Benzodiazepine or Z-hypnotic use during pregnancy and risk of psychiatric disorders in children: population based cohort study

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ABSTRACT

OBJECTIVE

To examine the association between prenatal exposure to benzodiazepines or Z-hypnotics and a spectrum of psychiatric disorders in children.

DESIGN

Population based cohort study with sibling controlled analysis.

SETTING

National Health Information Database of South Korea, 2009-23.

PARTICIPANTS

All liveborn children between 2010 and 2022 were followed until 2023. Pregnancies exposed to benzodiazepines or Z-hypnotics were compared with unexposed pregnancies and with pregnancies in women with previous use of these drugs (past users).

MAIN OUTCOME MEASURES

Overall and 12 specific psychiatric disorders in offspring. Propensity score overlap weighting was applied to balance covariates, and hazard ratios with 95% confidence intervals were estimated using Cox proportional hazards models. Sibling controlled analyses were conducted to account for shared familial factors.

RESULTS

Among 3 809 949 liveborn children, 94 482 (2.5%) were exposed to benzodiazepines or Z-hypnotics during pregnancy, 3 715 467 were unexposed, and 147 307 were born to past users. During the follow-up period, a total of 10 060, 311 997, and 15 645 events occurred in the exposed, unexposed, and past user groups, respectively. Prenatal exposure was associated with a higher risk of psychiatric disorders compared with unexposed pregnancies and past users; however, this association was attenuated in the sibling controlled analysis (hazard ratio 0.99, 95% confidence interval 0.94 to 1.04). No increased risk was observed for individual psychiatric disorders. In subgroup analyses, modestly elevated hazard ratios were observed for exposure during the second half of pregnancy (sibling controlled hazard ratios: 1.27 (0.95 to 1.71) for benzodiazepine; 1.81 (0.57 to 5.74) for Z-hypnotic), during both the first and second half of pregnancy (sibling controlled hazard ratios: 1.35 (0.93 to 1.96) for benzodiazepine; 1.44 (0.93 to 2.21) for Z-hypnotic), and for 30 or more days of Z-hypnotic exposure (sibling controlled hazard ratio 1.31, 0.96 to 1.78), although the confidence intervals in sibling analyses were wide and included the null.

CONCLUSIONS

In this large population based cohort, prenatal exposure to benzodiazepines or Z-hypnotics was not associated with an increased risk of psychiatric disorders in offspring after familial factors were accounted for. However, given the modest elevations in point estimates observed in certain subgroups—particularly with benzodiazepine and Z-hypnotic exposure during the latter half of pregnancy, as well as with exposure in both early and late pregnancy, and with longer durations of Z-hypnotic use—the potential for a slightly increased risk in these specific contexts could not be ruled out.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Benzodiazepines and Z-hypnotics are prescribed to alleviate anxiety and insomnia, which are common among women of reproductive age and may be aggravated by pregnancy

Previous studies have examined the short term safety of benzodiazepine and Z-hypnotic use in pregnancy, but evidence on their neuropsychiatric effects in offspring remains scarce

WHAT THIS STUDY ADDS

Maternal use of benzodiazepines or Z-hypnotics during pregnancy was not associated with an increased risk of psychiatric disorders in offspring after control for shared familial factors

Modestly elevated but non-significant estimates were seen with exposure during the latter half of pregnancy, as well as with exposures in both first and second half of pregnancy

Longer durations of Z-hypnotic use specifically also merit further investigation

Introduction

Psychiatric conditions such as anxiety and insomnia are common among women of reproductive age and often worsen during the later stages of pregnancy owing to physiological and psychosocial stressors.[1 2] Clinicians face a challenging dilemma when treating these conditions in pregnant women: untreated maternal psychiatric symptoms can adversely affect both mother and child, but drug treatments are used cautiously because of potential fetal risks.[3 4] Benzodiazepines and non-benzodiazepine hypnotics (Z-hypnotics) remain among the most frequently prescribed drugs in this population, with approximately 2% of pregnancies worldwide exposed, most commonly during the third trimester.[5] Moreover, given the high rate of unplanned pregnancies,[6] a substantial potential exists for inadvertent exposure during the early stages of gestation, which further necessitates the generation of real world evidence in this context.

Although previous studies have generally found no increased risk of congenital malformations associated with benzodiazepine or Z-hypnotic exposure during pregnancy,[7-9] the absence of teratogenic effects does not rule out potential neuropsychiatric harms, which remain insufficiently characterised to guide clinical decision making. Benzodiazepines and Z-hypnotics

readily cross the placenta and the fetal blood-brain barrier, raising concerns about their possible effects on fetal central nervous system development.[10] However, systematic reviews have identified a lack of robust evidence on neuropsychiatric outcomes in exposed offspring.[11 12] Although some recent studies reported no significant associations between prenatal exposure to sedatives and select developmental or psychiatric disorders, including autism spectrum disorder, attention deficit/hyperactivity disorder, and impaired scholastic abilities,[13-16] these investigations did not examine a broader range of potential psychiatric outcomes in children and some studies lacked statistical power to rule out elevated risks and conduct clinically relevant subgroup analyses (for example, duration-response). Furthermore, most previous studies did not consider familial, environmental, and genetic factors, which are important contributors to the aetiology of psychiatric disorders.[17]

Without comprehensive, large scale data that account for these confounders, the neurodevelopmental consequences of prenatal exposure to benzodiazepines or Z-hypnotics remain uncertain. We therefore conducted a nationwide cohort study of all live births in South Korea to examine associations between prenatal exposure to benzodiazepines and Z-hypnotics and the risk of psychiatric disorders in offspring across a broad spectrum of outcomes, using sibling comparisons to control for unmeasured familial confounding.

Methods

Study design and data source

This nationwide, population based cohort study used data covering 2009 to 2023 from the National Health Information Database (NHID), a comprehensive database including claims data for the entire Korean population of more than 52 million individuals. The database links data on mothers and their liveborn infants through a unique family subscriber number, with a linkage rate of over 90%.[18] The database collects longitudinal data on prescribed drugs, medical procedures, and diagnosis codes for both outpatient and inpatient settings until the occurrence of emigration or death. The NHID uses the ICD-10 (international classification of diseases, 10th revision), which has been the standard coding system in Korea since 1995. The ICD-10 codes are assigned exclusively by licensed physicians during clinical encounters. Because reimbursements for procedures and drugs are strictly tied to these physician certified diagnoses, they reflect clinical assessments.

Study population and exposure

We first identified all children born between 1 April 2010 and 31 December 2022. We selected this start date to ensure a sufficient look back period to fully capture data for the pregnancy period and the covariate assessment window. We then excluded children with a diagnosis of chromosomal abnormalities in their first year of life. To minimise exposure misclassification, we also excluded children whose mothers were exposed to benzodiazepines or Z-hypnotics within 90 days before the last menstrual period but not during pregnancy. We did this because prescriptions filled shortly before conception may result in ingestion during early pregnancy, potentially leading to misclassification of the unexposed comparator group. The last menstrual period date was estimated on the basis of a validated algorithm in a claims database that is based on diagnostic information on preterm birth.[19]

In the final cohort, we classified children whose mothers had at least one prescription of benzodiazepines or Z-hypnotics during pregnancy as the exposed group, and those not exposed during pregnancy served as the comparator group. Additionally, we did a preconception exposure analysis comparing the exposed group with a subset of the unexposed group whose mothers used benzodiazepines or Z-hypnotics 180 to 91 days before pregnancy but not during pregnancy—referred to as "past users." We used this group to further account for confounding by indication, as they share a history of the underlying condition motivating treatment.

Psychiatric disorders and follow-up

Psychiatric disorders include all ICD-10 F chapter codes, excluding F00 to F09, which correspond to organic brain disorders. Psychiatric disorders comprised two broad categories—general psychiatric disorders (substance use disorder, schizophrenia spectrum disorder, mood disorder, anxiety disorder, eating disorder, and personality disorder) and neurodevelopmental disorders (intellectual disability, autism spectrum disorder, other developmental disorders, attention deficit/hyperactivity disorder, tic disorder, and behavioural disorder). ICD-10 codes used to identify these disorders are listed in supplementary table A. For each eligible child, follow-up began at birth and ended at the occurrence of the outcome, death, or the end of the study period (31 December 2023), whichever came first.

Covariates

On the basis of the potential association with the exposure and outcome, we included 44 confounders or proxies of confounders, including demographics and socioeconomic characteristics (for example, birth year, maternal age, income level), obstetric characteristics (for example, nulliparity, multiple gestation), maternal medical conditions (for example, asthma, diabetes, hypertension), maternal medication use (for example, antipsychotics, anxiolytics, antidepressants), maternal healthcare utilisation (for example, inpatient visits, outpatient visits), and obstetric comorbidity index.[20 21] We categorised maternal medication use by therapeutic class to capture the underlying indication while ensuring sufficient sample size to satisfy the positivity assumption. We also considered maternal psychiatric comorbidities (for example, anxiety, depression/mood disorder, sleep disorder) and number of healthcare utilisations with psychiatric conditions as proxies for maternal psychiatric morbidity. Supplementary

figure A illustrates the measurement window and supplementary table A shows the full list of covariates.

Statistical analysis

For the comparisons with unexposed pregnancies and past users, we estimated propensity scores by using multivariable logistic regression models based on a set of identified covariates, representing the probability of exposure to the study drugs relative to each comparator group. We then applied propensity score overlap weighting by using the calculated propensity score to adjust for potential confounders.[22] We calculated the weights as the harmonic mean of the assignment probabilities divided by the probability of the observed group. This method minimises the variance of the weighted estimator and avoids the risk of extreme weights, thereby creating a pseudopopulation centred at clinical equipoise conditional on observed covariates. We compared both crude and weighted baseline characteristics of pregnant women exposed to benzodiazepines or Z-hypnotics with unexposed pregnancies and with past users. For each comparison, we calculated standardised mean differences to assess covariate balance, whereby an absolute standardised mean difference <0.1 was considered an adequate balance between groups.

To estimate the risk of psychiatric disorders, we used Cox proportional hazards regression models to estimate crude and propensity score weighted hazard ratios with 95% confidence intervals. We assumed an independent working correlation structure and used robust sandwich variance estimators clustered at the maternal level to account for within mother correlation and the propensity score weighting. We assessed the proportional hazards assumption by using Schoenfeld residuals. Given the large sample size, we evaluated the assumption on the basis of the magnitude of the correlation between residuals and time rather than hypothesis testing.[23] We used the Kaplan-Meier estimator to report the cumulative incidences of study outcomes across groups. We used SAS Enterprise Guide, version 9.4, for all data management and analyses.

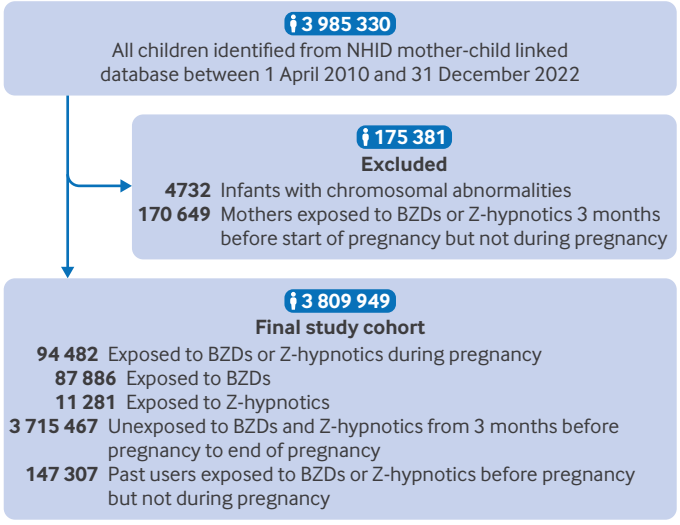


Fig 1 | Flowchart of study cohort selection. BZD=benzodiazepine; NHID=National Health Information Database

Sibling controlled analysis

As a pre-specified analysis to overcome potential unmeasured confounding from shared familial, genetic and environmental factors, we did a sibling controlled analysis, restricting the population to children with at least one sibling with a discordant exposure status identified during the study period. This design helps to control for time invariant family level confounders that are typically unmeasurable in the claims database. In this subset, we applied stratified Cox proportional hazards models, stratified at the maternal level, to estimate hazard ratios and 95% confidence intervals. Given that time invariant confounders are inherently controlled by the design, we used direct covariate adjustment to adjust for maternal characteristics specific to each pregnancy. We pre-specified an analytical approach to examine the robustness of the associations across different sources of confounding: comparison with unexposed pregnancies, comparison with past users, and sibling controlled analysis.

Secondary analysis

Whereas we evaluated the risk of exposure to benzodiazepines or Z-hypnotics in our main analyses, we did subgroup analyses to evaluate the risk for benzodiazepines and Z-hypnotics separately. For benzodiazepines, we also assessed the risk on the basis of the drug's duration of action (short acting and long acting). A list of short acting and long acting benzodiazepines is provided in supplementary table A. In addition, we estimated risks for the three most commonly used individual benzodiazepines in our data, which were diazepam, midazolam, and alprazolam (supplementary table B). For both benzodiazepines and Z-hypnotics, we did subgroup analyses based on the timing of exposure (early pregnancy only, late pregnancy only, and both periods) to assess whether the drug exposure in different time windows is associated with different risks of psychiatric disorders. We defined early pregnancy as the period from the last menstrual period to week 20 and late pregnancy as from week 21 to the day before delivery. We chose this stratification to capture the period of rapid synaptogenesis occurring primarily in the second half of gestation.[24] To evaluate a potential duration-response relation, we further stratified each exposure group into thirds on the basis of the total duration of drug use, calculated by summing the specific days of supply recorded for each prescription (benzodiazepines: <2 days, 2 to <6 days, 6 days or more; Z-hypnotics: <14 days, 14 to <30 days, 30 days or more). Lastly, we stratified the exposed group into new users and consistent users on the basis of the presence of a prescription in the 180 days before pregnancy.

We did six sensitivity analyses. Firstly, we redefined exposure as having two or more prescriptions during pregnancy, instead of one or more prescriptions, to account for potential exposure misclassification. Secondly, to increase the specificity of the outcome definition, we redefined the outcome as requiring two or more recorded diagnoses. Thirdly, to ensure a potential maximum follow-up of at least seven years, we restricted the study population to children born from 2010 to 2016. Fourthly, to account for the potential confounding effects of teratogenic exposure on neurodevelopment, we did a sensitivity analysis excluding pregnancies exposed to potential teratogens during the first trimester (up to last menstrual period plus 13 weeks). Fifthly, to assess the generalisability of the sibling cohort, which is inherently restricted to families with at least two children, we compared risk estimates derived from the sibling population with those from the overall population by using a non-stratified multivariable Cox model. Lastly, we provided

Maternal characteristics	Exposed (n=94 482)	Comparator group: Unexposed (n=3 715 467)	Comparator group: Past users (n=147 307)
Mean (SD) age at delivery (years)	33.1 (4.8)	32.2 (4.3)	32.5 (4.3)
Medical aid†	2435 (2.6)	19 506 (0.5)	1342 (0.9)
Income level			
1st (lowest)	21 817 (23.1)	728 901 (19.6)	30 005 (20.4)
2nd	22 355 (23.7)	885 776 (23.8)	35 274 (23.9)
3rd	30 115 (31.9)	1 296 598 (34.9)	50 272 (34.1)
4th (highest)	20 195 (21.4)	804 192 (21.6)	31 756 (21.6)
Obstetric conditions			
Nulliparity	51 393 (54.4)	1 921 664 (51.7)	81 939 (55.6)
Multiple gestation	9927 (10.5)	125 698 (3.4)	5914 (4.0)
Sex assigned at birth, boys	48 694 (51.5)	1 906 030 (51.3)	75,731 (51.4)
Maternal psychiatric conditions			
Anxiety	15 072 (16.0)	18 044 (0.5)	10 207 (6.9)
Bipolar disorder	2221 (2.4)	2209 (0.1)	756 (0.5)
Mood disorder	12 862 (13.6)	21 324 (0.6)	8111 (5.5)
Psychotic disorder	1464 (1.5)	1935 (0.1)	468 (0.3)
Eating disorder	272 (0.3)	920 (0.0)	155 (0.1)
Sleep disorder	14 375 (15.2)	12 108 (0.3)	8137 (5.5)
Personality disorders	258 (0.3)	389 (0.0)	109 (0.1)
ADHD	86 (0.1)	273 (0.0)	53 (0.0)
No of outpatient visits with psychiatric conditions			
0	74 486 (78.8)	3 677 092 (99.0)	125 515 (85.2)
1	3968 (4.2)	23 423 (0.6)	13 857 (9.4)
2	2107 (2.2)	6188 (0.2)	3630 (2.5)
≥3	13 921 (14.7)	8764 (0.2)	4305 (2.9)
No of inpatient visits with psychiatric conditions			
0	93 876 (99.4)	3 714 494 (100.0)	146 687 (99.6)
1	380 (0.4)	843 (0.0)	532 (0.4)
2	114 (0.1)	86 (0.0)	57 (0.0)
≥3	112 (0.1)	44 (0.0)	31 (0.0)
No of ED visits with psychiatric conditions			
0	93 962 (99.4)	3 714 444 (100.0)	146 595 (99.5)
1	393 (0.4)	965 (0.0)	671 (0.5)
2	81 (0.1)	48 (0.0)	32 (0.0)
≥3	46 (0.0)	10 (0.0)	9 (0.0)

Fig 2 | Selected baseline characteristics of benzodiazepine or Z-hypnotic exposed pregnancies compared with unexposed pregnancies before propensity score weighting (part 1). Values are numbers (percentages) unless stated otherwise. ADHD=attention deficit/hyperactivity disorder; ED=emergency department; PS=propensity score; SD=standard deviation. *Standardised mean differences describe balance in baseline characteristics across levels of adjustment for confounding. †Medical aid indicates government subsidised public assistance programme for low income individuals, used here as proxy for socioeconomic status

Maternal characteristics	Exposed (n=94 482)	Comparator group: Unexposed (n=3 715 467)	Comparator group: Past users (n=147 307)	Standardised mean difference*
Maternal medical conditions				
Asthma	5385 (5.7)	121 577 (3.3)	7580 (5.1)	
Diabetes	3619 (3.8)	81 098 (2.2)	4153 (2.8)	
Epilepsy	1131 (1.2)	5867 (0.2)	659 (0.4)	
Gastrointestinal disorder	54 165 (57.3)	1 225 845 (33.0)	84 359 (57.3)	
Hypertension	2656 (2.8)	40 837 (1.1)	2416 (1.6)	
Alcohol or drug dependence	848 (0.9)	1627 (0.0)	474 (0.3)	
Tobacco dependence	12 (0.0)	73 (0.0)	7 (0.0)	
Maternal medication use				
Antiepileptic drugs	3370 (3.6)	23 365 (0.6)	3611 (2.5)	
Antidepressants	13 275 (14.1)	34 241 (0.9)	12 685 (8.6)	
Antidiabetics	1563 (1.7)	20 828 (0.6)	1306 (0.9)	
Antihypertensives	7781 (8.2)	44 724 (1.2)	10 102 (6.9)	
Antipsychotics	17 034 (18.0)	282 663 (7.6)	27 532 (18.7)	
Anxiolytics	4494 (4.8)	99 385 (2.7)	7123 (4.8)	
Barbiturates	64 (0.1)	575 (0.0)	99 (0.1)	
Lithium	668 (0.7)	614 (0.0)	293 (0.2)	
NSAIDs	64 146 (67.9)	1 973 806 (53.1)	113 298 (76.9)	
Opioid	30 498 (32.3)	655 159 (17.6)	60 827 (41.3)	
Triptan	739 (0.8)	7700 (0.2)	1359 (0.9)	
Stimulants	264 (0.3)	415 (0.0)	144 (0.1)	
Smoking†				
Current	4426 (4.7)	106 212 (2.9)	5044 (3.4)	
None or past	40 030 (42.4)	1 697 574 (45.7)	64 453 (43.8)	
Missing data	50 026 (52.9)	1 911 681 (51.5)	77 810 (52.8)	
Maternal body mass index†				
Underweight	5756 (6.1)	254 456 (6.8)	10 147 (6.9)	
Normal	25 829 (27.3)	1 124 811 (30.3)	42 490 (28.8)	
Overweight	5613 (5.9)	209 752 (5.6)	8161 (5.5)	
Obesity	7094 (7.5)	208 173 (5.6)	8427 (5.7)	
Missing data	50 190 (53.1)	1 918 275 (51.6)	78 082 (53.0)	

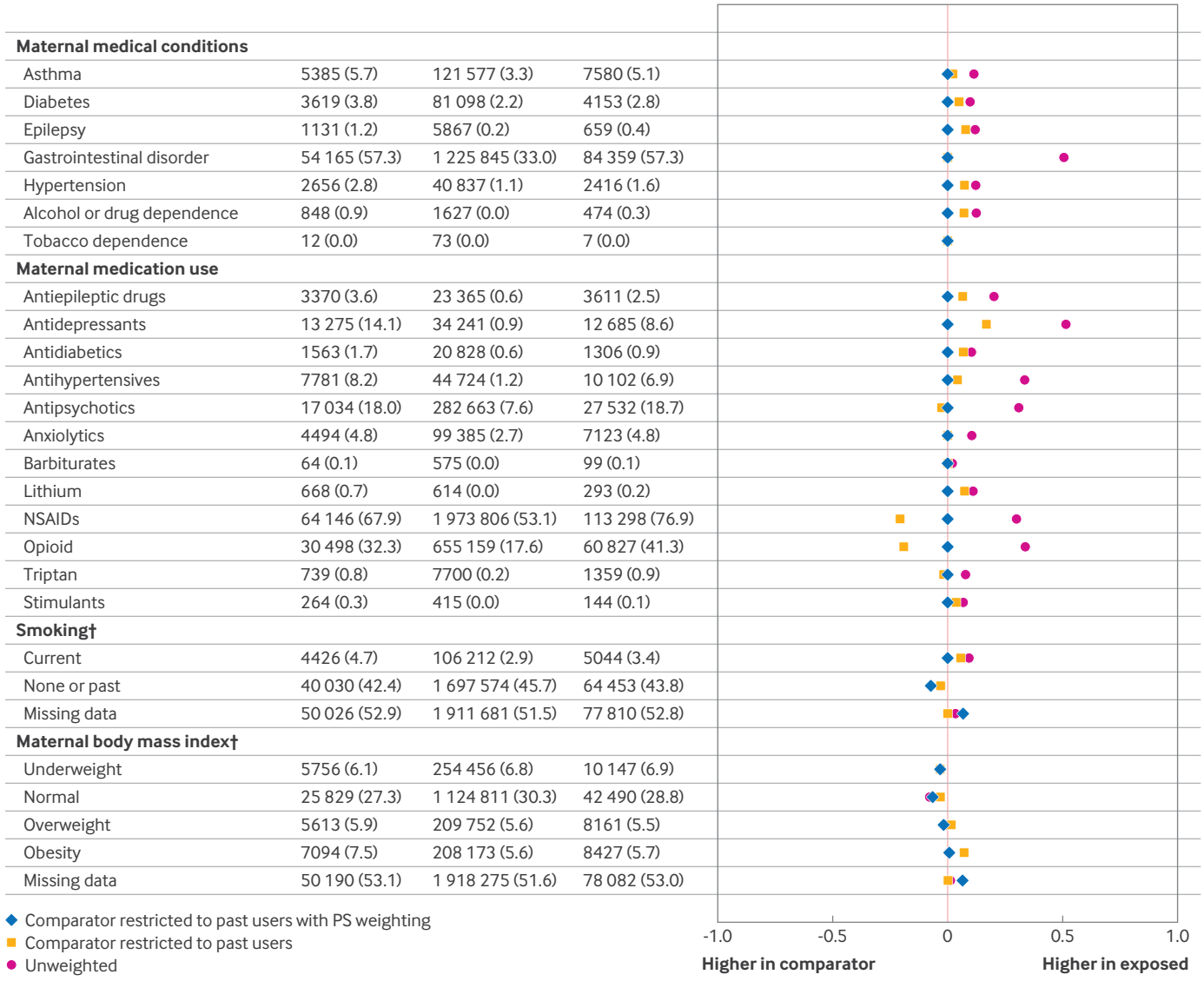


Fig 3 | Selected baseline characteristics of benzodiazepine or Z-hypnotic exposed pregnancies compared with unexposed pregnancies before propensity score weighting (part 2). Values are numbers (percentages) unless stated otherwise. NSAID=non-steroid anti-inflammatory drug; PS=propensity score; SD=standard deviation. *Standardised mean differences describe balance in baseline characteristics across levels of adjustment for confounding. † Not included in propensity score model owing to high prevalence of missing values

E-values for the hazard ratios from the sibling analysis to quantify the strength of the unmeasured confounder needed to shift the point estimate to the null.[25] We recalculated propensity scores for each subgroup and sensitivity analysis.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures. No patients were asked to advise on interpretation or writing up of results. Although we fully support involving patients and members of the public in conducting medical research, no funding was available for this purpose in our study.

Results

Cohort characteristics

We identified 3 809 949 children born to mothers who were pregnant during the study period. Of these, 94 482 (2.5%) were exposed to benzodiazepines or Z-hypnotics during pregnancy, and 3 715 467 (97.5%) were unexposed. Among the unexposed, 147 307 children were born to mothers who had previous use of study drugs but no use during pregnancy and were classified as past users (fig 1). Among 94 482 children exposed to benzodiazepines or Z-hypnotics, 87 886 (93.0%) were exposed to benzodiazepines, 11 281 (11.9%) were exposed to Z-hypnotics, and 4685 (5.0%) were exposed to both drug classes.

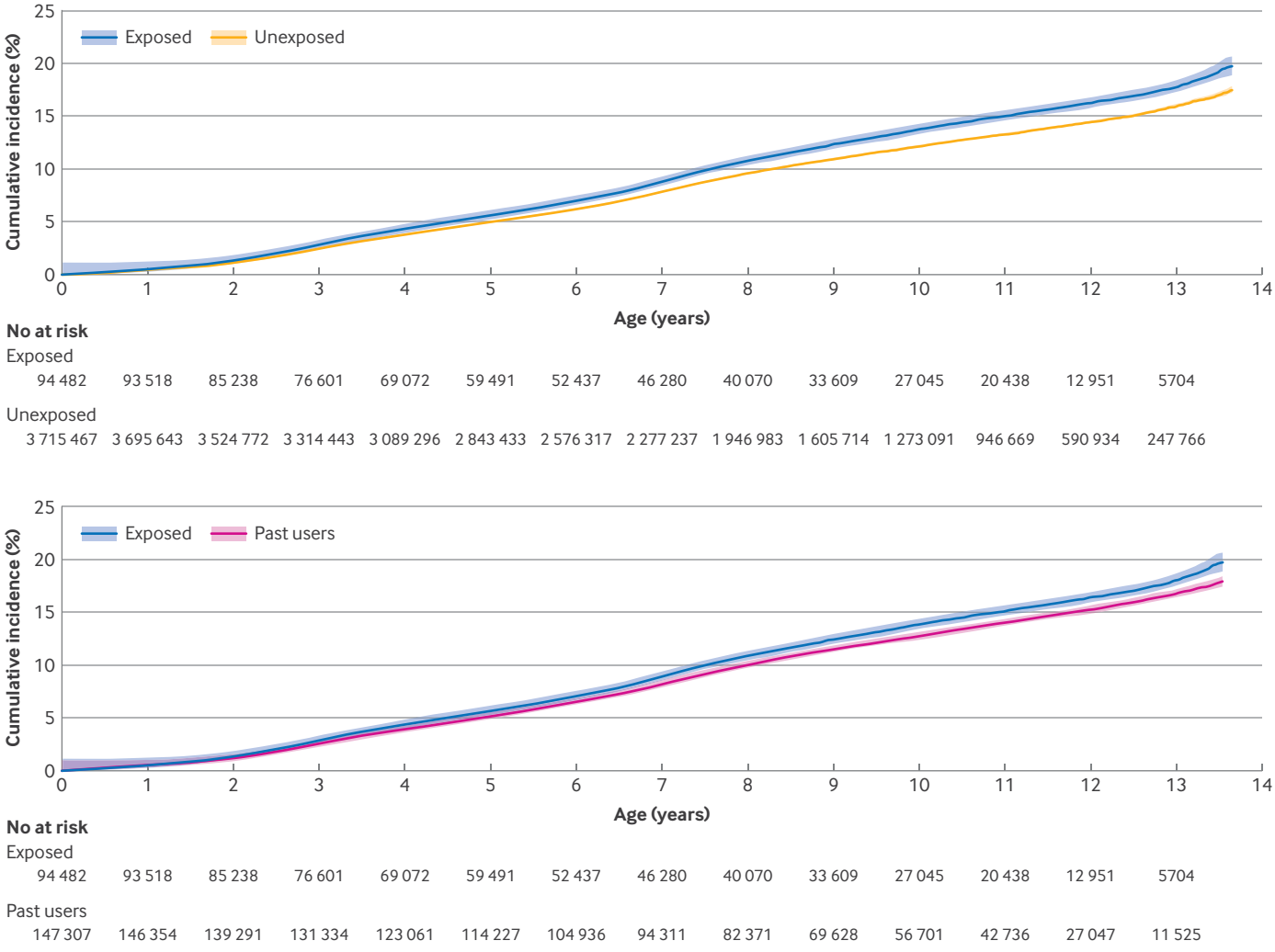
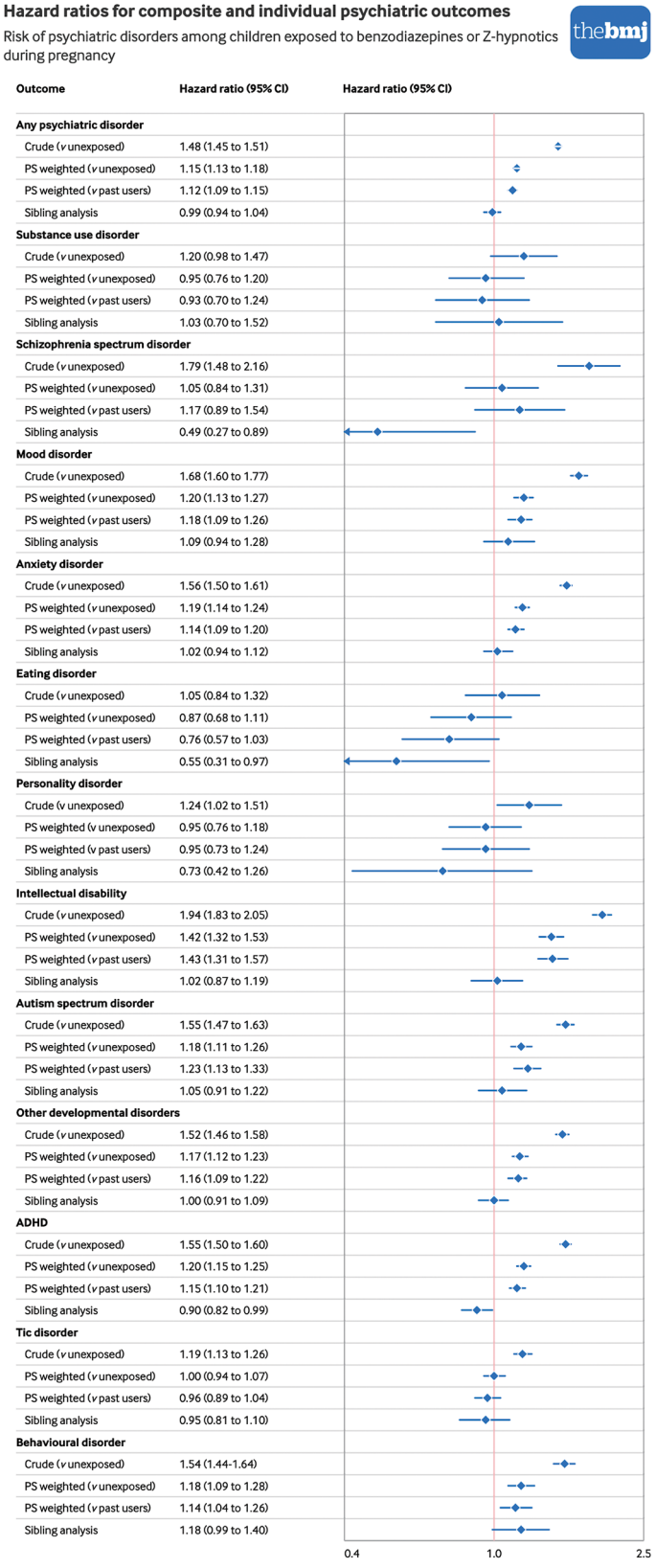


Fig 4 | Cumulative incidence curve of psychiatric disorders among benzodiazepine or Z-hypnotic exposed pregnancies, compared with unexposed pregnancies (top) and past users (bottom)

Compared with both unexposed pregnancies and past users, a higher proportion of exposed children were born to mothers receiving medical aid. Additionally, exposed children had mothers with a higher frequency of psychiatric conditions, including anxiety, mood disorders, and sleep disorders, relative to both unexposed children and those born to past users. Exposed children's mothers also had more frequent healthcare encounters for psychiatric conditions (fig 2 and fig 3; see supplementary tables C-G for full lists of characteristics). The propensity score distributions before and after application of the overlap weighting in our primary analysis are presented in supplementary figure B. After propensity score overlap weighting, the covariates included in the propensity score model were exactly balanced between groups.

Risk of psychiatric disorders

In the analysis of psychiatric disorders, the median follow-up duration was 6.85 (interquartile range 3.68-10.53) years for the exposed group, 8.28 (5.24-11.06) years for the unexposed group, and 8.71 (5.43-11.40) years for past users. The median follow-up duration for the individual outcome analysis is presented in supplementary table H. During the follow-up period, a total of 10 060, 311 997, and 15 645 events occurred in the exposed, unexposed, and past user groups, respectively. Median age in years at first diagnosis and the incidence rate of psychiatric disorders are presented in supplementary tables I and J, respectively. By the age of 13, the cumulative incidence of psychiatric disorders was 19.2% in exposed children, 13.8% in unexposed children, and 16.5% in the past user group (fig 4; supplementary tables K and L). The analysis of Schoenfeld residuals indicated no meaningful violation of the proportional hazards assumption for comparisons with unexposed pregnancies or past users, with correlation coefficients of 0.064 and 0.070, respectively. In the crude analysis, exposure to benzodiazepines or Z-hypnotics during pregnancy was associated with an increased risk of psychiatric disorders compared with unexposed children (hazard ratio 1.48, 95% confidence interval (CI) 1.45 to 1.51). This association was attenuated after application of



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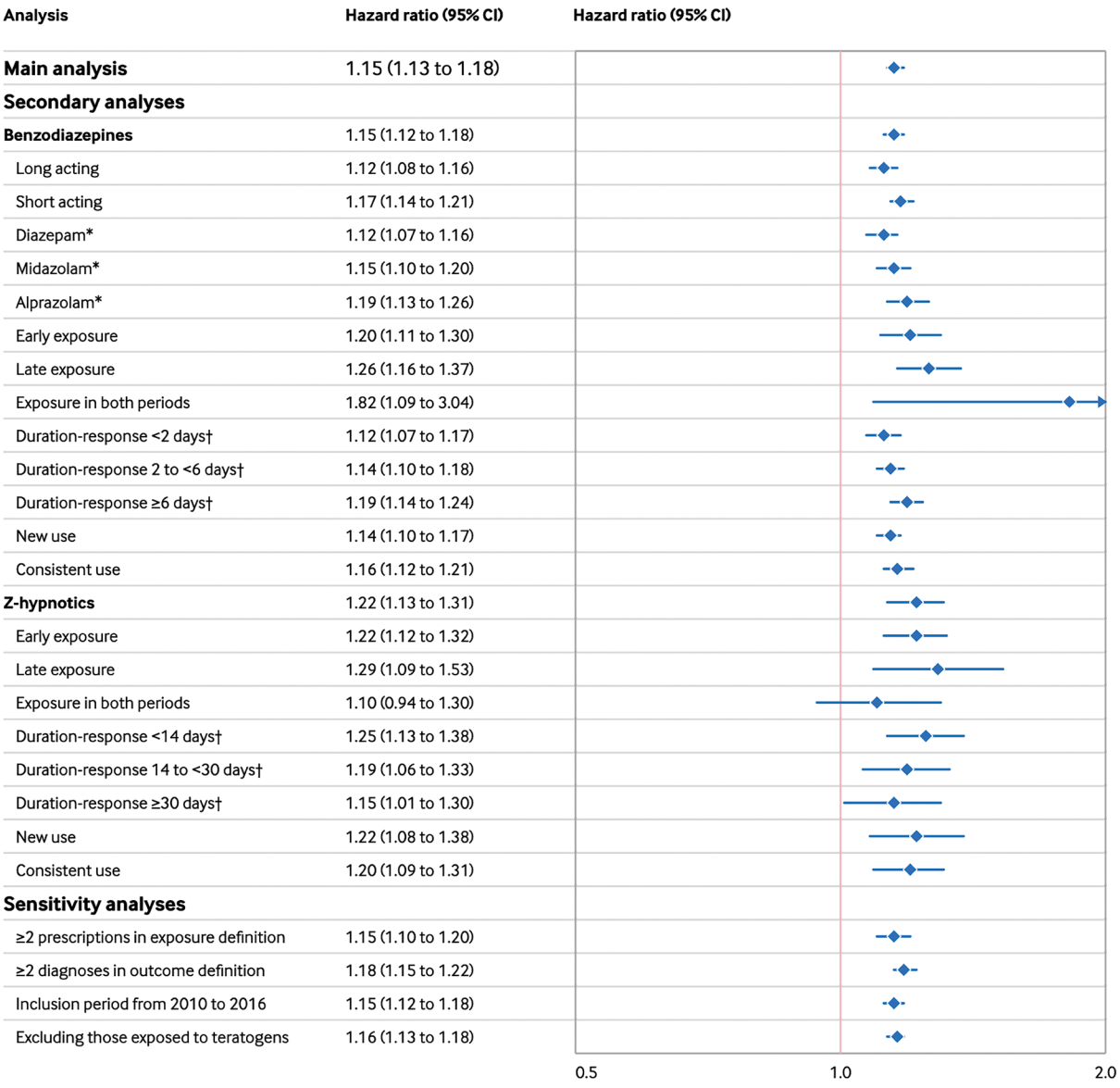
ADHD=attention deficit/hyperactivity disorder; CI=confidence interval; PS=propensity score

Fig 5 | Psychiatric disorders among children exposed to benzodiazepines or Z-hypnotics during pregnancy. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/28297827/

Secondary and sensitivity analyses (exposed *v* unexposed)

Risk of psychiatric disorders among children exposed to benzodiazepines or Z-hypnotics during pregnancy



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CI=confidence interval
*Top 3 most commonly prescribed benzodiazepines
†Based on thirds

Fig 6 | Secondary and sensitivity analyses on risk of psychiatric disorders among children exposed to benzodiazepines or Z-hypnotics during pregnancy (versus unexposed). An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/28334880/

propensity score weighting (hazard ratio 1.15, 1.13 to 1.18) and further slightly reduced when compared with children of past users (1.12, 1.09 to 1.15) (fig 5). The weighted cumulative incidence curves for each comparison are presented in figure 4.

When we examined individual psychiatric outcomes, prenatal benzodiazepine or Z-hypnotic exposure was associated with an increased risk of the following outcomes compared with the unexposed and past user groups: mood disorder, anxiety disorder,

intellectual disability, autism spectrum disorder, other developmental disorders, attention deficit/hyperactivity disorder, and behavioural disorder (fig 5).

In the sibling controlled analyses, 33 370 exposed siblings and 37 574 unexposed siblings from exposure discordant sibling pairs were included (supplementary table M). In contrast to the findings from the comparison with unexposed and past users in our main analyses, most of the associations showed no significant risks of overall and individual psychiatric disorders. The adjusted hazard ratio for overall psychiatric disorders was 0.99 (95% CI 0.94 to 1.04) (fig 5).

Secondary analyses

Results from subgroup analyses were generally consistent with the main findings (fig 6, fig 7, fig 8; supplementary table N). Comparisons with the unexposed and past users groups continued to show slightly elevated risks, which were attenuated after we accounted for shared familial factors in sibling analyses. However, point estimates remained elevated in certain subgroups even after control for within familial confounding. Exposure during both early and late pregnancy was associated with increased point estimates for both benzodiazepines (versus unexposed: hazard ratio 1.82, 95% CI 1.09 to 3.04; sibling controlled: 1.35, 0.93 to 1.96) and Z-hypnotics (versus unexposed: hazard ratio 1.10, 0.94 to 1.30; sibling controlled: 1.44, 0.93 to 2.21). This pattern persisted for exposure specifically during the second half of pregnancy, which also showed elevated estimates for benzodiazepines (versus unexposed: hazard ratio 1.26, 1.16 to 1.37; sibling controlled: 1.27, 0.95 to 1.71) and Z-hypnotics (versus unexposed: hazard ratio 1.29, 1.09 to 1.53; sibling controlled: 1.81, 0.57 to 5.74). Overall, Z-hypnotic exposure was also associated with a slightly elevated estimate (versus unexposed: hazard ratio 1.22, 1.13 to 1.31; sibling controlled: 1.12, 0.94 to 1.33), particularly for durations exceeding 30 days (versus unexposed: hazard ratio 1.15, 1.01 to 1.30; sibling controlled: 1.31, 0.96 to 1.78), although these findings did not reach statistical significance. Sensitivity analyses yielded results consistent with the primary analyses (fig 6, fig 7, fig 8). The results of the sensitivity analyses for secondary outcomes can be found in supplementary tables O–T.

Discussion

In this large nationwide cohort of pregnant women and their liveborn children, we found no association between prenatal exposure to benzodiazepines or Z-hypnotics and the risk of psychiatric disorders. Although we observed a modest elevation in risk in the crude analysis, these associations were attenuated when we applied propensity score weighting and were no longer significant in the sibling controlled analyses, suggesting that many potential confounders including maternal conditions and shared familial factors may have contributed to the observed associations. Although we used a composite endpoint to maximise statistical power and capture the broad spectrum of potential neurodevelopmental sequelae, we recognise that psychiatric disorders are aetiologically distinct. To ensure that this broad approach did not mask condition specific risks, we evaluated individual outcomes separately and did not find any elevated risk across distinct diagnostic categories. Taken together, these findings offer reassurance about the use of benzodiazepines or Z-hypnotics during pregnancy with respect to the psychiatric outcomes evaluated.

Sibling controlled analysis

In the sibling controlled analysis, we observed statistically significant reductions in the risk of certain outcomes, including schizophrenia spectrum disorder and eating disorder. However, these findings should be interpreted cautiously. The number of events for these outcomes in the sibling cohort was relatively small, limiting statistical power and potentially increasing the influence of random variation. The sibling design, while controlling for shared familial factors, may reduce precision owing to restricted exposure discordance within families. Importantly, these reduced estimates were not consistently observed in the propensity score weighted analyses comparing exposed individuals with unexposed individuals or discontinuers. Taken together, the overall pattern of findings does not suggest an increased risk of these outcomes.

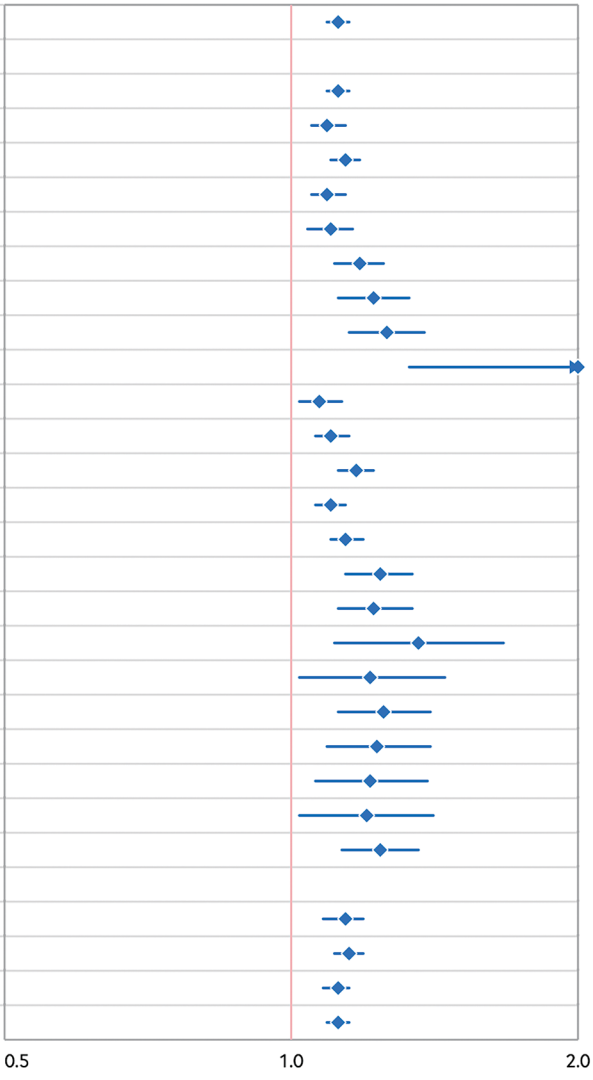
Comparison with other studies

Previous studies investigating the safety of benzodiazepine or Z-hypnotic use during pregnancy have reported an increased risk of adverse perinatal outcomes, including low birth weight and preterm birth,[26 27] and no association with congenital malformations.[7-9] By contrast, evidence on psychiatric outcomes remains limited.[11] Earlier research has primarily examined specific disorders such as autism spectrum disorder and attention deficit/hyperactivity disorder. Notably, three studies have used sibling controlled designs to account for shared familial confounding.[13 15 28] Among these, two studies found no association between prenatal sedative exposure and the risks of autism spectrum disorder or attention deficit/hyperactivity disorder, which is in line with our findings.[13 15] Another study found no association between short term prenatal benzodiazepine or Z-hypnotics exposure and internalising problems at age 1.5 and 3 but reported an increased risk associated with long term prenatal benzodiazepine or Z-hypnotics exposure—defined as two or more uses in distinct pregnancy periods (weeks 0 to 13, weeks 14 to 29, week 30 to birth)—in a sibling controlled analysis.[28] Regarding the exposure timing, these results are also in line with our results, in which we observed elevated point estimates associated with benzodiazepine or Z-hypnotic use in both early and late pregnancy. We also observed consistently elevated point estimates associated with benzodiazepine or Z-hypnotic use in later pregnancy (beyond 20 weeks of gestation). A plausible biological explanation for this trend involves

Secondary and sensitivity analyses (exposed *v* past users)

Risk of psychiatric disorders among children exposed to benzodiazepines or Z-hypnotics during pregnancy

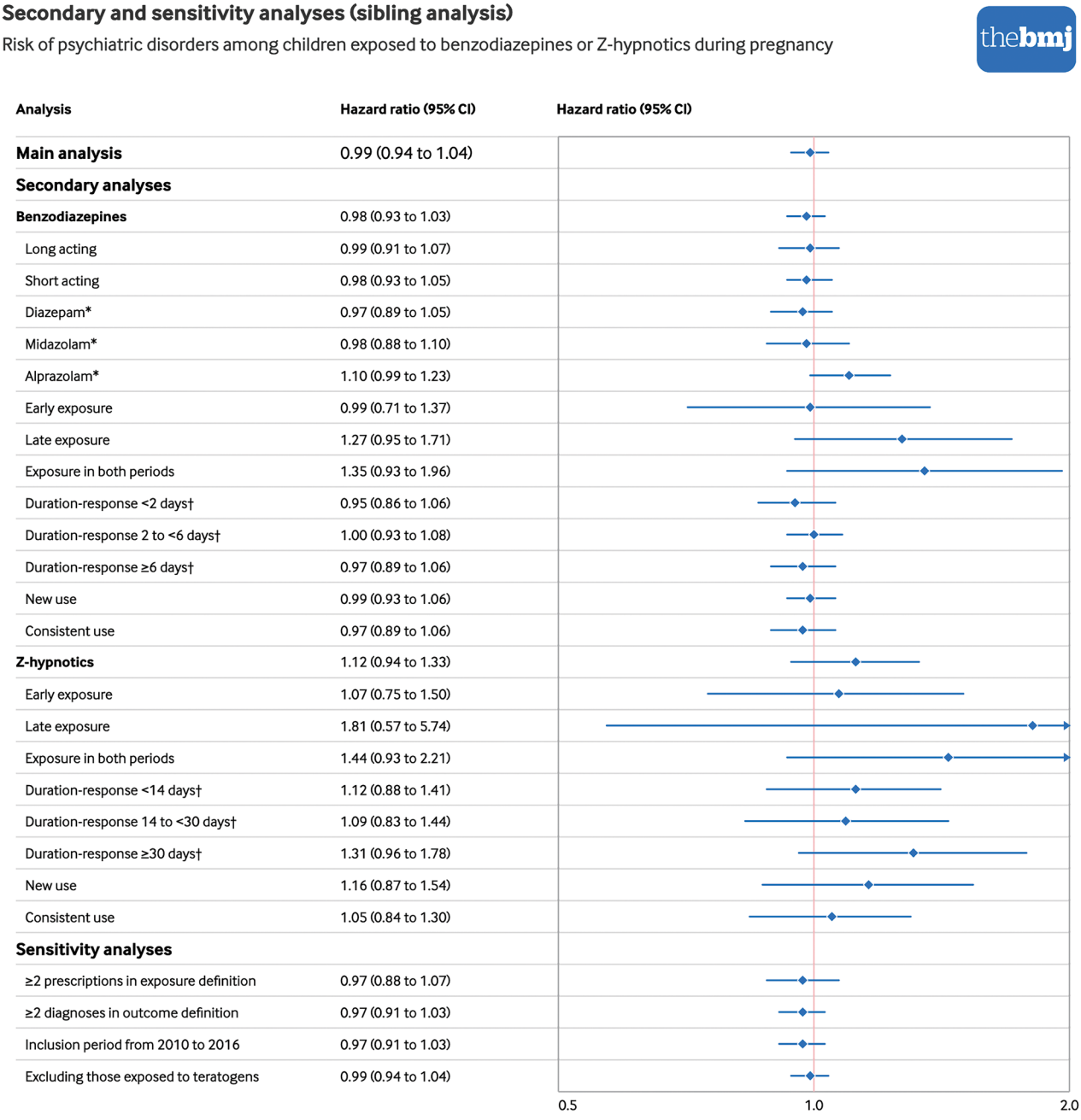
Analysis	Hazard ratio (95% CI)
Main analysis	1.12 (1.09 to 1.15)
Secondary analyses	
Benzodiazepines	1.12 (1.09 to 1.15)
Long acting	1.09 (1.05 to 1.14)
Short acting	1.14 (1.10 to 1.18)
Diazepam*	1.09 (1.05 to 1.14)
Midazolam*	1.10 (1.04 to 1.16)
Alprazolam*	1.18 (1.11 to 1.25)
Early exposure	1.22 (1.12 to 1.33)
Late exposure	1.26 (1.15 to 1.38)
Exposure in both periods	2.33 (1.33 to 4.10)
Duration-response <2 days†	1.07 (1.02 to 1.13)
Duration-response 2 to <6 days†	1.10 (1.06 to 1.15)
Duration-response ≥6 days†	1.17 (1.12 to 1.22)
New use	1.10 (1.06 to 1.14)
Consistent use	1.14 (1.10 to 1.19)
Z-hypnotics	1.24 (1.14 to 1.34)
Early exposure	1.22 (1.12 to 1.34)
Late exposure	1.36 (1.11 to 1.67)
Exposure in both periods	1.21 (1.02 to 1.45)
Duration-response <14 days†	1.25 (1.12 to 1.40)
Duration-response 14 to <30 days†	1.23 (1.09 to 1.40)
Duration-response ≥30 days†	1.21 (1.06 to 1.39)
New use	1.20 (1.02 to 1.41)
Consistent use	1.24 (1.13 to 1.36)
Sensitivity analyses	
≥2 prescriptions in exposure definition	1.14 (1.08 to 1.19)
≥2 diagnoses in outcome definition	1.15 (1.11 to 1.19)
Inclusion period from 2010 to 2016	1.12 (1.08 to 1.15)
Excluding those exposed to teratogens	1.12 (1.09 to 1.15)



Article DOI: 10.1136/bmj-2025-088671 • Download data
CI=confidence interval
*Top 3 most commonly prescribed benzodiazepines
†Based on thirds

Fig 7 | Secondary and sensitivity analyses on risk of psychiatric disorders among children exposed to benzodiazepines or Z-hypnotics during pregnancy (versus past users). An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/28334917/

the disruption of γ-aminobutyric acid (GABA)ergic signalling during late gestation, a period marked by rapid synaptogenesis beginning around week 20 and peaking in the third trimester.[24] During this developmental window, GABAergic activity transitions from excitatory to inhibitory, playing a critical role in shaping neuronal circuitry.[29] Experimental evidence indicates that excessive activation of $GABA_A$ receptors, such as that induced by sedative exposure, may interfere with this transition, impair synaptic plasticity, and thereby increase susceptibility to later neuropsychiatric disturbances.



Article DOI: 10.1136/bmj-2025-088671 • Download data
CI=confidence interval
*Top 3 most commonly prescribed benzodiazepines
†Based on thirds

Fig 8 | Secondary and sensitivity analyses on risk of psychiatric disorders among children exposed to benzodiazepines or Z-hypnotics during pregnancy (sibling analysis). An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/28334921/

Similarly, we observed modestly elevated estimates with Z-hypnotic exposure. Given that benzodiazepines and Z-hypnotics act through the same $GABA_A$ receptor pathway, the observed differences in risk are likely attributable to distinct patterns of drug use. Z-hypnotics are predominantly prescribed for insomnia, which tends to be chronic; in Korea, they are often used for longer durations than benzodiazepines, even for similar indications.[30] Although Z-hypnotics have shorter half lives than benzodiazepines, their prolonged use may lead to sustained modulation of GABAergic signalling.[31] Consistent with this, we

observed higher risk estimates among pregnancies exposed to Z-hypnotics for 30 days or more. However, because these estimates did not reach statistical significance, our findings should be interpreted as hypothesis generating; nevertheless, the consistent direction of the association suggests that sedative use should be approached cautiously and non-drug options, such as cognitive behavioural therapy for insomnia, should be more actively used.[32 33]

Strengths and limitations of study

Our study seeks to fill an important evidence gap by examining the neuropsychiatric outcomes associated with prenatal exposure to sedatives. Using a large, nationally representative database with a maximum follow-up of up to 14 years, we were able to assess specific psychiatric disorders. Importantly, we used rigorous methods to overcome confounding. Our propensity score models incorporated a range of potential covariates, including proxies of disease severity, and our sibling comparison design helped to disentangle drug effects from shared familial, genetic, and environmental factors.

Despite these strengths, our study has several limitations that warrant consideration. Firstly, a prescription for a benzodiazepine or a Z-hypnotic may not always reflect actual ingestion, particularly as these drugs are often prescribed on an "as needed" basis.[34] To counter this, we did a sensitivity analysis restricted to women with more than two prescriptions under the assumption that this population is more likely to have used the drug, which yielded results consistent with the main findings. Secondly, our outcome definitions were based on diagnosis codes, which precluded assessment of the severity or chronicity of symptoms. Moreover, our follow-up period may be insufficient to capture late onset conditions such as schizophrenia or personality disorders, which typically manifest in late adolescence. Further research incorporating more detailed clinical data and longer follow-up may clarify these aspects. Thirdly, the use of a composite primary outcome may have obscured condition specific associations. Although we analysed individual disorders as secondary outcomes to mitigate this, the results for individual psychiatric disorders should be interpreted with caution as the possibility of chance findings cannot be ruled out, given the large number of secondary outcomes evaluated. Fourthly, although we included an extensive list of potential confounders in the propensity score model, residual confounding from unmeasured factors cannot be completely ruled out. Similarly, although the sibling controlled design accounts for time invariant familial factors, it does not overcome confounders that vary between pregnancies. Thus, residual confounding may persist owing to unmeasured time varying factors specific to each pregnancy, such as acute psychosocial stressors. Fifthly, because the algorithm used to estimate gestational age has not been validated in the NHID, some degree of exposure misclassification is possible, particularly for preterm births. One potential source of bias is the misclassification of pre-pregnancy use as early pregnancy exposure, which may increase the likelihood of including preterm births in the exposed group and, consequently, result in higher estimated risks associated with exposure. Although our study generally did not observe an increased risk, this potential bias should be considered when interpreting the results. Sixthly, our exclusion criteria, although necessary to minimise confounding and exposure misclassification, may limit the scope of our findings. Further research is needed to evaluate the potential risk of chromosomal abnormalities associated with these drugs or the neurodevelopmental implications of exposure associated with use in the pre-conceptual period.

Conclusions

This large, population based cohort study found no substantial evidence that prenatal exposure to benzodiazepines or Z-hypnotics increases the risk of psychiatric disorders in children. Although these findings provide reassurance about neuropsychiatric safety, further research is needed to clarify the potential modest elevations in estimates observed with benzodiazepine or Z-hypnotic use during the second half of pregnancy, as well as with exposure in both first and second half of pregnancy, and with Z-hypnotic use for extended periods. Given the increasing prevalence of pregnancies complicated by psychiatric conditions and the potential risks of untreated maternal illness, our results will help to inform individualised risk-benefit discussions when considering sedative therapy in pregnancy.

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Ethical approval: This study was approved by the Institutional Review Board of Sungkyunkwan University, South Korea (No 2025-07-106). The requirement for informed consent was waived owing to the use of deidentified data.

Data sharing: Data generated and/or analysed during this study cannot be shared publicly owing to the data sharing policy of the National Health Insurance Service (NHIS) of Korea, governed by Article 18 of the Personal Information Protection Act ("Limitation to Out-of-Purpose Use and Provision of Personal Information" available at https://elaw.klri.re.kr/eng_service/lawView.do?hseq=53044&lang=ENG). However, the data are available from the NHIS (study identifier: NHIS-2024-1-429) on reasonable request for researchers who meet the criteria for access to confidential data (https://www.data.go.kr/en/tcs/eds/selectCoreDataView.do?coreDataInsttCode=B551182&coreDataSn=1&searchCondition2=coreDataNmEn&searchKeyword2=).

Transparency: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: Because the datasets are anonymised, dissemination of the results of the research to study participants is not possible.

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Web appendix: Supplementary materials