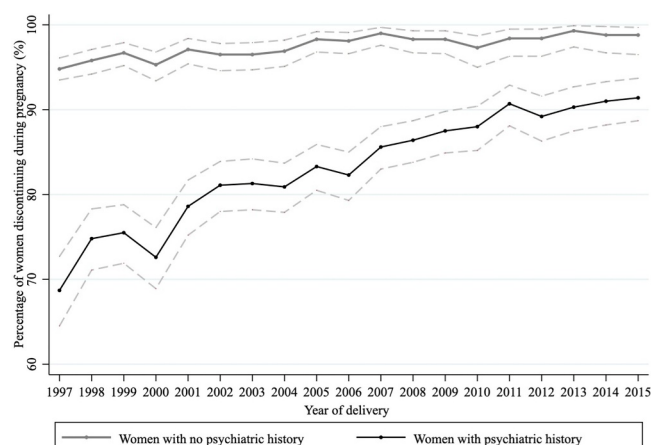


Fig. 3. Percentage of women with benzodiazepine dispensing in the year before pregnancy discontinuation during pregnancy in Denmark, 1997–2015. Dotted lines represent the 95% confidence intervals.

4. Discussion

In this population-based study, we found that the prevalence of benzodiazepine use before pregnancy is 1.9%, during pregnancy 0.6%, and after pregnancy 1.3%. In women with a psychiatric history before pregnancy, the prevalence was approximately 5 to 6 times higher than in women without such a history.

4.1. Prevalence comparison

Benzodiazepine use in the peripartum period has been studied worldwide, including Nordic countries. However, different time periods, definitions of medication use, study subjects, and data collection methods make it difficult to compare these findings directly. A population-based study conducted in Sweden found a prevalence of 0.16%

for benzodiazepines and of 0.12% for benzodiazepine-related drugs in the first trimester (Reis and Kallen, 2013). A Norwegian population-based study found a prevalence of 1.8% before pregnancy, of 1.5% during pregnancy and of 0.8% after pregnancy for benzodiazepines (Riska et al., 2014). Outside the Nordic countries, higher prevalences are observed in Europe (Ban et al., 2012; Hurault-Delarue et al., 2016; Radojcic et al., 2017), and particularly in North America, with prevalences ranging from 1.8% to 3.9% (Bergman et al., 1992; Daw et al., 2012; Hanley and Mintzes, 2014; Palmsten et al., 2015).

4.2. Change over time in prescriptions

Prescription drug use during pregnancy has increased over the past decades (Bjorn et al., 2011; Ingstrup et al., 2018; Mitchell et al., 2011; Smolina et al., 2015). However, benzodiazepine use during pregnancy throughout the years has not been studied to a great extent. One population-based study in Denmark studied the prescription rates of benzodiazepine-related drugs and found an increase from 0.18% in 1997 to 0.23% in 2010 (Askaa et al., 2014). However, this study, using the same registers, studied only benzodiazepine-related drugs, which is used by only a maximum of 10% by all benzodiazepine users (Fig. 1). The small increase of this class is obscured by the large decrease of benzodiazepines in general. A study from the United States also found an increase in benzodiazepine exposure from 0.3% in 2002 to 1.0% in 2009 (Martin et al., 2015). This is contrary to the findings from the present study, where a decrease in the prevalence of prescriptions was observed, especially in women with a psychiatric history. Many studies have reported various adverse effects on the fetus from maternal benzodiazepine use during pregnancy (Freeman et al., 2018; Ogawa et al., 2018; Sheehy et al., 2019; Yonkers et al., 2017), which may have increased awareness among women and their physicians, causing a decrease in prescriptions over the years. In the past, patients with anxiety disorders were often treated with benzodiazepines, but recent guidelines do not recommend benzodiazepines as first choice treatment for these indications (Bandelow et al., 2014). These patients are, therefore,

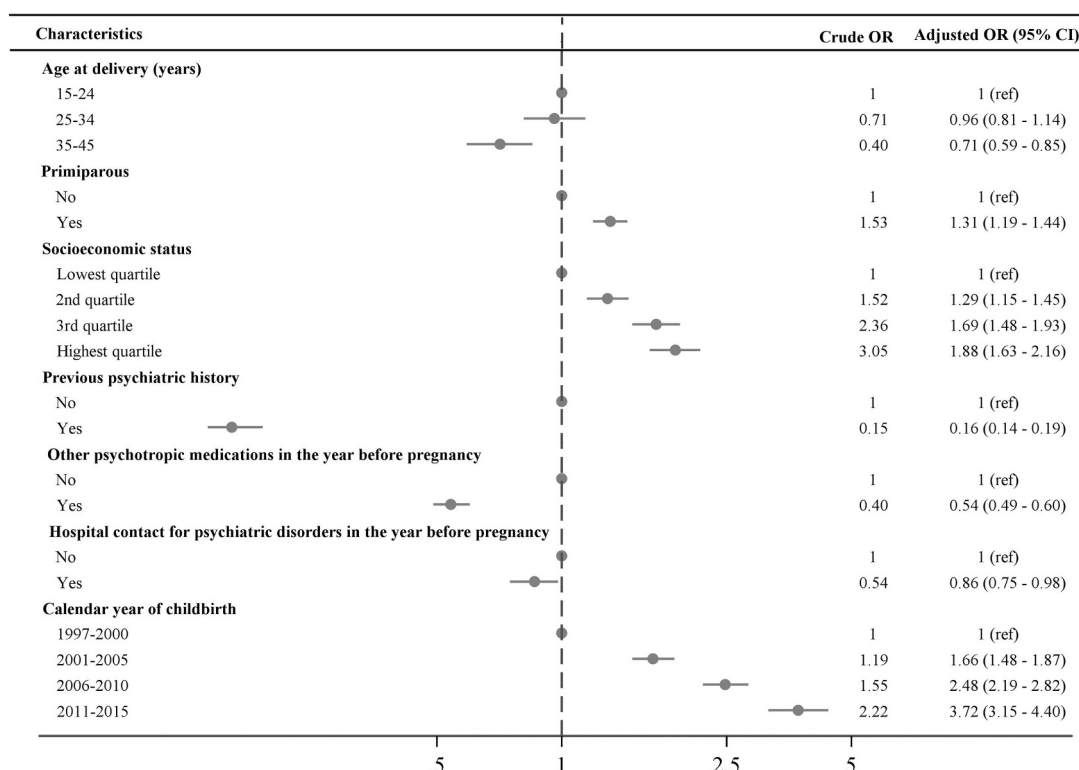


Fig. 4. The odds ratios of benzodiazepine discontinuation during pregnancy by characteristics ($N = 22,043$). All the covariates were mutually adjusted in the models.

treated more often with antidepressants instead of benzodiazepines (Berney et al., 2008; Offidani et al., 2013), which may contribute to the observed decrease in benzodiazepines in the past decades. We further speculate that women with a history of treatment at psychiatric facilities may get more information about the adverse effects of medication during pregnancy from health care providers than women without a psychiatric history, which would explain the differences in discontinuation between these groups.

4.3. Discontinuation of benzodiazepines during pregnancy

In the present study, approximately nine out of ten women discontinued benzodiazepines during pregnancy, a discontinuation pattern comparable to other studies (Askaa et al., 2014; Riska et al., 2014), which may be driven by not only a change in treatment guidelines (Berney et al., 2008; Offidani et al., 2013), but also by fear of potential adverse effects for the fetus (Arch, 2014; Einarson et al., 2001). The percentage of women discontinuing during pregnancy increased in the past years, especially among women with a psychiatric history. High discontinuation rates during pregnancy are not shown by all studies (Daw et al., 2012; Hanley and Mintzes, 2014; Palmsten et al., 2015). These differences in prescription patterns 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 national guidelines, prescribing behaviour of physicians, beliefs about medication use in the population, and available medical facilities.

4.4. Strengths and limitations

Our data were obtained from national registers, covering the entire Danish population. We studied over a million pregnancies and we are, therefore, to our knowledge, one of the largest studies studying benzodiazepine prescription patterns. However, there are some inbuilt limitations to describe use of medications using register-based data. First of all, we studied prescriptions for medication and not actual use. Non-compliance may overestimate our results, however contrarily, underestimation of the results may also have occurred, since women may sporadically use medication of family members or friends. Secondly, prescriptions are only captured from community pharmacies and not during inpatient stays, which could have underestimated our findings. However, if a woman was admitted, she would most likely be prescribed medication afterward. In this case, she would have been captured by using the prescription register. Further, we used the date of dispensing to determine the date of use. However, it is possible that women used the medication in a different trimester or peripartum phase from when the medication was dispensed. Finally, we only included pregnancies ending in live births. A recent study showed an association between benzodiazepine exposure and risk of spontaneous abortion during early pregnancy (Sheehy et al., 2019). Therefore, only including live births may have consequences for the generalizability of our findings.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2020.112993](https://doi.org/10.1016/j.psychres.2020.112993).

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