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Maternal exposure to zolpidem and risk of specific birth defects

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Summary

Zolpidem is a non-benzodiazepine agent indicated for treatment of insomnia. While zolpidem crosses the placenta, little is known about its safety in pregnancy. We assessed associations between self-reported zolpidem use 1 month before pregnancy through to the end of the third month (“early pregnancy”) and specific birth defects using data from two multi-site case–control studies: National Birth Defects Prevention Study and Slone Epidemiology Center Birth Defects Study. Analysis included 39,711 birth defect cases and 23,035 controls without a birth defect. For defects with ≥ 5 exposed cases, we used logistic regression with Firth’s penalised likelihood to estimate adjusted odds ratios and 95% confidence intervals, considering age at delivery,

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AUTHOR CONTRIBUTIONS

Meredith M Howley: Conceptualization; data curation; formal analysis; methodology; software; writing – original draft; writing – review and editing. **Martha M Werler**: Conceptualization; methodology; supervision; writing – review and editing. **Sarah C Fisher:** Methodology; writing – review and editing. **Melissa Tracy:** Conceptualization; methodology; supervision; writing – review and editing. **Alissa R Van Zutphen:** Methodology; writing – review and editing. **Eleni A Papadopoulos:** Methodology; writing – review and editing. **Craig Hansen:** Methodology; writing – review and editing. **Elizabeth C Ailes:** Methodology; writing – review and editing. **Jennita Reefhuis:** Methodology; writing – review and editing. **Mollie E Wood:** Methodology; writing – review and editing. **Mairlyn L Browne:** Conceptualization; methodology; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The findings and conclusions in this report are those of the authors, and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

race/ethnicity, education, body mass index, parity, early-pregnancy antipsychotic, anxiolytic, antidepressant use, early-pregnancy opioid use, early-pregnancy smoking, and study as potential covariates. For defects with three–four exposed cases, we estimated crude odds ratios and 95% confidence intervals. Additionally, we explored differences in odds ratios using propensity score-adjustment and conducted a probabilistic bias analysis of exposure misclassification. Overall, 84 (0.2%) cases and 46 (0.2%) controls reported early-pregnancy zolpidem use. Seven defects had sufficient sample size to calculate adjusted odds ratios, which ranged from 0.76 for cleft lip to 2.18 for gastroschisis. Four defects had odds ratios > 1.8. All confidence intervals included the null. Zolpidem use was rare. We could not calculate adjusted odds ratios for most defects and estimates are imprecise. Results do not support a large increase in risk, but smaller increases in risk for certain defects cannot be ruled out.

Keywords

birth defects; medications; pregnancy; sleep aid; zolpidem

1 | INTRODUCTION

Symptoms of insomnia, including difficulty initiating or maintaining sleep or having unrefreshing sleep, are prevalent among the general population, impacting an estimated 10%–20% (Buysse, 2013; Okun et al., 2015). Pregnant people report insomnia symptoms and poor sleep quality across all gestational months (Mindell et al., 2015; Okun et al., 2009; Okun et al., 2011; Okun & Coussons-Read, 2007; Okun, Kline et al., 2013; Okun, Luther et al., 2013). While poorer sleep patterns in later pregnancy are reported more frequently, over 25% of pregnant people report sleep issues during early pregnancy (Lee et al., 2000; Mindell et al., 2015; Okun et al., 2011; Okun et al., 2015; Okun & Coussons-Read, 2007), and an estimated 4% of pregnant people seek medications to facilitate improved sleep (Chong et al., 2013; Mindell et al., 2015). Of the variety of medications that are used both on and off label to promote sleep, non-benzodiazepine medications (zolpidem, zaleplon and zopiclone) were specifically designed to have fewer adverse effects on the central nervous system and a reduced potential for abuse compared with benzodiazepines (Creeley & Denton, 2019; Lie et al., 2015; Neubauer et al., 2018). Zolpidem (e.g. Ambien®, Zolpimist®) is one of the most commonly prescribed non-benzodiazepines (Creeley & Denton, 2019); it was approved in the USA in 1992 as an immediate-release formulation, and in 2005 as a modified-release formulation (Norman et al., 2017). Data on the prevalence of zolpidem use during pregnancy are unavailable, and data on the risks or benefits of its use during pregnancy are limited (Creeley & Denton, 2019; Okun et al., 2015). Zolpidem crosses the placenta so could potentially have teratogenic effects on the fetus, although there is no evidence of an increased risk in animal studies (Okun et al., 2015; Sasaki et al., 1993). Comparing the few existing epidemiological studies that have explored zolpidem use in pregnancy is challenging. These studies have examined different birth defect groupings, used a single combined birth defect outcome, or have grouped zolpidem use with the use of other sleep aid medications (Ban et al., 2014; Juric et al., 2009; Wikner et al., 2007; Wikner & Källén, 2011).

Investigators with the National Birth Defects Prevention Study (NBDPS), a large, population-based case–control study of risk factors for birth defects, periodically conduct screen-based exploratory analyses of the study database to detect signals for increased risks between medication components and specific birth defects (Louik et al., 2015). These analyses offer a useful method for generating new hypotheses. This is especially important as pre-marketing clinical trials generally do not include pregnant persons, and research on fetal safety is limited to animal studies. Hence, post-marketing surveillance of the teratogenicity of medications takes a long time to assess (Lisi et al., 2010). In a recent screen, elevated crude associations were observed between early-pregnancy zolpidem use (defined as 1 month before conception through to the end of the third month of pregnancy) and tetralogy of Fallot, a congenital heart defect.

Given the gap in the literature and the potential signal from the recent NBDPS screen, we sought to formally analyse self-reported zolpidem use in early pregnancy with a wide range of birth defects using data from two multi-site, case–control studies of birth defects, NBDPS and the Slone Epidemiology Center Birth Defects Study (BDS).

2 | METHODS

The NBDPS and BDS were both case–control studies designed to investigate risk factors for birth defects. Detailed methods can be found elsewhere (Parker et al., 2018; Reefhuis et al., 2015; Werler et al., 1999). Briefly, the NBDPS included pregnancies ending on or after 1 October 1997, with estimated delivery dates on or before 31 December 2011 (Reefhuis et al., 2015). Liveborn, stillborn or terminated pregnancies affected by one or more of 30 categories of major structural birth defects (“cases”), excluding those attributed to a known chromosomal or single-gene abnormality, were ascertained through birth defects surveillance programs in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah). Clinical geneticists reviewed cases to determine study eligibility, and to classify cases as isolated (one major birth defect or organ system involved), multiple (major birth defects in more than one organ system) or complex (Rasmussen et al., 2003). Congenital heart defect cases were further classified according to a protocol that considered cardiac phenotype, complexity and presence of non-cardiac defects (Botto et al., 2007). Oral clefts, glaucoma, cataracts, ventricular septal defects (VSDs) and pulmonary valve stenosis (PVS) were not ascertained by all sites for all years (Rasmussen et al., 2003). Only second- and third-degree hypospadias cases were included. Liveborn infants without any major birth defects (“controls”) were randomly selected from hospital records or birth certificates in the same catchment area as the cases.

From 1976 to 2015, BDS identified pregnancies with any major birth defect by review of discharge records at participating hospitals or birth defect registry data in greater metropolitan Boston, Massachusetts (1976–1998); areas of Massachusetts and greater metropolitan Boston (1998–2015); greater metropolitan Philadelphia, Pennsylvania (1977–2015); greater metropolitan Toronto, Ontario (1979–2006); San Diego County, California (2001–2015); parts of New York State (2004–2015); and Nashville, Tennessee (2012–2015; Parker et al., 2018; Werler et al., 1993; Werler et al., 1999). Liveborn infants without birth defects identified from study hospitals and birth certificates in the same catchment areas as

cases served as controls. For the present analysis, study subjects were restricted to those interviewed 1998–2015.

Although both studies had centres in Massachusetts, California and New York, differences in catchment areas and eligibility criteria prevented participants from being included in both studies (Parker et al., 2018). Although BDS included cases with chromosomal abnormalities and single-gene disorders, they were excluded from the present analysis to match the inclusion/exclusion criteria of NBDPS. Institutional review board approval was obtained for both NBDPS and BDS, as appropriate, and mothers provided informed consent.

The NBDPS and BDS collected self-reported pregnancy exposure information up to 24 months after delivery for NBDPS and 6 months after delivery for BDS via computer-assisted telephone interviews. In NBDPS, 67% of eligible case and 64% of eligible control mothers participated in the interview; in BDS, the participation rate approximated 65%. Neither study included specific questions about zolpidem use or sleep disorders. For both studies, participants were asked to report the name, dates and frequency of any medications used during pregnancy, but were not always asked specifically about dose or indication for each medication. Both studies used the Slone Epidemiology Center Drug Dictionary to code reported medications and link products to their active ingredient components.

Pregnancy timing was defined differently in the two studies. The NBDPS used the estimated date of conception as the reference date, defined pregnancy months as 30-day time periods around the estimated date of conception, and collected medication exposures in the 3 months before conception to the end of pregnancy. The BDS used the last menstrual period (LMP) date as the reference date, defined pregnancy months as 28-day time periods (lunar months) around the LMP, and collected medication exposures in the two lunar months before the LMP through to the end of pregnancy. To harmonise exposure dates between both studies, we calculated the estimated date of conception for BDS participants, and used the date of conception and 30-day months to define exposure periods, as was done in the NBDPS. Thus, we considered a woman exposed if she reported using zolpidem at any time in the month before pregnancy through to the end of the third month of pregnancy (“early pregnancy”). The first 3 months of pregnancy include the critical period in embryonic development associated with most structural birth defects. We included the month before conception because the exact date of conception is typically not known.

We calculated adjusted odds ratios (aORs) and profile likelihood 95% confidence intervals (CIs) using unconditional logistic regression with Firth’s penalised likelihood for defects with five or more exposed cases. Firth’s penalised likelihood estimates of model coefficients and 95% CIs do not assume symmetry of the CI around the coefficient estimate and are more appropriate for small samples (Firth, 1993). We identified potential confounders *a priori* based on the literature and hypothesised causal pathways in a directed acyclic graph (DAG; Figure S1), which included age at delivery, race/ethnicity, educational attainment, pre-pregnancy body mass index (BMI; kg m^{-2}), parity, early-pregnancy use of antipsychotics, anxiolytics or antidepressants, early-pregnancy opioid use, early-pregnancy smoking, and study (NBDPS or BDS). Given that there were small numbers of exposed for each birth defect, we minimised covariates in the final multivariable model for each

birth defect by comparing the aOR for zolpidem use from the full model with all covariates from the DAG to the aORs for zolpidem use from multivariable models with the various combinations of these potential confounders. The final multivariable model for each birth defect was selected using a change-in estimate approach such that the final multivariate model was the most parsimonious model for which the aOR and width of the CI were essentially the same as the full model (Kleinbaum & Klein, 2010). For defects with three or four exposed cases, we calculated crude odds ratios (cORs) and 95% CIs using logistic regression with Firth's penalised likelihood. We did not calculate ORs for defects with one or two exposed cases.

We conducted three sensitivity analyses. First, due to small numbers for certain birth defects, we used propensity scores to adjust for all covariates identified in the DAG described above (Glynn et al., 2006). We fit a logistic regression model among controls for the probability of zolpidem exposure conditional on the covariates, and used the parameter estimates to calculate the predicted probability of zolpidem exposure in all case and control mothers given their observed covariate values and checked balance of covariables across exposure groups (Austin, 2009; Kainz et al., 2017; Månsson et al., 2007). We adjusted exposure-outcome logistic regression models for quintiles of the propensity score, and compared the estimates from the main analysis that used standard multivariable adjustment with the estimates from the propensity score-adjusted approach.

Second, to attempt to partially control for factors prompting treatment with zolpidem, we compared the risk of each defect among early-pregnancy zolpidem users with the risk among those who reported zolpidem use only later in pregnancy (pregnancy month 4 or later).

Given the retrospective exposure assessment, misreporting of the presence or timing of sleep aid use is possible. In a third sensitivity analysis, we performed a probabilistic bias analysis to assess the impact of misclassification of zolpidem use. No internal validation data exist for the self-report of medications in the NBDPS or BDS. Instead, we used estimates from the literature for sensitivity and specificity of maternal recall of sleep aid medications in early pregnancy, and assigned bias parameters based on these values. Our bias analysis was largely informed by a medication validation conducted among a sample of participants in the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS; Howley et al., 2023). BD-STEPS is a subsequent study to NBDPS with similar methods and conducted at a subset of NBDPS sites (Tinker et al., 2015). A BD-STEPS medication validation study among a subset of participants from New York found that, when comparing self-reports with medical records, agreement and validity of medication use in early pregnancy did not differ by case/control status. Thus, we conducted a non-differential misclassification bias analysis. Using estimates from the BD-STEPS validation and two other studies comparing medication use in early pregnancy from self-report and medical records/pharmacy claims, we assumed that the sensitivities of self-reported zolpidem use were lower than specificities (Evandt et al., 2019; Howley et al., 2023; Sarangarm et al., 2012). We used the methods and SAS macro developed by Fox et al. to obtain bias-adjusted, confounder-aOR estimates (adjusting for the same confounders for each defect from the main analysis), assigning a trapezoidal distribution (minimum, mode 1, mode 2 and maximum) to the sensitivity (0.55, 0.65, 0.75,

0.90) and specificity (0.998, 0.999, 0.9995, 1.0) for use of zolpidem use (Fox et al., 2005). We sampled each bias parameter 5000 times and calculated 5000 aORs. We summarised the 5000 aORs as the median aOR and 95% simulation interval (SI), the 2.5th and 97.5th percentile of the OR distribution (Fox et al., 2005; Lash et al., 2009). We incorporated both random and systematic error into the bias-adjusted estimates by multiplying the standard error from the conventional analyses by a random standard normal deviate (Fox et al., 2005; Lash et al., 2009). We conducted all analyses in SAS (9.4; SAS, Cary, NC).

3 | RESULTS

Our analysis included 39,711 cases and 23,035 controls (30,644 cases and 11,614 controls from NBDPS; 9067 cases and 11,421 controls from BDS). Early-pregnancy zolpidem use was reported by mothers of 84 (0.2%) cases and 46 (0.2%) controls. The overall prevalence of use among mothers of controls was similar across both studies. Table 1 contains the distributions of selected characteristics among mothers of controls and cases with specific defects (defects with ≥ 5 exposed cases). Compared with control mothers, case mothers more frequently reported early-pregnancy antidepressant, antipsychotic or anti-anxiety medication use; early-pregnancy smoking; and early-pregnancy opioid use. Case mothers more frequently reported having lower educational attainment, and overweight or obese BMI than controls.

Among controls, zolpidem use was more frequent among women with non-Hispanic White race/ethnicity, higher education attainment, overweight BMI, early-pregnancy smoking, early-pregnancy antidepressant, antipsychotic or anti-anxiety medication use, and early-pregnancy opioid use (Table S1). The majority of case mothers reported sustained zolpidem use for more than 60 days in early pregnancy (n = 58, 69%), whereas 43% (n = 24) of control mothers reported sustained use in early pregnancy (Table 2).

We initially considered 47 specific birth defects (29 non-cardiac birth defects and 18 cardiac birth defects), of which seven had five or more exposed cases, and five had three or four exposed cases (Tables 3 and 4). As shown in Table 4, aORs ranged from 0.72 for cleft lip to 2.18 for gastroschisis. aORs were greater than 1.8 for cleft palate (OR = 1.83), anorectal atresia (OR = 1.89), gastroschisis (OR = 2.18) and tetralogy of Fallot (OR = 2.07). The corresponding 95% CIs for all defects included the null.

Results were generally similar in our sensitivity analysis that adjusted for a larger set of covariates using propensity scores (Table S2) in that the CIs for all defects included the null value. Yet, there were some differences. Of the four defects with aORs greater than 1.8 in the main analysis, the propensity score-aOR was further from the null for cleft palate (OR = 1.97), anorectal atresia (OR = 1.95) and tetralogy of Fallot (OR = 2.40). The propensity score-aOR for gastroschisis was attenuated (OR = 1.95). Additionally, the propensity score-aOR for PVS was 1.25, which is strengthened compared with the main analysis (OR = 0.99). Given the wide CIs, all of the propensity-aORs failed to reach statistical significance.

To partially control for underlying disease and factors prompting treatment, we compared early zolpidem users with those who reported only later-pregnancy zolpidem use (Table S3).

Results were largely similar to our main analysis. The ORs for cleft palate, anorectal atresia, gastroschisis and tetralogy of Fallot were all further from the null than in the main analysis, and were greater than 2.0. The biggest difference was for gastroschisis, where the aOR in this sub-analysis was 4.44 (compared with 2.18 in the main analysis) and the lower limit of the CI was 1.0. All the CIs in this sub-analysis were wide due to small numbers.

Analyses to assess the impact of misclassification bias were reassuring in that there was minimal impact of exposure misclassification on the estimates, assuming the assumptions and values assigned to the bias parameters underlying these analyses were accurate. The results were of similar magnitude and in the same direction (or null, in the case of PVS) as results that adjusted only for confounding (Figure 1). The ORs adjusted for confounding and non-differential exposure misclassification bias for cleft palate, anorectal atresia, gastroschisis and tetralogy of Fallot were further from the null and all greater than 2.8, although the 95% SIs were wide, reflecting the rare exposure and greater uncertainty. The SIs largely included the null value, although the lower bound of the 95% SI for cleft palate and tetralogy of Fallot were both slightly above 1.0.

4 | DISCUSSION

In our analysis of data from two large case–control studies, NBDPS and BDS, early-pregnancy use of zolpidem was rare and reported by 0.2% of control participants. For the vast majority of the 47 specific birth defects examined, we did not have enough exposed cases to calculate estimates. We had sufficient sample size (> 5 exposed cases) to calculate adjusted estimates for the association of early-pregnancy zolpidem use compared with no treatment for seven specific defects. aORs for specific defects ranged from 0.72 for cleft lip to 2.18 for gastroschisis. We observed elevated adjusted associations greater than 1.8 for four specific defects: cleft palate only, anorectal atresia, gastroschisis, and tetralogy of Fallot. The corresponding 95% CIs were wide, and all CIs included the null value of 1.0, so should be interpreted cautiously. While we cannot rule out residual confounding, the elevated associations for these four defects were robust to multiple approaches to control for a range of measured confounders.

This analysis was partially motivated by a recent NBDPS medication screen that flagged a statistical association between zolpidem use and tetralogy of Fallot (cOR > 2). Such screens can yield important information that can generate new hypotheses about medication use in pregnancy that were not assessed in pre-marketing clinical trials, especially when post-marketing surveillance does not exist (Lisi et al., 2010; Louik et al., 2015). In our analysis of combined data from NBDPS and BDS, the association with tetralogy of Fallot was one of the strongest observed (aOR = 2.07). The estimate was consistently elevated and further from the null in our three sub-analyses (propensity score-adjusted analysis, misclassification bias analysis, and when comparing with those who used zolpidem only later in pregnancy). While the CIs for tetralogy of Fallot included the null value in the main analysis, the propensity score analysis, and in the sub-analysis comparing with later in pregnancy, the CI for the estimate adjusted for confounding and misclassification bias excluded the null.

Similar to the estimate for tetralogy of Fallot, the association between zolpidem use and gastroschisis was greater than 2.0 (aOR = 2.18) and remained consistently elevated in our three sub-analyses. Younger women have a much higher risk of gastroschisis compared with older women (Jones et al., 2016), and others have identified maternal age as an important modifier of risks between other maternal exposures and gastroschisis (Feldkamp et al., 2019; Fisher et al., 2022; Haddow et al., 1993; Siega-Riz et al., 2009). In our analysis, however, there were not enough exposed gastroschisis cases to formally analyse additive or multiplicative interaction between zolpidem and maternal age. Among the six exposed zolpidem cases, four occurred in women older than 25 years at delivery. This corresponds to an unadjusted OR of 5.8 (1.9, 14.0) when the analysis is restricted to women older than 25 years. This estimate is much further from the null than the gastroschisis finding in our main analysis [unadjusted OR of 1.80 (0.72, 3.81), aOR of 2.18 (0.81, 5.03)]. This suggests that there may be some interaction worth exploring in future analyses of zolpidem and gastroschisis. Past studies have not observed statistically significant associations between zolpidem and tetralogy of Fallot or any other specific birth defect, although these studies have grouped zolpidem with other medications and assessed grouped birth defects (Ban et al., 2014; Juric et al., 2009; Wikner et al., 2007; Wikner & Källén, 2011). A cohort study conducted using data from a large UK primary care database explored benzodiazepine and hypnotic non-benzodiazepine medications (which included zopiclone, zaleplon and zolpidem) and the risk of system-specific birth defects (Ban et al., 2014). The authors did not observe an association between first trimester prescriptions for benzodiazepines and non-benzodiazepines and any defect groups (including heart defects), although they did not specifically examine zolpidem use or more specific defects. Similarly, a cohort study using data from the Swedish Medical Birth Register examined the association between hypnotic non-benzodiazepine medications and birth defects, finding largely null associations for this combined medication exposure group (Wikner et al., 2007; Wikner & Källén, 2011). An update of the same data identified a possible association with intestinal defects (not intestinal atresia/stenosis) based on four exposed cases. The authors stressed that this may be due to chance because of multiple testing (Wikner & Källén, 2011). The Swedish Medical Birth Register analyses did not explore specific non-benzodiazapines (Wikner et al., 2007; Wikner & Källén, 2011). Lastly, a smaller study compared birth outcomes among 45 zolpidem-exposed and 45 unexposed pregnant people; none of these pregnancies was affected by a major birth defect (Juric et al., 2009).

Zolpidem is known to cross the placenta, so theoretically could have an impact on fetal development (Juric et al., 2009). Sleep is important for metabolism, tissue restoration, memory consolidation and homeostatic balance (Fuller et al., 2006). Poor sleep quality has been associated with elevations in pro-inflammatory cytokine levels (Okun & Coussons-Read, 2007; Okun, Kline et al., 2013) and depressive symptoms in pregnancy (Okun et al., 2009; Okun et al., 2011; Okun, Luther et al., 2013). Poor sleep quality has also been associated with preterm birth and preeclampsia (Okun et al., 2009, 2011; Okun Luther et al., 2013), but the association between poor sleep quality or sleep disorders and birth defects has not been examined.

The NBDPS and BDS relied on detailed clinical review of all birth defect cases, so we expect very little to no disease misclassification within our study. Both studies, however,

relied on maternal self-reported exposure information, up to 2 years after the delivery for some NBDPS participants. Thus, there is potential for recall error and possibly inaccurate reporting of maternal zolpidem use. We do not believe that we have underestimated early-pregnancy zolpidem use because our prevalence estimates (0.2% of both NBDPS and BDS controls) are similar to other estimates of the prevalence of zolpidem use in pregnancy based on prescription claims data (Askaa et al., 2014; Wikner & Källén, 2011). We explored the impact of potential exposure misclassification through a quantitative bias analysis, relying on the literature for parameter estimates (Evandt et al., 2019; Howley et al., 2023; Sarangarm et al., 2012). A recent validation study among birth defect cases and controls in New York found that there was no difference in agreement by case/control status for medications used chronically or those used episodically. Thus, we assumed that exposure misclassification of early-pregnancy medication use within NBDPS and BDS would be non-differential. While our probabilistic bias analysis suggested that the main results could have been biased towards the null under the assumption of high specificity and lower sensitivity of self-reported zolpidem use, SIs were wide and changes to the point estimates were relatively small.

Other limitations stem from the lack of specific questions within NBDPS and BDS on zolpidem use or its indications. We were unable to estimate associations with sleep disorders and cannot rule out the possibility of confounding by the underlying disease or by factors that influence one's decision to use a medication. Based only on reported medication use, with no information on indication or dose, it is difficult to understand the severity of sleep disorders, as medication use is influenced by disease severity, patient preferences, medication compliance and by pregnancy itself. Nevertheless, we at least partially attempted to control for this unmeasured confounding in a sub-analysis by comparing early-pregnancy zolpidem users with those who reported using zolpidem only in later pregnancy. We observed OR estimates similar to the main analysis in terms of direction, but CIs were more imprecise. The ORs for some birth defects were further elevated when later exposure was the comparator, raising the question as to whether use of early-pregnancy zolpidem is indeed associated with those birth defects or whether confounding is exacerbated due to difference in underlying disease severity or control among those who reported early versus later zolpidem use.

Participants using zolpidem in our analysis reported taking other medications as well, most notably antidepressants, anxiolytics, antipsychotics and opioids. While we included these as variables in DAGs, we narrowed down the covariates in the final model based on changes to the point estimate due to the small number of exposed. This resulted in the final model for anorectal atresia and secundum atrial septal defect being unadjusted as the adjusted models yielded point estimates and CI widths that were similar to unadjusted estimates. Thus, there may be uncontrolled confounding by unmeasured factors or residual confounding by measured factors. To address residual confounding by measured factors, we conducted a sub-analysis using propensity score adjustment, finding results that were largely similar in direction, significance and magnitude.

Our relatively large sample in this analysis relied on harmonising and combining data from two large case–control studies that collected exposure information similarly. The NBDPS

was population-based while the BDS was hospital/registry-based, and both studies had clinical review of eligible cases. The large size of these studies allowed us to consider risk for some specific birth defects, even with this rare exposure. Yet, the number of exposed cases in most of our analyses was small, leading to imprecise estimates and the inability to assess risk for all defects. We had limited statistical power to assess many of the associations with specific defects, resulting in an inability to estimate ORs for most of the 47 examined defects and unstable OR estimates with wide CIs for the associations we were able to examine. Additionally, we required a minimum number of exposed cases within the analysis so were more likely to observe associations above the null. Nevertheless, we were able to calculate adjusted estimates of the associations with seven specific defects, including tetralogy of Fallot, which was the observed signal from the NBDPS medication screen. The adjusted estimates for the defects that were calculated did not support a large increase in risk; however, smaller increases in risk of cleft palate, anorectal atresia, gastroschisis and tetralogy of Fallot were suggested but not conclusive. Although we cannot entirely rule out increased risks for some specific defects analysed due to the imprecise estimates and potential bias, our results add to the evidence supporting the safety of zolpidem use during pregnancy. We conducted analyses to explore the impact of common systematic errors on the main results and did not find large impacts. Nevertheless, our results should be interpreted cautiously given the above limitations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The study questionnaires and process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html. The code book and analytic code may be made available upon request.

REFERENCES

Askaa B, Jimenez-Solem E, Enghusen Poulsen H, & Traerup Andersen J (2014). Maternal characteristics of women exposed to hypnotic benzodiazepine receptor agonist during pregnancy. Obstetrics and Gynecology International, 2014, 945621. 10.1155/2014/945621 [PubMed: 24817891]

Austin PC (2009). The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. Medical Decision Making, 29(6), 661–677. 10.1177/0272989X09341755 [PubMed: 19684288]

Ban L, West J, Gibson JE, Fiaschi L, Sokal R, Doyle P, … Tata LJ (2014). First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. PLoS One, 9(6), e100996. 10.1371/journal.pone.0100996 [PubMed: 24963627]

Botto LD, Lin AE, Riehle-Colarusso T, Malik S, & Correa A (2007). Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Research. Part A: Clinical and Molecular Teratology, 79(10), 714–727. 10.1002/bdra.20403 [PubMed: 17729292]

Buysse DJ (2013). Insomnia. *JAMA*, 309(7), 706–716. 10.1001/jama.2013.193 [PubMed: 23423416]

Chong Y, Fryer CD, & Gu Q (2013). Prescription sleep aid use among adults: United States, 2005–2010. NCHS Data Brief, 127, 1–8.

Creeley CE, & Denton LK (2019). Use of prescribed psychotropics during pregnancy: A systematic review of pregnancy, neonatal, and childhood outcomes. Brain Sciences, 9(9), 235. 10.3390/brainsci9090235 [PubMed: 31540060]

Evandt J, Skurtveit S, Oftedal B, Krog NH, Nafstad P, Skovlund E, … Aasvang GM (2019). Agreement between self-reported and registry-based use of sleep medications and tranquilizers. Pharmacoepidemiology and Drug Safety, 28(10), 1336–1343. 10.1002/pds.4854 [PubMed: 31407838]

Feldkamp ML, Arnold KE, Krikov S, Reefhuis J, Almli LM, Moore CA, & Botto LD (2019). Risk of gastroschisis with maternal genitourinary infections: The US National birth defects prevention study 1997–2011. BMJ Open, 9(3), e026297. 10.1136/bmjopen-2018-026297

Firth D (1993). Bias reduction of maximum likelihood estimates. Biometrika, 80(1), 27–38. 10.2307/2336755

Fisher SC, Howley MM, Romitti PA, Desrosiers TA, Jabs EW, & Browne ML (2022). Maternal periconceptional alcohol consumption and gastroschisis in the National Birth Defects Prevention Study, 1997–2011. Paediatric and Perinatal Epidemiology, 36(6), 782–791. 10.1111/ppe.12882 [PubMed: 35437856]

Fox MP, Lash TL, & Greenland S (2005). A method to automate probabilistic sensitivity analyses of misclassified binary variables. International Journal of Epidemiology, 34(6), 1370–1376. 10.1093/ije/dyi184 [PubMed: 16172102]

Fuller PM, Gooley JJ, & Saper CB (2006). Neurobiology of the sleep-wake cycle: Sleep architecture, circadian regulation, and regulatory feedback. Journal of Biological Rhythms, 21(6), 482–493. 10.1177/0748730406294627 [PubMed: 17107938]

Glynn RJ, Schneeweiss S, & Stürmer T (2006). Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clinical Pharmacology Toxicology, 98(3), 253–259. 10.1111/j.1742-7843.2006.pto_293.x [PubMed: 16611199]

Haddow JE, Palomaki GE, & Homan MS (1993). Young maternal age and smoking during pregnancy as risk factors for gastroschisis. Teratology, 47(3), 225–228. 10.1002/tera.1420470306 [PubMed: 8475465]

Howley MM, Fisher SC, Fuentes MA, Werler MM, Tracy M, & Browne ML (2023). Agreement between maternal report and medical records on use of medications during early pregnancy in New York. Birth Defects Research, 115(4), 498–509. 10.1002/bdr2.2151 [PubMed: 36640121]

Jones AM, Isenburg J, Salemi JL, Arnold KE, Mai CT, Aggarwal D, … Honein MA (2016). Increasing prevalence of gastroschisis–14 states, 1995–2012. Morbidity and Mortality Weekly Report, 65(2), 23–26. 10.15585/mmwr.mm6502a2 [PubMed: 26796490]

Juric S, Newport DJ, Ritchie JC, Galanti M, & Stowe ZN (2009). Zolpidem (Ambien) in pregnancy: Placental passage and outcome. Archives of Women's Mental Health, 12(6), 441–446. 10.1007/s00737-009-0100-7

Kainz K, Greifer N, Givens A, Swietek K, Lombardi BM, Zietz S, & Koh JL (2017). Improving causal inference: Recommendations for covariate selection and balance in propensity score methods. Journal of the Society for Social Work Research, 8(2), 279–303. 10.1086/691464

Kleinbaum DG, & Klein M (2010). Logistic regression: A self-learning text (3rd ed.). Springer Publishers New York, Inc.

Lash TL, Fox MP, & Fink AK (2009). Applying quantitative bias analysis to epidemiologic data Springer.

Lee KA, Zaffke ME, & McEnany G (2000). Parity and sleep patterns during and after pregnancy. Obstetrics and Gynecology, 95(1), 14–18. 10.1016/s0029-7844(99)00486-x [PubMed: 10636494]

Lie JD, Tu KN, Shen DD, & Wong BM (2015). Pharmacological treatment of insomnia. Pharmacy Theraputics, 40(11), 759–771.

Lisi A, Botto LD, Robert-Gnansia E, Castilla EE, Bakker MK, Bianca S, … Mastroiacovo P (2010). Surveillance of adverse fetal effects of medications (SAFE-Med): Findings from the international clearinghouse of birth defects surveillance and research. Reproductive Toxicology, 29(4), 433–442. 10.1016/j.reprotox.2010.03.005 [PubMed: 20347959]

Louik C, Werler M, Anderka M, & Mitchell AA (2015). Application of data screening to drug exposure in large risk factor studies of birth defects. Birth Defects Research. Part A: Clinical and Molecular Teratology, 103(8), 713–717. 10.1002/bdra.23407 [PubMed: 26259777]

Månsson R, Joffe MM, Sun W, & Hennessy S (2007). On the estimation and use of propensity scores in case-control and case-cohort studies. American Journal of Epidemiology, 166(3), 332–339. 10.1093/aje/kwm069 [PubMed: 17504780]

Mindell JA, Cook RA, & Nikolovski J (2015). Sleep patterns and sleep disturbances across pregnancy. Sleep Medicine, 16(4), 483–488. 10.1016/j.sleep.2014.12.006 [PubMed: 25666847]

Neubauer DN, Pandi-Perumal SR, Spence DW, Buttoo K, & Monti JM (2018). Pharmacotherapy of insomnia. Journal of Central Nervous System Disease, 10, 1179573518770672. 10.1177/1179573518770672 [PubMed: 29881321]

Norman JL, Fixen DR, Saseen JJ, Saba LM, & Linnebur SA (2017). Zolpidem prescribing practices before and after Food and Drug Administration required product labeling changes. SAGE Open Medicine, 5, 2050312117707687. 10.1177/2050312117707687 [PubMed: 28515934]

Okun ML, & Coussons-Read ME (2007). Sleep disruption during pregnancy: How does it influence serum cytokines? Journal of Reprodroductive Immunology, 73(2), 158–165. 10.1016/j.jri.2006.06.006

Okun ML, Ebert R, & Saini B (2015). A review of sleep-promoting medications used in pregnancy. American Journal of Obstetrics and Gynecology, 212(4), 428–441. 10.1016/j.ajog.2014.10.1106 [PubMed: 25448509]

Okun ML, Kline CE, Roberts JM, Wettlaufer B, Glover K, & Hall M (2013). Prevalence of sleep deficiency in early gestation and its associations with stress and depressive symptoms. Journal of Womens Health, 22(12), 1028–1037. 10.1089/jwh.2013.4331

Okun ML, Luther JF, Wisniewski SR, & Wisner KL (2013). Disturbed sleep and inflammatory cytokines in depressed and nondepressed pregnant women: an exploratory analysis of pregnancy outcomes. Psychosomatic Medicine, 75(7), 670–681. 10.1097/PSY.0b013e31829cc3e7 [PubMed: 23864582]

Okun ML, Roberts JM, Marsland AL, & Hall M (2009). How disturbed sleep may be a risk factor for adverse pregnancy outcomes. Obstetrical Gynecological Survey, 64(4), 273–280. 10.1097/OGX.0b013e318195160e [PubMed: 19296861]

Okun ML, Schetter CD, & Glynn LM (2011). Poor sleep quality is associated with preterm birth. Sleep, 34(11), 1493–1498. 10.5665/sleep.1384 [PubMed: 22043120]

Parker SE, Van Bennekom C, Anderka M, & Mitchell AA (2018). Ondansetron for treatment of nausea and vomiting of pregnancy and the risk of specific birth defects. Obstetrics and Gynecology, 132(2), 385–394. 10.1097/aog.0000000000002679 [PubMed: 29995744]

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, & Moore CA (2003). Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Research. Part A: Clinical and Molecular Teratology, 67(3), 193–201. 10.1002/bdra.10012 [PubMed: 12797461]

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, … Honein MA (2015). The National Birth Defects Prevention Study: a review of the methods. Birth Defects Research. Part A: Clinical and Molecular Teratology, 103(8), 656–669. 10.1002/bdra.23384 [PubMed: 26033852]

Sarangarm P, Young B, Rayburn W, Jaiswal P, Dodd M, Phelan S, & Bakhireva L (2012). Agreement between self-report and prescription data in medical records for pregnant women. Birth Defects Research. Part A: Clinical and Molecular Teratology, 94(3), 153–161. 10.1002/bdra.22888 [PubMed: 22253196]

Sasaki M, Nakajima I, & Kawakami T (1993). Study on administration of zolpidem tartrate during the period of organogenesis in rats. Kiso to Rinsho, 27(1), 137–147.

Siega-Riz AM, Herring AH, Olshan AF, Smith J, & Moore C (2009). The joint effects of maternal prepregnancy body mass index and age on the risk of gastroschisis. Paediatric and Perinatal Epidemiology, 23(1), 51–57. 10.1111/j.1365-3016.2008.00990.x

Tinker SC, Carmichael SL, Anderka M, Browne ML, Caspers Conway KM, Meyer RE, … Reefhuis J (2015). Next steps for birth defects research and prevention: The birth defects study to evaluate pregnancy exposures (BD-STEPS). Birth Defects Research. Part A: Clinical and Molecular Teratology, 103(8), 733–740. 10.1002/bdra.23373 [PubMed: 25846741]

Werler MM, Hayes C, Louik C, Shapiro S, & Mitchell AA (1999). Multivitamin supplementation and risk of birth defects. American Journal of Epidemiology, 150(7), 675–682. 10.1093/oxfordjournals.aje.a010070 [PubMed: 10512421]

Werler MM, Shapiro S, & Mitchell AA (1993). Periconceptional folic acid exposure and risk of occurrent neural tube defects. JAMA, 269(10), 1257–1261. [PubMed: 8437302]

Wikner BN, & Källén B (2011). Are hypnotic benzodiazepine receptor agonists teratogenic in humans? Journal of Clinical Psychopharmacology, 31(3), 356–359. 10.1097/JCP.0b013e3182197055 [PubMed: 21508851]

Wikner BN, Stiller CO, Bergman U, Asker C, & Källén B (2007). Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: Neonatal outcome and congenital malformations. Pharmacoepidemiology and Drug Safety, 16(11), 1203–1210. 10.1002/pds.1457 [PubMed: 17894421]

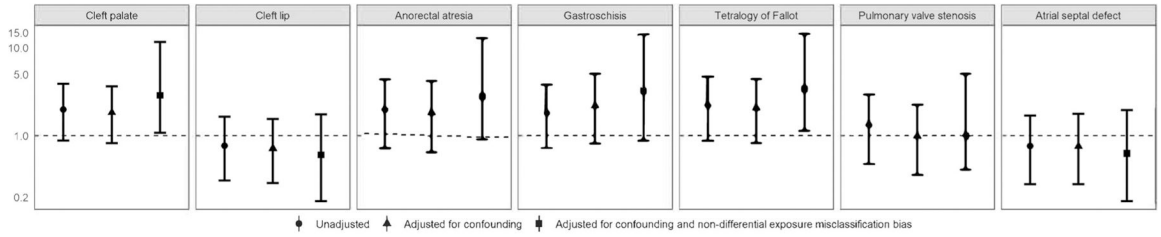

FIGURE 1.

Comparison of odds ratio (OR) estimates for association between early-pregnancy zolpidem use and specific birth defects, adjusting for different potential biases in the National Birth Defects Prevention Study (NBDPS; 1997–2011) and Birth Defects Study (BDS; 1998–2015). Adjusted models were built based on a change-in estimate approach for each birth defect. The confounder-adjusted (a)ORs for cleft palate, cleft lip and tetralogy of Fallot were adjusted for early-pregnancy opioid use. The confounder-aOR for anorectal atresia was adjusted for parity. The confounder-adjusted model for gastroschisis was adjusted for early-pregnancy opioid use and maternal age at delivery. The confounder-aOR for pulmonary valve stenosis (PVS) was adjusted for early-pregnancy opioid use and early-pregnancy use of an antidepressant, anti-anxiety or antipsychotic. The confounder-aOR for atrial septal defect was adjusted for maternal age at delivery. Non-differential misclassification bias models for each birth defect were adjusted for the same confounders as the adjusted models, and used a trapezoidal distribution (minimum, mode 1, mode 2, maximum) and the following parameters: sensitivity: 0.55, 0.65, 0.75, 0.90; specificity: 0.998, 0.999, 0.9995, 1.0

TABLE 1

Selected characteristics of mothers of controls and select birth defects, NBDPS (1997–2011) and BDS (1998–2015)

Maternal characteristics[a]	**Controls (*n* = 23,035)**	**Cleft palate (*n* = 2170)**	**Cleft lip**[b] **(*n* = 4245)**	**Anorectal atresia (*n* = 1443)**	**Gastroschisis (*n* = 1790)**	**Tetralogy of Fallot (*n* = 1466**	**PVS (*n* = 2073)**	**Secundum ASD (*n* = 3580)**
Maternal age at delivery in years, mean (SD)	28.4 (6.0)	28.5 (6.1)	27.6 (6.1)	28.0 (6.1)	21.7 (4.4)	28.5 (6.3)	28.4 (6.0)	28.0 (6.4)
Missing	25 (0.1)	3 (0.1)	2 (0.1)	0	0	0	0	0
Race/ethnicity								
Non-Hispanic white	14,584 (63.4)	1400 (64.6)	2614 (61.7)	775 (53.7)	914 (51.1)	815 (55.6)	1277 (61.6)	1938 (54.2)
Non-Hispanic black	2293 (10.0)	173 (8.0)	278 (6.6)	154 (10.7)	168 (9.4)	197 (13.4)	271 (13.1)	406 (11.3)
Hispanic	3491 (15.2)	376 (17.4)	931 (22.0)	358 (24.8)	501 (28.0)	316 (21.6)	297 (14.3)	912 (25.5)
Other	2637 (11.5)	218 (10.1)	417 (9.8)	156 (10.8)	207 (11.6)	138 (9.4)	227 (11.0)	323 (9.0)
Missing	30 (0.1)	3 (0.1)	5 (0.1)	0	0	0	1 (< 0.1)	1 (< 0.1)
Educational attainment								
Less than high school (< 12 years)	2966 (13.0)	311 (14.4)	801 (19.0)	249 (17.4)	477 (27.2)	212 (14.6)	285 (13.8)	629 (17.8)
High school (12 years)	4901 (21.4)	557 (25.8)	1109 (26.3)	379 (26.5)	674 (38.4)	382 (26.3)	532 (25.8)	948 (26.8)
More than high school (> 12 years)	15,037 (65.7)	1288 (59.7)	2308 (54.7)	803 (56.1)	604 (34.4)	859 (59.1)	1242 (60.3)	1961 (55.4)
Missing	131 (0.6)	14 (0.7)	27 (0.6)	12 (0.8)	35 (2.0)	13 (0.9)	14 (0.7)	42 (1.2)
Multiparous (parity > 1)	13,730 (59.7)	1315 (60.7)	2561 (60.5)	835 (58.0)	615 (34.4)	822 (56.2)	1293 (62.5)	2131 (59.6)
Missing	19 (0.1)	3 (0.1)	9 (0.2)	3 (0.2)	2 (0.1)	2 (0.1)	4 (0.2)	4 (0.1)
Pre-pregnancy BMI (kg m^{-2})								
Underweight (< 18.5)	1071 (4.8)	110 (5.2)	2418 (6.1)	56 (4.1)	151 (8.7)	60 (4.3)	88 (4.4)	200 (5.9)
Normal weight (18.5–24.9)	12,735 (57.2)	1089 (51.7)	2125 (52.4)	663 (48.4)	1171 (67.3)	708 (50.1)	914 (45.9)	1634 (47.8)
Overweight (25.0–29.9)	4904 (22.0)	510 (24.2)	908 (22.4)	311 (22.7)	322 (18.5)	340 (24.1)	538 (27.0)	814 (23.8)
Obese (≥ 30)	3565 (16.0)	399 (18.9)	778 (19.2)	341 (24.9)	96 (5.5)	304 (21.5)	452 (22.7)	772 (22.6)
Missing	760 (3.3)	62 (2.9)	186 (4.4)	72 (5.0)	50 (2.8)	54 (3.7)	81 (3.9)	160 (4.5)
Early-pregnancy smoking[c]	3817 (16.6)	456 (21.1)	954 (22.6)	286 (19.9)	646 (36.5)	251 (17.2)	420 (20.4)	774 (21.8)
Missing	96 (0.4)	11 (0.5)	20 (0.5)	7 (0.5)	22 (1.2)	9 (0.6)	9 (0.4)	29 (0.8)
Folic acid-containing supplement use[d]	9427 (40.9)	982 (45.3)	1813 (42.7)	644 (44.6)	594 (33.2)	722 (49.3)	969 (46.7)	1647 (46.0)
Missing	0	0	0	0	0	0	0	0

Maternal characteristics[a]	Controls (*n* = 23,035)	Cleft palate (*n* = 2170)	Cleft lip[b] (*n* = 4245)	Anorectal atresia (*n* = 1443)	Gastroschisis (*n* = 1790)	Tetralogy of Fallot (*n* = 1466	PVS (*n* = 2073)	Secundum ASD (*n* = 3580)
Early-pregnancy antidepressant, antipsychotic or anti-anxiety medication use[c]	1265 (5.5)	147 (6.8)	281 (6.6)	94 (6.5)	114 (6.4)	109 (7.4)	176 (8.5)	230 (6.4)
Missing	11 (< 0.1)	7 (0.3)	6 (0.1)	3 (0.2)	1 (< 0.1)	0	1 (0.1)	6 (0.2)
Early-pregnancy antidepressant use	1004 (4.4)	114 (5.3)	207 (4.9)	70 (4.9)	91 (5.1)	90 (6.1)	143 (6.9)	182 (5.1)
Early-pregnancy anti-anxiety medication use	311 (1.4)	34 (1.6)	85 (2.0)	25 (1.7)	32 (1.8)	29 (2.0)	49 (2.4)	57 (1.6)
Early-pregnancy antipsychotic use	94 (0.4)	14 (0.7)	23 (0.5)	13 (0.9)	8 (0.5)	8 (0.6)	12 (0.6)	18 (0.5)
Early-pregnancy opioid use[c]	531 (2.3)	71 (3.3)	131 (3.1)	47 (3.3)	62 (3.5)	45 (3.1)	78 (3.8)	106 (3.0)
Missing	8 (< 0.1)	2 (0.1)	1 (< 0.2)	0	3 (0.2)	0	4 (0.2)	5 (0.1)
Study								
BDS	11,421 (49.6)	567 (26.1)	1125 (26.5)	367 (25.4)	378 (21.1)	255 (17.4)	514 (24.8)	501 (14.0)
NBDPS	11,614 (50.4)	1603 (73.9)	3120 (73.5)	1076 (75.6)	1412 (78.9)	1211 (82.6)	1559 (75.2)	3079 (86.0)

Abbreviations: ASD, atrial septal defect; BDS, Birth Defects Study; BMI, body mass index; NBDPS, National Birth Defects Prevention Study; PVS, pulmonary valve stenosis; SD, standard deviation.

[a] All numbers in the table are *N*(%) unless otherwise specified.

[b] Includes cleft lip with or without cleft palate.

[c] From 1 month before pregnancy through to the third month of pregnancy.

[d] From 1 month before pregnancy through to the first month of pregnancy.

TABLE 2

Duration and patterns of zolpidem use in early pregnancy by case–control status in the NBDPS (1997–2011) and BDS (1998–2015)[a]

	Total		NBDPS		BDS	
	Cases (*n* = 84)	**Controls (*n* = 46)**	**Cases (*n* = 51)**	**Controls (*n* = 20)**	**Cases (*n* = 33)**	**Controls (*n* = 26)**
Duration of use[b]						
Sustained use (> 60 days)	58 (69.0)	24 (52.2)	33 (64.7)	9 (45.0)	25 (75.8)	15 (57.7)
Moderate use (11–60 days)	18 (21.4)	13 (28.3)	15 (29.4)	7 (35.0)	3 (9.1)	6 (23.1)
Infrequent use (< 11 days)	7 (8.3)	9 (19.6)	3 (5.9)	4 (20.0)	4 (12.1)	5 (19.2)
Pattern of use[c]						
All trimesters	30 (35.7)	15 (32.6)	23 (45.1)	6 (30.0)	7 (21.2)	9 (34.6)
Trimester 1 only	50 (59.5)	25 (54.3)	27 (52.9)	12 (60.0)	23 (69.7)	13 (50.0)
Trimesters 1 and 2	4 (4.8)	3 (6.5)	1 (2.0)	2 (10.0)	3 (9.1)	1 (3.8)
Trimesters 1 and 3	0	3 (6.5)	0	0	0	3 (11.5)

Abbreviations: BDS, Birth Defects Study; NBDPS, National Birth Defects Prevention Study.

[a] All numbers in the table are *N*(%).

[b] One case participant was excluded due to missing information on duration of use.

[c] Trimester 1 is defined as the month before pregnancy through to the third month of pregnancy. Trimester 2 is defined as the 4th month of pregnancy through to the 6th month of pregnancy; trimester 3 is defined as the 7th month of pregnancy through to the end of pregnancy.

TABLE 3

Number of zolpidem-exposed and unexposed cases and controls included in the NBDPS (1997–2011) and BDS (1998–2015)

Birth defect	Total Exposed/unexposed	NBDPS Exposed/unexposed	BDS Exposed/unexposed
Amniotic band sequence	1/440	1/333	0/107
Central nervous system			
Anencephaly	1/700	1/646	0/54
Spina bifida	0/1536	0/1277	0/259
Encephalocele	1/284	1/225	0/59
Holoprosencephaly	1/228	1/171	0/57
Dandy-Walker malformation	0/278	0/185	0/93
Hydrocephaly	1/789	0/511	1/278
Eye			
Anophthalmos/microphthalmos	1/312	1/231	0/81
Congenital cataracts	0/468	0/355	0/113
Glaucoma	2/236	1/181	1/55
Anotia/microtia	0/859	0/690	0/169
Orofacial			
Choanal atresia	0/283	0/166	0/117
Cleft palate only	8/2162	6/1597	2/565
Cleft lip with or without palate	6/4239	4/3116	2/1123
Gastrointestinal			
Oesophageal atresia	1/988	0/756	1/232
Intestinal atresia/stenosis	3/1150	1/768	2/382
Anorectal atresia	5/1438	1/1075	4/363
Biliary atresia	1/255	1/198	0/57
Genito-urinary			
Hypospadias	3/2845	3/2558	0/286
Renal agenesis	0/218	0/189	0/29
Bladder exstrophy	0/110	0/74	0/36
Cloacal exstrophy	1/113	1/99	0/14
Musculoskeletal			

Birth defect	Total Exposed/unexposed	NBDPS Exposed/unexposed	BDS Exposed/unexposed
Longitudinal limb deficiency	1/687	0/538	1/149
Transverse limb deficiency	1/929	0/721	1/208
Craniosynostosis	4/1775	4/1595	0/180
Diaphragmatic hernia	2/1108	1/873	1/235
Omphalocele	1/640	1/438	0/202
Gastroschisis	6/1784	3/1409	3/375
Sacral agenesis	1/144	1/109	0/35
Congenital heart defects			
Truncus arteriosus	0/227	0/138	0/89
Tetralogy of Fallot	6/1460	5/1206	1/254
d-TGA	1/1004	1/770	0/234
DORV-TGA	1/520	1/191	0/329
Conoventricular VSD	0/214	0/117	0/97
Atrioventricular septal defect	2/742	1/372	1/370
TAPVR	2/422	0/303	2/119
Hypoplastic heart syndrome	4/926	2/659	2/267
Coarctation of the aorta	0/1492	0/1174	0/318
Aortic valve stenosis	1/643	1/512	0/131
Pulmonary atresia	1/370	0/265	1/105
PVS	5/2068	4/1555	1/513
Tricuspid atresia	0/251	0/179	0/72
Ebstein anomaly	0/270	0/180	0/90
Perimembranous VSD	4/2036	2/1443	2/593
Secundum atrial septal defect	5/3575	3/3076	2/499
Single ventricle defects	0/225	0/174	0/51
Heterotaxy	2/497	1/345	1/152
Controls	46/22,989	20/11,594	26/11,395

Abbreviations: BDS, Birth Defects Study; d-TGA, dextro-transposition of the great arteries; DORV-TGA, double outlet right ventricle transposition of the great arteries; NBDPS, National Birth Defects Prevention Study; PVS, pulmonary valve stenosis; TAPVR, total anomalous pulmonary venous return; VSD, ventricular septal defect.

TABLE 4

Unadjusted ORs and aORs for the associations between early-pregnancy zolpidem use and specific birth defects in the NBDPS (1997–2011) and BDS (1998–2015)

Birth defect[a]	Exposed/unexposed	Unadjusted OR (95% CI)[b]	aOR (95% CI)[c]
Cleft palate only	8/2162	1.97 (0.88, 3.90)	1.83 (0.82, 3.63)
Cleft lip with or without palate	6/4239	0.77 (0.31, 1.63)	0.72 (0.29, 1.54)
Intestinal atresia/stenosis	3/768	1.51 (0.41, 3.88)	
Anorectal atresia	5/1075	1.89 (0.69, 4.20)	1.89 (0.69, 4.21)
Hypospadias	3/2845	0.56 (0.15, 1.50)	
Craniosynostosis	4/1775	1.25 (0.41, 2.97)	
Gastroschisis	6/1784	1.80 (0.72, 3.81)	2.18 (0.81, 5.03)
Tetralogy of Fallot	6/1460	2.20 (0.88, 4.66)	2.07 (0.82, 4.39)
Hypoplastic left heart syndrome	4/926	2.40 (0.78, 5.69)	
PVS	5/2068	1.32 (0.48, 2.93)	0.99 (0.36, 2.23)
Perimembranous VSD	4/2036	1.10 (0.35, 2.63)	
Secundum atrial septal defect	5/3575	0.76 (0.28, 1.69)	0.78 (0.29, 1.75)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.

[a]Most analyses include 46 exposed and 22,989 unexposed controls. The cleft palate and cleft lip with or without palate analyses included 45 exposed and 22,856 unexposed controls. The hypospadias analyses include 25 exposed and 11,520 unexposed male controls. The PVS analysis included 45 exposed and 22,521 unexposed controls. The perimembranous VSD analysis include 36 exposed and 18,108 unexposed controls.

[b]cORs and 95% CIs using Firth's penalised likelihood are presented for defects with three or four exposed cases.

[c]Two controls who were missing values of covariates in the final multivariate models have been excluded. The multivariable model for cleft palate, cleft lip and tetralogy of Fallot were adjusted for early-pregnancy opioid use. The multivariate model for anorectal atresia was adjusted for parity. The multivariable model for gastroschisis was adjusted for early-pregnancy opioid use and maternal age at delivery. The multivariate model for PVS was adjusted for early-pregnancy opioid use and early-pregnancy use of an antidepressant, anti-anxiety or antipsychotic. The multivariate model for atrial septal defect was adjusted for maternal age at delivery.