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Maternal Benzodiazepines and Z-Drugs Use during Pregnancy and Adverse Birth and Neurodevelopmental Outcomes in Offspring: A Population-Based Cohort Study

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Abstract

Introduction: The use of benzodiazepines and/or z-drugs in women of childbearing age has increased. ***Objective:*** The aim of the study was to evaluate whether gestational benzodiazepine and/or z-drug exposure is associated with adverse birth and neurodevelopmental outcomes. ***Methods:*** A population-based cohort including mother-child pairs from 2001 to 2018 in Hong Kong was analysed to compare gestationally exposed and nonexposed children on the risk of preterm birth, small for gestational age, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) through logistic/Cox proportional hazards regression with a 95% confidence interval (CI). Sibling-matched analyses and negative control analyses were applied. ***Results:*** When comparing gestationally exposed with gestationally nonexposed children, the weighted odds ratio (wOR) was 1.10 (95% CI = 0.97–1.25) for preterm birth and 1.03 (95% CI = 0.76–1.39) for small for gestational age, while the weighted hazard ratio (wHR) was 1.40 (95% CI = 1.13–1.73) for ASD and 1.15 (95% CI = 0.94–1.40) for ADHD. Sibling-matched analyses showed no association between gestationally exposed

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children and their gestationally nonexposed siblings for all outcomes (preterm birth: wOR = 0.84, 95% CI = 0.66–1.06; small for gestational age: wOR = 1.02, 95% CI = 0.50–2.09; ASD: wHR = 1.10, 95% CI = 0.70–1.72; ADHD: wHR = 1.04, 95% CI = 0.57–1.90). Similarly, no significant differences were observed when comparing children whose mothers took benzodiazepines and/or z-drugs during pregnancy to children whose mothers took benzodiazepines and/or z-drugs before but not during pregnancy for all outcomes. ***Conclusions:*** The findings do not support a causal relationship between gestational benzodiazepines and/or z-drugs exposure and preterm birth, small for gestational age, ASD, or ADHD. Clinicians and pregnant women should carefully balance the known risks of benzodiazepines and/or z-drugs use against those of untreated anxiety and sleep problems.

Introduction

Pregnancy is often a stressful experience as women undergo tremendous changes, which can lead to anxiety and sleep problems for some [1, 2]. Sleep problems during pregnancy are found to have a strong bidirectional relationship with anxiety disorders and may arise from discomforts such as back pain and foetal movements, gastroesophageal reflux, and hormonal modifications [3]. In addition, up to one in five pregnant women experiences some form of anxiety disorder, while 75% report having sleep problems in the third trimester [2, 4]. When untreated, maternal anxiety and sleep problems during pregnancy pose risks to both the mothers' and infants' health. Reported negative consequences of maternal anxiety and sleep problems include preterm birth, small for gestational age, placental abruption, and other gestational conditions; most of which are also predictors of poor neurodevelopmental outcomes for the child [3, 5].

Benzodiazepines and benzodiazepine-related drugs (z-drugs), hereafter referred to as sedatives, may be prescribed to pregnant women to treat anxiety and sleep disorders. Prevalence of sedative use during pregnancy ranges from 1% to 14%, depending on the geographical region studied, and is highest during the third trimester, mirroring the trends for anxiety and sleep problems [6]. In recent years, the use of benzodiazepines and z-drugs in women of childbearing age has increased, especially during the COVID-19 pandemic [7, 8]. Sedatives readily cross the placenta and the foetal blood-brain barrier

when used during pregnancy and may interfere with foetal brain development due to their effects on the γ-aminobutyric acid transmission [9, 10]. Besides studies suggesting the association between gestational sedative exposure and risk of adverse birth outcomes including preterm birth and low birth weight [11–14], recent reviews pinpointed that there is a scarcity of data on neurodevelopmental outcomes such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) [15, 16]. To address these gaps, we conducted a large-scale pharmacoepidemiological study nested in a territory-wide electronic healthcare database to evaluate the association between gestational exposure to sedatives and birth and neurodevelopmental complications (preterm birth, small for gestational age, ASD, and ADHD) in children.

Materials and Methods

Data Source and Study Design

This is a cohort study using the Clinical Data Analysis and Reporting System (CDARS). We specified target trials following protocol components listed in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000529141) CDARS contains anonymised electronic health records of all residents (over 7.4 million) from public hospitals and health institutes of the Hospital Authority (HA) in Hong Kong (HK) [17]. The HA currently manages 43 hospitals, 49 specialist outpatient clinics, and 73 general outpatient clinics [18]. The clinical information is directly recorded by clinicians and other healthcare professionals before being routinely transferred to CDARS. Diagnosis records in CDARS were coded using ICD-9-CM [International Classification of Diseases, Ninth Revision, Clinical Modification] codes instead of ICD-10 codes. Nevertheless, data validation has demonstrated high coding accuracy in CDARS [19–21] which has been used for various pharmacoepidemiological studies [22–24], including studies on prenatal psychotropic use [25] and neurodevelopmental disorders [26–29]. Study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (approval number: UW20-051). Informed consent was waived as this study did not have patient contact and used anonymised data.

Study Population

Our study cohort included all pregnancy episodes of women who delivered a live birth between January 1, 2001, and December 31, 2018, with follow-up until December 31, 2020. We defined a valid mother-child linkage as the exact match of mother and child identification numbers and delivery date which is linked permanently after delivery [26]. We excluded children without valid mother-child linkage or complete birth information (such as sex, birth date, and gestational age). As some sedatives may be used for the management of epilepsies, we removed the pregnancy episodes where mothers had a history of epilepsy [30].
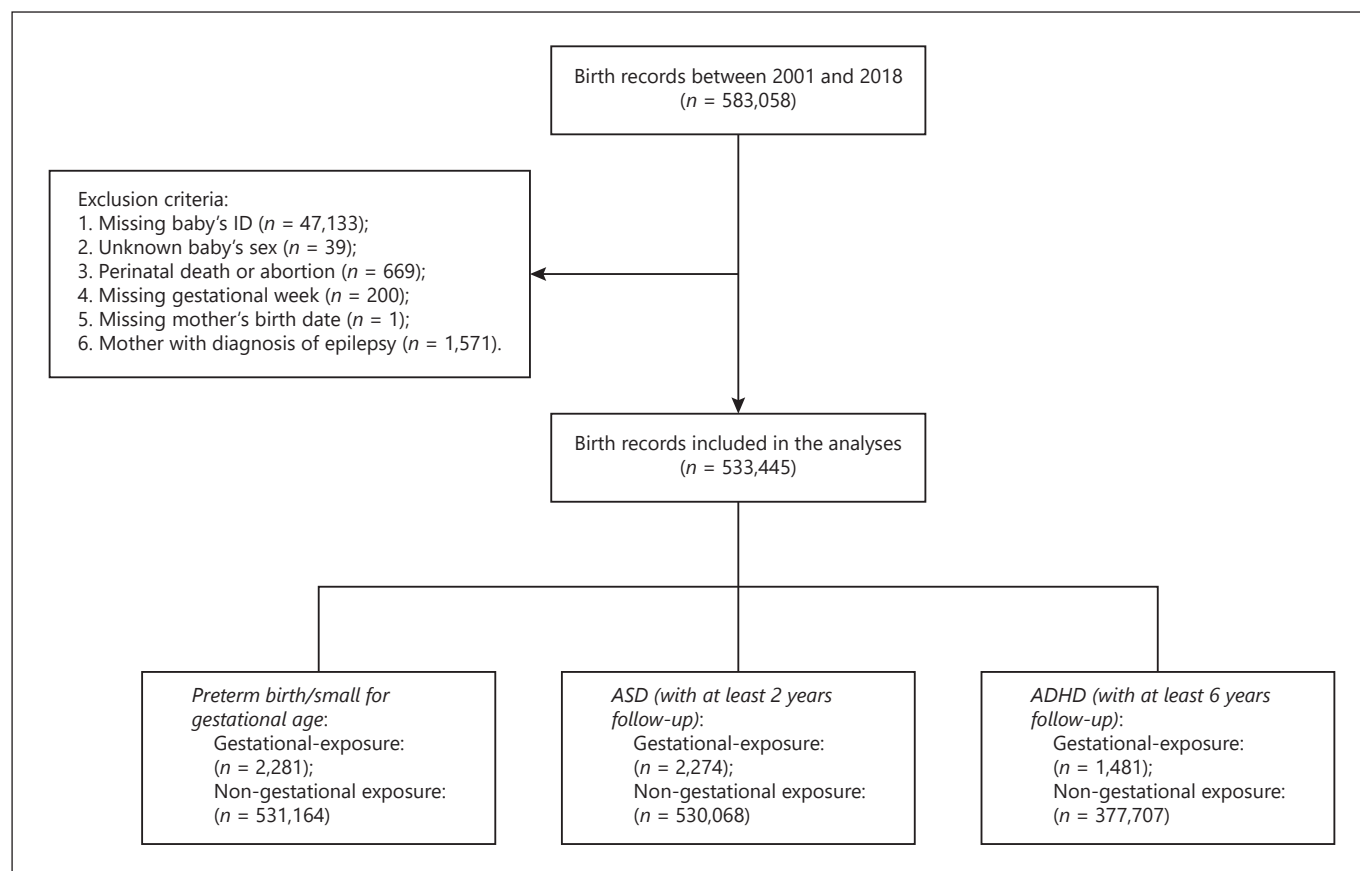
Fig. 1. Flow chart of the mother-child pairs selection. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

Pregnancy Period

To identify the date of conception and trimesters of pregnancy, the last menstrual period (LMP) was estimated by the date of delivery minus gestational age at birth. The gestational age at birth was recorded by healthcare professionals based on ultrasound performed at the first obstetric visit and was directly retrieved from CDARS [26]. The pregnancy period was defined as the period between the LMP and delivery date. To examine the potential effects on the timing of sedative use, we further separated the pregnancy period into trimesters: first trimester (0–90 days after the LMP), second trimester (91–180 days after the LMP), and third trimester (181 days after the LMP to delivery to the date of delivery) [26, 31].
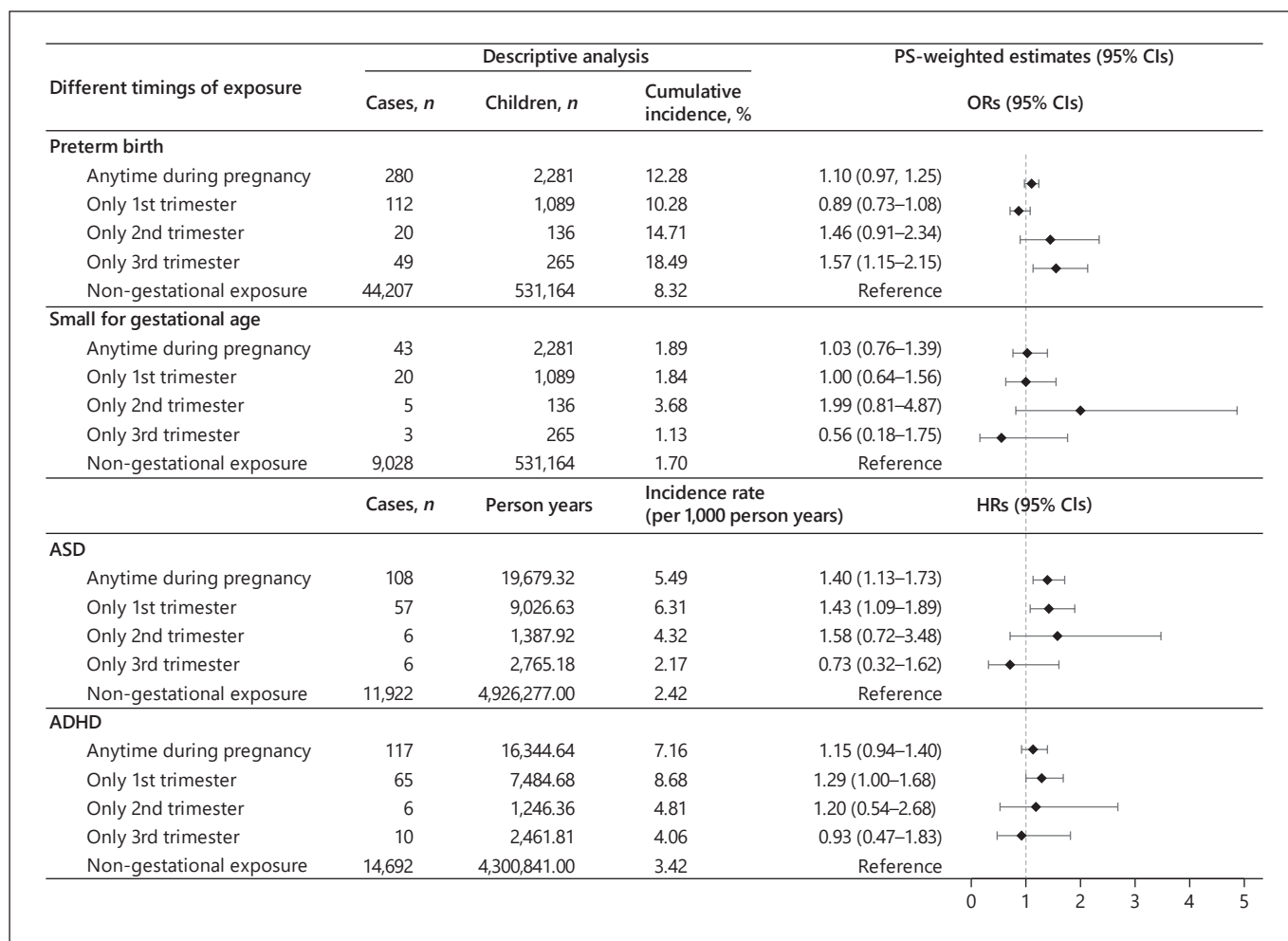
Exposure and Comparator Cohorts

Prescriptions of any sedatives listed in Chapter 4.1 of the British National Formulary (BNF) were extracted from CDARS (online suppl. Table 2). Z-drugs included zopiclone and zolpidem, the only z-drugs prescribed in the HA. Children were considered to have been exposed gestationally if their mothers were prescribed any sedatives during the pregnancy period (*gestationally exposed*). In cases where the prescription start date was missing, dispensing date was used; where the prescription end date was missing, imputation was applied to determine the prescription end date based on the median prescription duration of the same drug. Children

whose mothers did not use sedatives during pregnancy were used to construct three comparator groups: (1) children whose mothers did not use sedatives during pregnancy, regardless of sedative use history (*gestationally nonexposed*); (2) children whose mothers used sedatives before but not during pregnancy (*past-exposed*); and (3) children whose mothers never used sedatives both before and during pregnancy (*never-exposed*), we further classified this group into those (a) *with anxiety disorders* and (b) *without anxiety disorders* (coded using ICD-9-CM 293.84, 300) (online suppl. Fig. 1). There are concerns for psychotropic medication use during pregnancy regarding the risks of various adverse outcomes in offspring [32]. However, we did not exclude pregnant women who were on antidepressants or other psychotropic medication in view of the low exposure rates in the control groups (antidepressants: 0.67%, antipsychotics: 0.23%; antiepileptics: 0.07%; antiparkinson drugs: 0.07%; stimulants: 0.002%).

Outcome

Study outcomes were preterm birth (<37 gestational weeks), small for gestational age (birth weight <2 standard deviations [SD] below the mean for gestational age) [27], ASD (ICD-9-CM: 299), and ADHD (ICD-9-CM: 314, or prescription for ADHD medication, namely methylphenidate or atomoxetine – the only available medications for ADHD in HK during the study period) [26, 33].

Different timings of exposure	Descriptive analysis			PS-weighted estimates (95% CIs)
	Cases, n	Children, n	Cumulative incidence, %	ORs (95% CIs)
Preterm birth				
Anytime during pregnancy	280	2,281	12.28	1.10 (0.97, 1.25)
Only 1st trimester	112	1,089	10.28	0.89 (0.73–1.08)
Only 2nd trimester	20	136	14.71	1.46 (0.91–2.34)
Only 3rd trimester	49	265	18.49	1.57 (1.15–2.15)
Non-gestational exposure	44,207	531,164	8.32	Reference
Small for gestational age				
Anytime during pregnancy	43	2,281	1.89	1.03 (0.76–1.39)
Only 1st trimester	20	1,089	1.84	1.00 (0.64–1.56)
Only 2nd trimester	5	136	3.68	1.99 (0.81–4.87)
Only 3rd trimester	3	265	1.13	0.56 (0.18–1.75)
Non-gestational exposure	9,028	531,164	1.70	Reference

	Cases, n	Person years	Incidence rate (per 1,000 person years)	HRs (95% CIs)
ASD				
Anytime during pregnancy	108	19,679.32	5.49	1.40 (1.13–1.73)
Only 1st trimester	57	9,026.63	6.31	1.43 (1.09–1.89)
Only 2nd trimester	6	1,387.92	4.32	1.58 (0.72–3.48)
Only 3rd trimester	6	2,765.18	2.17	0.73 (0.32–1.62)
Non-gestational exposure	11,922	4,926,277.00	2.42	Reference
ADHD				
Anytime during pregnancy	117	16,344.64	7.16	1.15 (0.94–1.40)
Only 1st trimester	65	7,484.68	8.68	1.29 (1.00–1.68)
Only 2nd trimester	6	1,246.36	4.81	1.20 (0.54–2.68)
Only 3rd trimester	10	2,461.81	4.06	0.93 (0.47–1.83)
Non-gestational exposure	14,692	4,300,841.00	3.42	Reference

Fig. 2. Results from the main analysis comparing gestational users and non-gestational users. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CIs: confidence intervals; HRs, hazard ratios; ORs, odds ratios; PS, propensity score.

Participants were followed up until the outcome onset, the end of study period, or death, whichever occurred first. Preterm birth and small for gestational age were identified and recorded at the delivery date. For ASD and ADHD analyses, all children had at least two- and six-year follow-ups, respectively, by the end of study period.

Covariates

We selected covariates a priori based on known confounders for the study association and risk factors for the study outcomes [27]. These include maternal age at delivery, calendar year at delivery, parity, birth hospital, multiple pregnancy, infant's sex, maternal psychiatric and neurological conditions, maternal physical conditions, maternal medication history, maternal behaviours including smoking, alcohol consumption, illicit drug use, and maternal socioeconomic status. Definitions of covariates by ICD-9-CM codes, BNF chapters, or BMI categories are available in online supplementary Table 3.

Statistical Analyses

Odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate the associations for birth outcomes (preterm birth, small for gestational age) by logistic regression models. Hazard ratios (HRs) with 95% CIs were estimated to study the associations for neurodevelopmental outcomes (ASD, ADHD) using Cox proportional hazard regression models. Propensity score (PS) fine-stratification weighting was used to address the differences in baseline covariates. We used PS fine-stratification weighting for greater precision, less residual, and equivalent bias control at low exposure prevalence when compared to traditional PS methods [34, 35]. PS was used to estimate the average treatment effect by creating 250 equally sized fine strata. Following stratification, weights for exposure and reference individuals in all strata were calculated based on the total number of individuals within each stratum, while strata with no participants were dropped out [35]. Robust standard error was applied to adjust for data clustering. All variables listed in the covariates section were included in the PS

model. CIs not overlapping 1.0 were considered statistically significant. Statistical Analysis System (SAS) v9.4 (SAS Institute, Cary, NC, USA) and R Foundation for Statistical Computing version 3.6.0 (Vienna, Austria) were used for data analysis.

We conducted negative control analyses to evaluate the effect of confounding by indication. (1) We compared children born to *past-exposed* mothers with those who were *never-exposed;* an increased risk of outcomes in the children of mothers among the *past-exposed* indicates confounding by indication as the infant was not exposed to sedatives. (2) Similarly, *gestationally exposed* infants were compared with *past-exposed* infants to assess whether there is a difference in the risk of study outcomes. (3) To assess the role of maternal anxiety disorder, we restricted comparison cohorts to *never-exposed*; if maternal anxiety disorder is associated with risk of outcomes in the children, this introduces the possibility of confounding by indication. Sibling-matched analyses were conducted to control for shared genetic and social confounding factors at the family level. Stratified Cox/logistic regression with a separate stratum for each family identified by the mother's unique identification number was used. Only inconsonant sibling pairs for gestational sedative exposure and study outcomes were included in sibling-matched analysis.

Subgroup analyses were conducted by drug class and sex. First, we conducted analyses in benzodiazepine only and Z-hypnotics only subgroups to identify the risk of study outcomes in different drug classes. Second, as neurodevelopmental outcomes are more common in boys than girls [36], we conducted analyses in boy and girl subgroups to explore sex differences. Sensitivity analyses were conducted to test the validity of the initial analyses. First, to assess the impact of potential exposure misclassification, we extended the prescription period by 14 days to test the effect of the length of prescription. Second, to investigate the potential clustering effect of children who were born to the same mother, we restricted analyses to the first pregnancy episode only. Third, as history of preterm birth is a strong predictor of future preterm birth, we conducted analyses by removing the first pregnancy episode and included history of preterm birth as an additional covariate. Fourth, as there might be children who received ADHD diagnosis or prescription before 6 years old, or received ASD diagnosis before 2 years old, we conducted analyses without restricting the follow-up time.

Results

We retrieved 583,058 birth records from 2001 to 2018 from CDARS. The final analytic cohorts included 533,445 mother-child pairs for preterm birth and small for gestational age analyses, 532,342 mother-child pairs for ASD analysis with a median follow-up time of 8.76 years (interquartile range [IQR] = 5.35–12.96 years), and 379,188 mother-child pairs for ADHD analysis with a median follow-up time of 10.91 years (IQR = 8.28–14.20 years) (Fig. 1 and online suppl. Fig. 2). Characteristics of included babies and mothers were summarised in online supplementary Table 4.

Table 1. Results from the sibling-matched analysis

Outcome	Gestationally exposed			Gestationally nonexposed siblings			Crude estimates, ORs (95% CIs)	PS-weighted estimates, ORs (95% CIs)
	No. of cases	No. of children	Cumulative incidence (%)	No. of cases	No. of children	Cumulative incidence (%)		
Preterm birth	77	933	8.25	120	1,218	9.85	0.82 (0.61–1.11)	0.84 (0.66–1.06)
Small for gestational age	13	933	1.39	32	1,218	2.63	0.52 (0.27–1.00)	1.02 (0.50–2.09)
	No. of cases	Person years	Incidence rate (per 1,000 person years)	No. of cases	Person years	Incidence rate (per 1,000 person years)	Crude estimates, HRs (95% CIs)	PS-weighted estimates, HRs (95% CIs)
ASD	34	7,215.10	4.71	54	12,489.08	4.32	1.11 (0.72–1.70)	1.10 (0.70–1.72)
ADHD	34	5,085.81	6.69	54	7,356.37	7.34	0.96 (0.62–1.47)	1.04 (0.57–1.90)

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CIs, confidence intervals; HRs, hazard ratios; ORs, odds ratios; PS, propensity score.

Comparisons	Exposure group			Comparison group			PS-weighted estimates
	Cases, n	Children, n	Cumulative incidence, %	Cases, n	Children, n	Cumulative incidence, %	ORs (95% CIs)
Preterm birth							
Gestational users vs. past users	280	2,281	12.28	1,503	14,184	10.60	1.07 (0.93–1.22)
Past users vs. never users	1,503	14,184	10.60	42,704	516,980	8.26	1.02 (0.96–1.07)
Never users with anxiety vs. never users without anxiety	265	2,920	9.08	42,439	514,060	8.26	1.06 (0.94–1.20)
Small for gestational age							
Gestational users vs. past users	43	2,281	1.89	263	14,184	1.85	1.08 (0.78–1.49)
Past users vs. never users	263	14,184	1.85	8,765	516,980	1.70	0.94 (0.83–1.07)
Never users with anxiety vs. never users without anxiety	53	2,920	1.82	8,712	514,060	1.69	1.12 (0.85–1.47)
	Cases, n	Person years	Incidence rate (per 1,000 person years)	Cases, n	Person years	Incidence rate (per 1,000 person years)	HRs (95% CIs)
ASD							
Gestational users vs. past users	108	19,679.32	5.49	481	114,462.80	4.20	1.21 (0.96–1.51)
Past users vs. never users	481	114,462.80	4.20	11,441	4,811,814.00	2.38	1.13 (0.98–1.30)
Never users with anxiety vs. never users without anxiety	75	26,023.86	2.88	11,366	4,785,790.00	2.37	1.13 (0.89–1.43)
ADHD							
Gestational users vs. past users	117	16,344.64	7.16	627	94,098.38	6.66	1.02 (0.83–1.26)
Past users vs. never users	627	94,098.38	6.66	14,065	4,206,742.00	3.34	1.16 (1.01–1.34)
Never users with anxiety vs. never users without anxiety	131	21,899.09	5.98	13,934	4,184,843.00	3.33	1.40 (1.16–1.69)

Fig. 3. Results from the main analysis of other comparisons. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CIs: confidence intervals; HRs, hazard ratios; ORs, odds ratios; PS, propensity score.

Overall, 2,281 children (0.43%) were gestationally exposed to sedatives between 2001 and 2018, where 280 (12.28%) and 43 (1.89%) had preterm birth and small for gestational age, respectively. 2,274 children (0.43%) were gestationally exposed to sedatives between 2001 and 2016, where 108 (4.75%) had a diagnosis of ASD. 1,481 children (0.39%) were gestationally exposed to sedatives between 2001 and 2012, while 117 (7.90%) had a diagnosis of ADHD. Covariate balances were achieved after PS weighting, with all standardised differences less than 10% (online suppl. Table 5).

Primary Analyses and Sibling Comparisons

When comparing with gestationally nonexposed children, gestational sedative exposure was associated with ASD (PS-weighted HR [wHR] = 1.40, 95% CI = 1.13–1.73) but not with preterm birth (PS-weighted OR [wOR] = 1.10, 95% CI = 0.97–1.25), small for gestational age (wOR = 1.03, 95% CI = 0.76–1.39), or ADHD (wHR = 1.15, 95% CI = 0.94–1.40). Results stratified by trimester showed that sedative exposure during the first trimester was associated with an increased risk of ASD (wHR = 1.43, 95% CI = 1.09–1.89) and ADHD (wHR = 1.29, 95% CI = 1.00–1.68), while sedative exposure during the third trimester was associated with an increased risk of preterm birth (wOR = 1.57, 95% CI = 1.15–2.15) (Fig. 2 and online suppl. Table 6). The sibling-matched analyses included 896 mothers with 2,151 children in the preterm birth and small for gestational age cohort, 893 mothers with 2,139

children in the ASD cohort, and 461 mothers with 1,081 children in the ADHD cohort. When gestationally exposed children were compared with their siblings who were not exposed to sedatives gestationally, no significant differences in the risk of all outcomes were observed (preterm birth: wOR = 0.84, 95% CI = 0.66–1.06; small for gestational age: wOR = 1.02, 95% CI = 0.50–2.09; ASD: wHR = 1.10, 95% CI = 0.70–1.72; ADHD: wHR = 1.04, 95% CI = 0.57–1.90; Table 1).

Other Comparisons

Gestationally Exposed versus Past-Exposed

No significant differences were observed when comparing children who were gestationally exposed to sedatives with children whose mothers were exposed to sedatives before but not during pregnancy for all outcomes – preterm birth (wOR = 1.07, 95% CI = 0.93–1.22), small for gestational age (wOR = 1.08, 95% CI = 0.78–1.49), ASD (wHR = 1.21, 95% CI = 0.96–1.51), and ADHD (wHR = 1.02, 95% CI = 0.83–1.26; Fig. 3 and online suppl. Table 6).

Past-Exposed versus Never-Exposed

An increased risk of ADHD (wHR = 1.16, 95% CI = 1.01–1.34) was observed when comparing children whose mothers used sedatives before but not during pregnancy with children whose mothers never used sedatives. No significant differences between the two comparison groups were observed for preterm birth (wOR = 1.02,

95% CI = 0.96–1.07), small for gestational age (wOR = 0.94, 95% CI = 0.83–1.07), and ASD (wHR = 1.13, 95% CI = 0.98–1.30; Fig. 3 and online suppl. Table 6).

Never-Exposed with Anxiety Disorders versus Never-Exposed without Anxiety Disorders

When we restricted the analyses to mothers who never used sedatives, an increased risk of ADHD (wHR = 1.40, 95% CI = 1.16–1.69) was observed when comparing children born to mothers with anxiety disorders with mothers without anxiety disorders. No significant differences between the two comparison groups were observed for preterm birth (wOR = 1.06, 95% CI = 0.94–1.20), small for gestational age (wOR = 1.12, 95% CI = 0.85–1.47), and ASD (wHR = 1.13, 95% CI = 0.89–1.43; Fig. 3 and online suppl. Table 6).

Subgroup Analyses

Children whose mothers used benzodiazepines exclusively during pregnancy had a higher risk of ASD (wHR = 1.42, 95% CI = 1.06–1.90) and preterm birth (wOR = 1.19, 95% CI = 1.00–1.42) when compared with children who were not exposed to any sedatives gestationally (Table 2). No significant differences were observed for small for gestational age (wHR = 0.61, 95% CI = 0.34–1.07) and ADHD (wHR = 1.03, 95% CI = 0.77–1.37). When comparing children who were exposed to z-hypnotics gestationally with nonexposed children, no significant differences were observed in all outcomes, except small for gestational age (wOR = 1.60, 95% CI = 1.08–2.36). Direct comparisons for newborns whose mothers were exposed to z-hypnotics versus benzodiazepines during pregnancy found a higher risk of small for gestational age (wHR = 2.31, 95% CI = 1.16–4.59) in the z-hypnotics group but not for other outcomes.

When stratified by children's sex, a higher risk of ASD (wHR = 1.45, 95% CI = 1.16–1.83) was observed in boys who were gestationally exposed to sedatives when compared to gestationally nonexposed boys. No significant differences between gestationally exposed and nonexposed boys were observed for other outcomes. No significant differences between gestationally exposed and nonexposed girls were observed for all study outcomes, except for preterm birth with a higher wOR of 1.24 (95% CI = 1.03–1.48) in the exposed group.

Sensitivity Analyses

The results of sensitivity analyses extending the prescription duration by 14 days as the exposure were similar to the main analyses, i.e., non-statistical significance for

Table 2. Results of subgroup analysis

Subgroups	Preterm birth		Small for gestational age		ASD		ADHD	
	No. of cases/ No. of children*	PS-wORs (95% CIs)	No. of cases/ No. of children*	PS-wORs (95% CIs)	No. of cases/ person years*	PS-wHRs (95% CIs)	No. of cases/ person years*	PS-wHRs (95% CIs)
Drug types								
Only z-drugs	103/919 44,207/531,164	1.06 (0.87–1.31)	26/919 9,028/531,164	**1.60 (1.08–2.36)**	40/7,665.26 11,922/4,926,277	1.22 (0.88–1.69)	44/6,209.18 14,692/4,300,841	1.11 (0.81–1.51)
Only benzodiazepines	142/1,060 44,207/531,164	**1.19 (1.00–1.42)**	12/1,060 9,028/531,164	0.61 (0.34–1.07)	49/9,603.70 11,922/4,926,277	**1.42 (1.06–1.90)**	51/8,176.98 14,692/4,300,841	1.03 (0.77–1.37)
Z-drugs versus benzodiazepines	103/919 142/1,060	0.79 (0.60–1.04)	26/919 12/1,060	**2.31 (1.16–4.59)**	40/7,665.26 49/9,603.70	1.25 (0.76–2.07)	44/6,209.18 51/8,176.98	1.40 (0.83–2.37)
Sex								
Boys	142/1,234 24,403/275,406	1.00 (0.84–1.20)	16/1,234 3,291/275,406	0.92 (0.56–1.51)	94/10,517.80 10,082/2,540,848	**1.45 (1.16–1.83)**	93/8,721.08 11,347/2,218,152	1.16 (0.92–1.47)
Girls	138/1,047 19,804/255,758	**1.24 (1.03–1.48)**	27/1,047 5,737/255,758	1.07 (0.73–1.57)	14/9,161.52 1,840/2,385,429	1.00 (0.57–1.76)	24/7,623.56 3,345/2,082,689	0.95 (0.61–1.49)

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CIs, confidence intervals; wHRs, weighted hazard ratios; wORs, weighted odds ratios; PS, propensity score. * Data are shown in two rows; the first row is the No. of cases/No. of children in exposure group, and the second row is the No. of cases/No. of children in reference group.

preterm birth, small for gestational age, ADHD; and an increased risk of ASD. After additionally adjusting history of preterm birth, the association between gestational exposure to sedative and the risk of preterm birth was similar to the main analysis, i.e., remained statistically non-significant. The results of sensitivity analyses including only first pregnancies were similar to the main analyses for preterm birth, small for gestational age, and ADHD, i.e., non-statistical significance. When including only first pregnancies in the analyses, the effect estimates for ASD decreased from an HR of 1.40 (95% CI = 1.13–1.73) in the main analysis to 1.12 (95% CI = 0.80–1.56) in the sensitivity analysis. We did not observe any meaningful differences in the sensitivity analyses without restriction for follow-up duration from the main analyses (ASD: HR = 1.40, 95% CI = 1.14–1.72; ADHD: HR = 1.23, 95% CI = 1.02–1.48; online suppl. Table 7).

Discussion

Our primary analyses found no association between maternal sedative use during pregnancy and ADHD, preterm birth, or small for gestational age in offspring. Although an increased risk of ASD was identified in children with gestational exposure to sedatives, results from sibling-matched analyses and negative control analyses suggest that this association may be confounded by shared social and familial factors.

Previous findings on sedative exposure during pregnancy and the risk of adverse birth outcomes were mixed [11–14, 37]. Furthermore, they may be limited by small sample sizes, poor representativeness of data, recall bias, inadequate adjustment of confounders such as indication (i.e., anxiety and sleep disorders), and unmeasured variables such as illicit drug use. In particular, sedatives could be used for other psychiatric comorbidities or epilepsy which were not accounted for in some studies. In our current study, using a large-scale population-based design with adequate adjustment for potential confounders, there is a lack of evidence suggesting sedative use during pregnancy is associated with adverse birth outcomes.

Evidence on the relationship between sedative use and neurodevelopmental outcomes in offspring was scarce at the conception of this study. Two studies evaluated the association between gestational sedative use and ADHD in offspring using parent reports and diagnosis records, respectively [38, 39]. Similar to our findings, both concluded there is insufficient evidence to substantiate the claims that maternal sedative use during pregnancy is associated with ADHD in offspring. To our knowledge, this is the first study to investigate the association between gestational sedative use and the risk of ASD. Although we detected an increased risk of ASD in children who were exposed to sedatives during pregnancy when compared with nonexposed children, no significant difference was observed when we compared gestational users with past users as negative exposure control. A null association was also observed when comparing exposed children with their siblings who were nonexposed during gestation. These findings suggest that shared genetic and social factors may at least partly explain the association observed in the primary analysis. However, we cannot completely dismiss the possibility that gestational sedative exposure is causally associated with ASD development in offspring.

Strengths and Limitations

This is the first cohort study based on a large-scale population database to examine the association between gestational sedative exposure and the risk of ADHD or ASD in children with adequate follow-up time for the detection of neurodevelopmental disorders (at least six and two years, respectively). Electronic dispensing and prescribing records were used to identify the exposures, which are free from recall bias. Pregnancy information, including the deterministic mother-child link where patient identification numbers are linked permanently after delivery and explicit gestational age records, were directly retrieved from CDARS, which were highly accurate [40]. Moreover, complementary negative control analyses and sibling-matched analyses were applied to control for both measured and unmeasured confounding.

Our study had several limitations. First, CDARS only captures public healthcare medical records; data from private hospitals and medical practitioners are not included. However, children with neurodevelopmental disorders require comprehensive long-term treatment; thus, they usually receive health services from the public sector in HK [41]. Furthermore, most children were delivered at public hospitals which provide approximately 90% of hospital medical services in HK [42]. Second, poor medication adherence among patients with psychiatric disorders is common, and we cannot confirm whether patients took their medication as prescribed or if they had taken the medication at all, and this may affect the accuracy of the results [43]. We addressed the potential for misclassification bias by extending the prescription duration by 14 days in the exposed group in the sensitivity analyses,

which had similar results to our primary analyses. Third, our analyses could not account for differences in the severity of indicated illnesses. Women with more severe illnesses may have stayed on the drug, whereas women whose illnesses were less severe may stop taking sedatives during pregnancy given the risk-benefit assessment. However, we used complementary negative control and sibling-matched analyses which controlled for confounding by indication and shared familial factors to support the interpretation of our findings. Fourth, as analyses were conducted with HK population, it is unclear whether the results are generalizable to other populations. Fifth, like other studies using electronic health records, there could be missing records for behavioural factors. We thus compared the rates of these factors with the HK government statistics and found a lower rate in our data (smoking – our study: 1.12%, government statistics: 1.9–7.0% for female aged 20–29 between 2001–2018 [44]; alcohol drinking – our study: 0.9%, government statistics: 3.2% for females of all ages [45]; illicit drug use – our study: 0.93%, government statistics: 0.03% for female ever abusers aged 21 and above in 2019 [46, 47]). Nonetheless, our population comprised of pregnant women and women with childbearing or breastfeeding intention who may engage in less unhealthy behaviours than the general population. Furthermore, as our study results suggested a null association between sedative exposure and our study outcomes, even if these behavioural factors could explain the association, it is unlikely to affect our conclusion. Sixth, we were only able to control for maternal but not paternal medical history in the analyses, as paternal linkage is not established in the HK CDARS. However, we have accounted for the effects of familial confoundings including family history by the sibling-matched analysis where shared familial and environmental factors were controlled for by the study design and yielded similar results to the main analysis. This supported the robustness of our results.

Clinical Implications and Future Research Directions
Sedative use during pregnancy was previously suggested to be associated with congenital malformations; this notion has been rejected recently, with meta-analyses concluding that there is no evidence for teratogenicity associated with gestational sedative use [48]. We now show here that there is also unlikely to be a causal association with preterm birth, small for gestational age, ADHD or ASD in offspring. While our results do not suggest withholding sedative treatment due to the fear of our study outcomes, risks of sedative use such as dependence and

abuse have been well established. Therefore, the use of sedatives during pregnancy still requires careful and personalised consideration of the potential harms against the benefits. Furthermore, the general scarcity of studies on the long-term safety of gestational sedative use for mothers and offspring suggests that more attention should be devoted to this area, given the current rise in psychiatric illnesses during pregnancy [49]. Future studies should include head-to-head comparisons of different sedative drugs to address the growing concerns for the comparative safety of z-hypnotics [50].

Conclusion

The findings of this study do not support a causal relationship between gestational sedative exposure and the risk of preterm birth, small for gestational age, ASD, or ADHD in offspring. Given that untreated anxiety and sleep disorders bear undesirable effects on birth and neurodevelopmental outcomes in offspring, clinicians should pay close attention when treating pregnant women with these conditions.

Statement of Ethics

Study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (approval number: UW20-051). This was a pharmacoepidemiology study without patient contact and therefore informed consent was exempted by the Institutional Review Board.

Conflict of Interest Statement

Author Contributions

A.Y.L Chan, L. Gao, I.C.K. Wong, and K.K.C. Man designed the study. A.Y.L Chan and L. Gao extracted the data, conducted and cross-checked the statistical analyses, and wrote the first draft of the manuscript. L.M. Howard, E. Simonoff, D. Coghill, P. Ip, W.C.Y. Lau, and K. Taxis critically reviewed and interpreted the manuscript. I.C.K. Wong and K.K.C. Man are the principal investigators, providing resources and supervising all steps of this project. All authors contributed to the interpretation, review, and editing the manuscript and approved the submission of the final version.

Data Availability Statement

Data cannot be shared as the data custodian – Hong Kong Hospital Authority did not give permission due to the concerns of patient confidentiality and privacy. Local academic institutions, government departments, or non-governmental organizations may apply for the access to data through the Hospital Authority's data sharing portal (https://www3.ha.org.hk/data). Further enquiries can be directed to the corresponding author.

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