Concomitant use of antidepressants and benzodiazepines during pregnancy and associated risk of congenital malformations: a population-based cohort study in Taiwan

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Summary

Background Despite the frequent co-administration of antidepressants and benzodiazepines, the association between such concomitant use during pregnancy and the risk of congenital malformations remains inadequately explored. This study aims to examine the association between concomitant use of antidepressants and benzodiazepines during the first trimester and organ-specific congenital malformations.

Methods We conducted a population-based cohort study using Taiwan's National Birth Certificate Application database, the Maternal and Child Health database, and Taiwan's National Health Insurance database. Pregnant people aged 15–50 years with singleton births between Jan 1, 2004, and Dec 31, 2018, were included. Use of antidepressants and benzodiazepines was defined as at least one prescription during the first trimester, and concomitant use was defined as the overlapping prescription of both drugs with an overlapping prescription period. The primary outcomes were overall congenital malformations and eight organ-specific malformations, consisting of the nervous system, heart, respiratory system, oral cleft, digestive system, urinary system, genital system, and limb malformations. Logistic regression models with propensity score fine stratification weighting approach were used to control for measured confounders. Analyses controlling for confounding by indication and sibling comparison analyses were done to address unmeasured confounders. No individuals with lived experience participated in the research or writing process.

Findings The cohort included 2 634 021 singleton pregnancies, and 8599 (0·3%) individuals were concomitant users of antidepressants and benzodiazepines during the first trimester (mean age at delivery was 31·8 years [SD 5·2] for pregnancies with exposure to antidepressants and benzodiazepines *vs* 30·7 years [SD 4·9] for pregnancies without exposure). All study participants were female, and information about ethnicity was not available. Absolute risk of overall malformations was 3·81 per 100 pregnancies with exposure, compared with 2·87 per 100 pregnancies without exposure. The propensity score-weighted odds ratios (weighted ORs) did not suggest an increased risk for overall malformations (weighted OR 1·10, 95% CI 0·94–1·28), heart defects (1·01, 0·83–1·23), or any of the other organ-specific malformations, except for digestive system malformations, for which the weighted OR remained statistically significant after adjustment (1·63, 1·06–2·51). The absence of an increased risk for overall congenital malformations associated with concomitant use of antidepressants and benzodiazepines was supported by the analyses controlling for confounding by indication and sibling-matched comparisons.

Interpretation The findings of this study suggest that the concomitant use of antidepressants and benzodiazepines during the first trimester is not associated with a substantial increase in risk for most malformation subtypes. However, considering other potential adverse effects of using both medications concomitantly, a thorough assessment of the risks and benefits is crucial for clinical decision making.

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Introduction

Pregnancy is a period characterised by physiological and psychological changes, making pregnant people susceptible to mental disorders. The estimated global prevalence of antenatal depression is 20%, and it is often comorbid with anxiety and insomnia.[1,2] Pregnant people experiencing these mental health conditions frequently use psychotropic agents, which are among the most used medications during pregnancy.[3] Additionally, a large proportion of pregnant people use more than one type of psychotropic agent, with the most common combination being antidepressants and anxiolytic agents (primarily benzodiazepines and benzodiazepine-like medications).[4]

Both antidepressants and benzodiazepines have a biologically plausible teratogenic effect as they can readily cross the placental barrier.[5,6] Antidepressants might interfere with serotonergic signalling, while benzodiazepines modulate GABA receptors, potentially

Research in context

Evidence before this study

There is sparse evidence regarding the safety of concomitant use of antidepressants and benzodiazepines during pregnancy, despite their frequent co-administration. We searched PubMed from database inception to Oct 31, 2023, for articles published in English, using the following search terms, along with synonyms and related terms: ("antidepressant" OR "benzodiazepine") AND ("pregnancy" OR "pregnant women" OR "first trimester") AND ("congenital malformation" OR "birth defect"). We identified two studies investigating the potential associations between concomitant use of antidepressants and benzodiazepines and risks of congenital malformations. A meta-analysis based on three studies has reported a higher risk of congenital malformation with such concomitant use (odds ratio [OR] 1·40, 95% CI 1·09–1·80). Additionally, a 2022 study conducted in South Korea revealed an increased risk of heart defects (relative risk 1·26, 95% CI 1·08–1·46), with no significant rise in overall malformations. However, these findings are mainly derived from subgroup analyses within studies focused on benzodiazepines, which could result in misclassification of exposure and confounding by indication.

Added value of this study

This study is the first specifically designed to investigate the association between the concomitant use of antidepressants and benzodiazepines and the risk of congenital malformations. In this population-based cohort study in Taiwan, we adopted the propensity score fine stratification approach to address the potential confounders. The results showed the concomitant use of these medications during the first trimester was not associated with an increased risk of overall congenital malformations or with organ-specific malformations in a wide range of organs, including nervous system, respiratory system, oral cleft, urinary system, genital system, and limb malformations. In contrast to previous studies, our findings indicated that the concomitant use of these medications was not associated with a higher risk of heart defects, after excluding minor heart defects as defined by the European Surveillance of Congenital Anomalies (known as EUROCAT). However, an increased risk of digestive system defects was observed (OR 1·63, 95% CI 1·06–2·51).

Implications of all the available evidence

The concomitant use of antidepressants and benzodiazepines during pregnancy does not significantly increase the risk of overall congenital malformations, suggesting they can be used during pregnancy under careful consideration. The observed association with digestive system defects warrants further investigation.

leading to distinct effects on fetal development. Although there is existing literature on the reproductive safety of antidepressants, and to a lesser extent of benzodiazepines, many studies have primarily focused on antidepressants or benzodiazepines individually.[7–12] Therefore, despite frequent co-administration of antidepressants and benzodiazepines,[13] evidence on the reproductive safety of the concomitant use remains insufficient and inconclusive.

Although some studies have suggested an increased risk for congenital malformations associated with concomitant use of antidepressants and benzodiazepines,[11,12] methodological limitations exist. First, the ambiguity in the definition of concomitant medication use might lead to exposure misclassification and hinder a comprehensive assessment of risks.[14] Second, underlying conditions such as depression have been associated with unhealthy behaviours that adversely affect pregnancy outcomes,[15] which might therefore cause confounding by indication, and could explain the associations observed in previous studies. Moreover, previous research has mainly focused on the risk of overall congenital malformations or heart defects, leaving a gap in the understanding of the risks associated with organ-specific congenital malformations. Using data from the National Birth Certificate Application (BCA) database, the Maternal and Child Health (MCH) database, and the National Health Insurance (NHI) database in Taiwan, we conducted a nationwide cohort study to investigate the association between the concomitant use of antidepressants and benzodiazepines during the first trimester and the risk of major congenital malformations (both overall and for eight organ-specific anomalies).

See Online for appendix

Methods

Study design

In this population-based cohort study, data sources were the National BCA database from Jan 1, 2004, to Dec 31, 2018, the MCH database from Jan 1, 2004, to Dec 31, 2018, and the NHI database from Jan 1, 2002, to Dec 31, 2019 (appendix p 18). Patient identification numbers were encrypted and used for data linkage. The BCA database contains essential birth information (eg, singleton or multiple pregnancy, birth date, and gestational age at birth of newborns), maternal demographics (eg, nationality and high-risk health behaviours), and fetal outcomes (eg, birthweight and birth defects). The MCH database comprises encrypted identifiers of livebirths and their parents, allowing for the linkage of family members. The NHI database, covering approximately 99% of the Taiwanese population, provides detailed information on disease diagnoses, prescriptions, and health-care use.[16] The study was approved by the Institutional Review Board of the National Taiwan University Hospital (202101129RINC). Anonymised data were used, and individual informed consent was not required.

Participants

We included pregnant people aged 15–50 years who were linked to a live singleton birth between Jan 1, 2004, and Dec 31, 2018. Pregnant people with invalid or suspected inaccurate data were excluded. Additionally, pregnant people whose infants had a diagnosis of chromosomal abnormality, and those who were exposed to known teratogens during the first trimester, were excluded (appendix pp 2, 16). The end of pregnancy was defined as the date of delivery, and the last menstrual period was estimated by subtracting gestational age from the date of delivery (appendix p 17). Sex data were collected from the NHI database.

Procedures

The first trimester is the period most susceptible to the development of congenital malformations. Therefore, the main exposure was defined as concomitant exposure to antidepressants and benzodiazepines during the first trimester (appendix pp 3–4). Exposure was defined as having received at least one prescription for antidepressants or benzodiazepines during the first trimester, and the concomitant use of antidepressants and benzodiazepines was defined as any overlap in days of supply for these two drug classes. Additionally, types of antidepressants and benzodiazepines used among the concomitant users were assessed, stratified by the classes and the risk levels defined by the US Food and Drug Administration (FDA) pregnancy categories. To minimise misclassification, the unexposed group consisted of pregnant people with no prescription for antidepressants or benzodiazepines from 30 days before the date of the estimated last menstrual period to the end of the first trimester.

Outcomes

The primary outcomes were overall major congenital malformations and heart defects, defined by the ICD-9 and ICD-10, documented in either the maternal or infant medical records during the first 90 days after delivery (appendix p 5). Major congenital malformations were further categorised into eight organ-specific anomalies as secondary outcomes, following the European Surveillance of Congenital Anomalies (EUROCAT) classification: nervous system, heart, respiratory system, oral cleft, digestive system, urinary system, genital system, and limb malformations. Heart defects were classified into three subtypes: left ventricular outflow tract obstruction, right ventricular outflow tract obstruction, and septal defect. Anomalies related to prematurity, such as patent ductus arteriosus and atrial septal defect, were excluded in preterm infants.

Statistical analysis

We considered a broad range of covariates as potential confounders or proxies for potential confounders, namely maternal demographics (eg, maternal age and nationality, sex of the infant, and infant's year of birth), psychiatric conditions (ie, depression, anxiety, bipolar disorder, insomnia, and schizophrenia), comorbidities (ie, epilepsy, hyperlipidaemia, hypertension, hyperthyroidism, and diabetes), lifestyle factors, co-medications, and obstetric comorbidity index.[17] Health-care use and proxies for severity of mental health conditions (measured by number of emergency room visits and admissions associated with psychiatric disorders) were also captured (appendix p 6).

Baseline characteristics of pregnant people with and without exposure to antidepressants and benzodiazepines were compared using standardised differences, and a standardised difference greater than 0·1 was considered a meaningful difference.[18] The absolute risks of congenital malformations were calculated, and logistic regression analysis was used to estimate odds ratios (ORs) with 95% CIs. To reduce the residual bias at low exposure levels, the propensity score fine stratification weighting (PS-FSW) approach was applied to control for potential confounders and estimate the average treatment effect among the exposed people. The propensity score for exposure was derived using a multivariable logistic regression model that included all covariates without further selection. After trimming observations from non-overlapping regions of the propensity score distribution, we created 150 equally sized strata based on the distribution among the exposed group. The weights for the exposed group were set to 1, and the unexposed pregnancies were weighted based on the distribution of exposed pregnancies for each stratum (appendix p 19). CIs that did not cross 1·0 were considered statistically significant. All statistical analyses were performed using SAS (version 9.4).

Two study designs were adopted to address confounding by indication. First, the study cohort was restricted to individuals with a diagnosis of depression to mitigate confounding by indication. Second, individuals with previous concomitant use of antidepressants and benzodiazepines before pregnancy were targeted, and continuers (those who continued using both medications) were compared with discontinuers (those who discontinued both medications). This careful selection ensured a more comparable and homogeneous comparison group, minimising variations in unmeasured covariates.

To account for shared genetic and environmental factors, we performed a sibling-matched analysis, which assessed the risk of congenital malformations in offspring of the same mothers but with discordant exposure. Only sibling pairs discordant for both exposures and outcomes contributed to the estimated within-pair association, controlling for the time-fixed unmeasured confounders shared by siblings.

Several subgroup and sensitivity analyses were done for all outcomes to assess the robustness of the primary findings. First, to evaluate the effect of concomitant duration of antidepressants and benzodiazepines, we

	Before PS-FSW			After PS-FSW		
	Exposed pregnancy (n=8599)	Unexposed pregnancy (n=2 625 422)	Standardised difference	Exposed pregnancy (n=8580)	Unexposed pregnancy (n=2 610 580)	Standardised difference
Maternal age at delivery	31·8 (5·2)	30·7 (4·9)	0·228	31·8 (5·2)	31·5 (5·3)	0·067
Infant sex						
Male	4495 (52·3%)	1 366 662 (52·1%)	0·004	4481 (52·2%)	1 366 902 (52·4%)	–0·003
Female	4104 (47·7%)	1 258 760 (48·0%)	–0·004	4099 (47·8%)	1 243 678 (47·6%)	0·003
Nationality						
Taiwanese	8426 (98·0%)	2 486 449 (94·7%)	0·176	8407 (98·0%)	2 556 276 (97·9%)	0·005
Other	173 (2·0%)	138 973 (5·3%)	–0·176	173 (2·0%)	54 304 (2·1%)	–0·005
Year of delivery						
2004–08	2087 (24·3%)	879 820 (33·5%)	–0·205	2083 (24·3%)	679 004 (26·0%)	–0·040
2009–13	2610 (30·4%)	843 108 (32·1%)	–0·038	2604 (30·4%)	814 663 (31·2%)	–0·019
2014–18	3902 (45·4%)	902 494 (34·4%)	0·226	3893 (45·4%)	1 116 913 (42·8%)	0·052
Lifestyle factors						
Alcohol use	157 (1·8%)	691 (<0·1%)	0·189	155 (1·8%)	41 889 (1·6%)	0·016
Drug misuse	154 (1·8%)	322 (<0·1%)	0·189	142 (1·7%)	30 920 (1·2%)	0·040
Obesity	25 (0·3%)	2340 (0·1%)	0·046	25 (0·3%)	6619 (0·3%)	0·007
Tobacco use	153 (1·8%)	3956 (0·2%)	0·167	150 (1·8%)	46 334 (1·8%)	–0·002
Maternal conditions						
Anxiety	3618 (42·1%)	15 701 (0·6%)	1·174	3599 (42·0%)	1 194 740 (45·8%)	–0·077
Bipolar disorder	623 (7·2%)	1033 (<0·1%)	0·392	604 (7·0%)	193 974 (7·4%)	–0·015
Depression	5194 (60·4%)	7496 (0·3%)	1·728	5175 (60·3%)	1 490 936 (57·1%)	0·065
Diabetes	101 (1·2%)	9313 (0·4%)	0·094	101 (1·2%)	29 795 (1·1%)	0·003
Epilepsy	79 (0·9%)	2451 (0·1%)	0·117	78 (0·9%)	20 109 (0·8%)	0·015
Insomnia	3025 (35·2%)	17 559 (0·7%)	1·007	3006 (35·0%)	955 380 (36·6%)	–0·033
Hyperlipidaemia	110 (1·3%)	10 313 (0·4%)	0·097	110 (1·3%)	33 890 (1·3%)	–0·001
Hypertension	161 (1·9%)	10 559 (0·4%)	0·139	160 (1·9%)	51 862 (2·0%)	–0·009
Hyperthyroid	142 (1·7%)	21 799 (0·8%)	0·074	142 (1·7%)	49 257 (1·9%)	–0·018
Schizophrenia	215 (2·5%)	772 (<0·1%)	0·222	209 (2·4%)	72 312 (2·8%)	–0·021
Medication use						
Anticonvulsants	1211 (14·1%)	41 310 (1·6%)	0·479	1194 (13·9%)	342 513 (13·1%)	0·023
Antipsychotics	4506 (52·4%)	398 349 (15·2%)	0·856	4487 (52·3%)	1 345 103 (51·5%)	0·015
Opioid analgesics	2465 (28·7%)	457 780 (17·4%)	0·269	2451 (28·6%)	711 419 (27·3%)	0·029
Suspected teratogens	1009 (11·7%)	79 659 (3·0%)	0·337	1000 (11·7%)	279 627 (10·7%)	0·030
Z-hypnotics	4206 (48·9%)	32 658 (1·2%)	1·317	4187 (48·8%)	1 386 094 (53·1%)	–0·086
Other anxiolytics	1769 (20·6%)	167 144 (6·4%)	0·425	1757 (20·5%)	522 277 (20·0%)	0·012
Obstetric comorbidity index						
1	2286 (26·6%)	498 114 (19·0%)	0·182	2282 (26·6%)	657 450 (25·2%)	0·032
2	647 (7·5%)	92 803 (3·5%)	0·175	642 (7·5%)	190 581 (7·3%)	0·007
≥3	176 (2·0%)	14 045 (0·5%)	0·134	176 (2·1%)	58 239 (2·2%)	–0·012
Health-care use						
Number of outpatient visits						
1–2	443 (5·2%)	626 804 (23·9%)	–0·551	443 (5·2%)	122 329 (4·7%)	0·022
3–4	634 (7·4%)	513 520 (19·6%)	–0·363	634 (7·4%)	199 170 (7·6%)	–0·009
>4	7396 (86·0%)	1 101 346 (42·0%)	1·033	7377 (86·0%)	2 269 691 (86·9%)	–0·028
Number of emergency room visits						
1	671 (7·8%)	108 676 (4·1%)	0·155	1657 (19·3%)	515 245 (19·7%)	–0·011
>1	196 (2·3%)	13 358 (0·5%)	0·151	1219 (14·2%)	360 113 (13·8%)	0·012
Number of inpatient visits						
1	1659 (19·3%)	236 115 (9·0%)	0·299	664 (7·7%)	194 484 (7·5%)	0·011
>1	1234 (14·4%)	51 580 (2·0%)	0·465	195 (2·3%)	51 795 (2·0%)	0·020

(Table continues on next page)

	Before PS-FSW			After PS-FSW		
	Exposed pregnancy (n=8599)	Unexposed pregnancy (n=2 625 422)	Standardised difference	Exposed pregnancy (n=8580)	Unexposed pregnancy (n=2 610 580)	Standardised difference
(Continued from previous page)						
History of emergency room visits related to psychiatric disorders	289 (3·4%)	884 (<0·1%)	0·260	282 (3·3%)	69 602 (2·7%)	0·037
History of inpatient visits related to psychiatric disorders	108 (1·3%)	138 (<0·1%)	0·158	108 (1·3%)	25 513 (1·0%)	0·027

Data are mean (SD) or n (%) unless otherwise specified. Exposed pregnancy refers to concomitant use of antidepressants and benzodiazepines. Unexposed pregnancy refers to no use of antidepressants or benzodiazepines. PS-FSW=propensity score fine stratification weighting.

Table: **Baseline characteristics before and after PS-FSW**

stratified the concomitant duration into short-term (<30 days) and long-term (≥30 days) exposure. Second, to minimise exposure misclassification, we redefined the exposure as having at least two prescriptions for both antidepressants and benzodiazepines during the first trimester. Third, we used two analyses to address potential outcome misclassification, including redefining congenital malformations based solely on inpatient diagnoses and extending the follow-up period to 1 year after delivery. Fourth, we assessed the association between congenital malformations, maternal diabetes, and the use of valproic acid as a positive control study.[19,20] Fifth, we included an analysis restricted to individuals with alcohol disorder to address the potential confounding effects of alcohol consumption (appendix p 20). Finally, we performed a quantitative bias analysis to account for the effect of potential selection bias (appendix pp 21–23).

In the confirmatory analyses, we individually evaluated the association between the use of antidepressants or benzodiazepines during the first trimester and the risk of congenital malformations. This approach strengthened the validity and reliability of the analyses regarding the concomitant use of these medications during this period. Additionally, given the clinical perception of benzodiazepines and Z-hypnotics as similar, we conducted analyses incorporating benzodiazepines and Z-hypnotics simultaneously (appendix pp 24–26).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

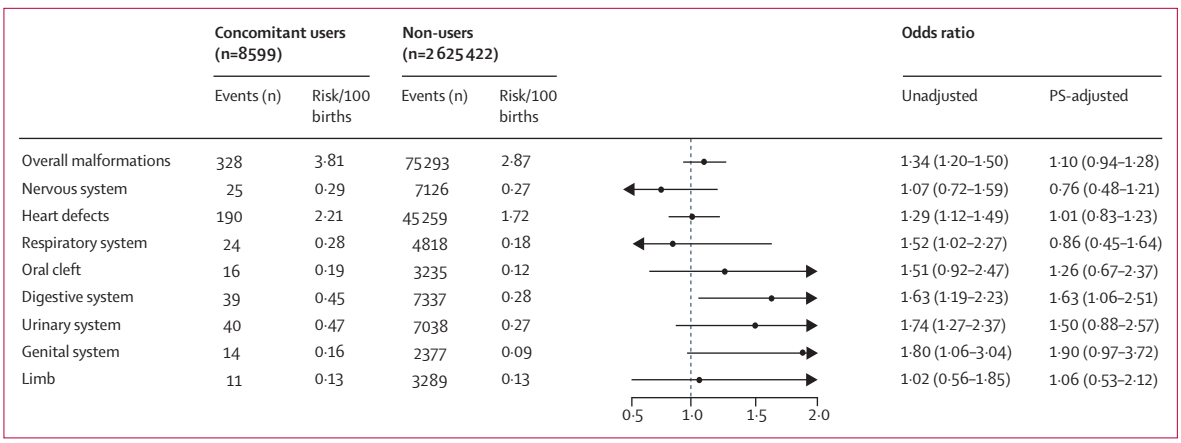
Results

Between Jan 1, 2004, and Dec 31, 2018, 2 634 021 singleton pregnancies occurred, of which 8599 (0·3%) were attributed to concomitant users of antidepressants and benzodiazepines during the first trimester (appendix p 16). Substantial baseline differences were observed between pregnant individuals with concomitant use and pregnant individuals without exposure (table). Individuals with concomitant use were older (mean age at delivery 31·8 years, SD 5·2) and more likely to have mental disorders, other medical conditions, and unhealthy lifestyle behaviours than pregnant individuals without exposure. After PS-FSW, all measured characteristics were well balanced between pregnant people with and without exposure, with standardised differences less than 0·1.

The absolute risk of overall malformations was 3·81 per 100 pregnancies in the individuals with concomitant use, compared with 2·87 per 100 pregnancies in individuals without exposure (figure 1). Compared with individuals without exposure, the unadjusted risk estimates were higher for individuals with exposure for overall malformations, heart defects, respiratory system defects, digestive system defects, urinary system defects, and genital system defects. After adjusting for all measured covariates using PS-FSW, the risk estimates shifted substantially towards the null. The propensity score-weighted odds ratios (weighted ORs) did not suggest an increased risk for overall malformations (weighted OR 1·10, 95% CI 0·94–1·28), heart defects (1·01, 0·83–1·23), and most of the other organ-specific malformations. However, the risk estimates for digestive system defects remained significantly increased after adjustment (1·63, 1·06–2·51). No evidence of increased risk was found for specific subtypes of heart defects (appendix p 8).

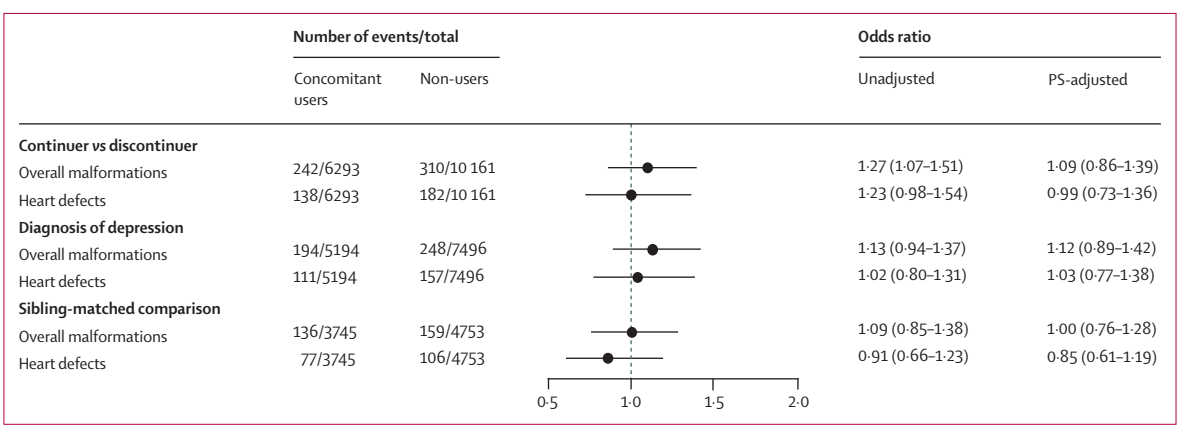
The absence of an increased risk for congenital malformations associated with concomitant use of antidepressants and benzodiazepines was further supported by the analyses controlling for confounding by indication (figure 2). In sibling-matched comparisons accounting for genetic factors, the risk did not differ substantially between siblings with and without exposure in the crude analyses or after adjustment for overall malformations (adjusted OR 1·00, 95% CI 0·76–1·28) and heart defects (0·85, 0·61–1·19).

Subgroup analysis revealed that both long-term (≥30 days) and short-term (<30 days) concomitant use of antidepressants and benzodiazepines did not increase the risk of overall malformations or heart defects (figure 3), although the point estimate for long-term concomitant users (weighted OR 1·18, 95% CI 0·92–1·50) was slightly higher than that for short-term concomitant users (1·05, 0·89–1·24).



	Concomitant users (n=8599)		Non-users (n=2 625 422)		Odds ratio	
	Events (n)	Risk/100 births	Events (n)	Risk/100 births	Unadjusted	PS-adjusted
Overall malformations	328	3·81	75 293	2·87	1·34 (1·20–1·50)	1·10 (0·94–1·28)
Nervous system	25	0·29	7126	0·27	1·07 (0·72–1·59)	0·76 (0·48–1·21)
Heart defects	190	2·21	45 259	1·72	1·29 (1·12–1·49)	1·01 (0·83–1·23)
Respiratory system	24	0·28	4818	0·18	1·52 (1·02–2·27)	0·86 (0·45–1·64)
Oral cleft	16	0·19	3235	0·12	1·51 (0·92–2·47)	1·26 (0·67–2·37)
Digestive system	39	0·45	7337	0·28	1·63 (1·19–2·23)	1·63 (1·06–2·51)
Urinary system	40	0·47	7038	0·27	1·74 (1·27–2·37)	1·50 (0·88–2·57)
Genital system	14	0·16	2377	0·09	1·80 (1·06–3·04)	1·90 (0·97–3·72)
Limb	11	0·13	3289	0·13	1·02 (0·56–1·85)	1·06 (0·53–2·12)

Figure 1: **Association between concomitant use of antidepressants and benzodiazepines and the risk of congenital malformations in offspring**
PS=propensity score.



	Number of events/total		Odds ratio	
	Concomitant users	Non-users	Unadjusted	PS-adjusted
Continuer *vs* discontinuer				
Overall malformations	242/6293	310/10 161	1·27 (1·07–1·51)	1·09 (0·86–1·39)
Heart defects	138/6293	182/10 161	1·23 (0·98–1·54)	0·99 (0·73–1·36)
Diagnosis of depression				
Overall malformations	194/5194	248/7496	1·13 (0·94–1·37)	1·12 (0·89–1·42)
Heart defects	111/5194	157/7496	1·02 (0·80–1·31)	1·03 (0·77–1·38)
Sibling-matched comparison				
Overall malformations	136/3745	159/4753	1·09 (0·85–1·38)	1·00 (0·76–1·28)
Heart defects	77/3745	106/4753	0·91 (0·66–1·23)	0·85 (0·61–1·19)

Figure 2: **Analyses to assess confounding by indication and sibling-matched comparison**
Continuers were individuals with previous concomitant use of antidepressants and benzodiazepines before pregnancy who continued using both medications: discontinuers were individuals who discontinued both medications.

Sensitivity analyses to address the potential for misclassification remained consistent with the main analyses. In addition, we replicated the association between malformations and maternal diabetes or maternal use of valproic acid in the positive control studies. Selection bias due to restriction to livebirths was thoroughly examined, and the risk estimates for malformations of interest remained consistently below 1·3, even under the strongest assumption (appendix p 21).

The risk of congenital malformations was evaluated individually for antidepressants and benzodiazepines (figure 4; appendix pp 9–15). In the analysis regarding antidepressants, the study cohort comprised 2 708 312 pregnancies, among which 14 463 (0·5%) pregnant individuals took antidepressants during the first trimester. Maternal use of antidepressants was not linked to an increased risk for overall malformations (weighted OR 1·03, 95% CI 0·92–1·15) or heart defects (0·98, 0·85–1·14). Similarly, the benzodiazepine-specific analysis included 2 683 005 pregnancies, of which 50 272 (1·9%) pregnant individuals took benzodiazepines during the first trimester. No evidence of elevated risk for overall malformations (weighted OR 1·03, 95% CI 0·98–1·09) or heart defects (1·03, 0·96–1·11) was found for maternal use of benzodiazepines.

Discussion

In this nationwide cohort study of 2·6 million pregnancies, we found that the concomitant use of antidepressants and benzodiazepines during the first trimester was not associated with an increased risk of overall malformations or heart defects after accounting for maternal pregnancy covariates, confounding by indication, and genetic and environmental factors. To the best of our knowledge, this study is the first to use sibling comparison studies, positive control analyses, and quantitative bias analysis to examine the association between the concomitant use of antidepressants and benzodiazepines during the first trimester and neonatal malformations. All findings in the sensitivity analyses were consistent with the primary findings, and the confirmatory analyses further indicated that exposure

	Number of events/total		Odds ratio	
	Concomitant users	Non-users	Unadjusted	PS-adjusted
Overall malformations				
Main analysis	328/8599	75293/2625422	1·34 (1·20–1·50)	1·10 (0·94–1·28)
Subgroup analysis				
Concomitant use duration				
Less than 30 days	214/5952	75293/2625422	1·26 (1·10–1·45)	1·05 (0·89–1·24)
Greater than 30 days	114/2647	75293/2625422	1·52 (1·26–1·84)	1·18 (0·92–1·50)
Sensitivity analysis				
≥2 prescriptions dispensed	139/3413	75293/2625422	1·44 (1·21–1·70)	1·16 (0·93–1·45)
Inpatient diagnosis	171/8599	40065/2625422	1·31 (1·12–1·52)	1·11 (0·89–1·37)
1-year follow-up	545/8599	137654/2625422	1·22 (1·12–1·33)	1·08 (0·96–1·22)
Positive control (diabetes)	911/10016	77340/2704109	3·40 (3·17–3·64)	2·57 (2·36–2·81)
Positive control (VPA use)	70/1019	78181/2713106	2·49 (1·95–3·17)	1·54 (1·06–2·25)
Heart defects				
Main analysis	190/8599	45259/2625422	1·29 (1·12–1·49)	1·01 (0·83–1·23)
Subgroup analysis				
Concomitant use duration				
Less than 30 days	124/5952	45259/2625422	1·21 (1·02–1·45)	0·98 (0·79–1·21)
Greater than 30 days	66/2647	45259/2625422	1·46 (1·14–1·86)	1·03 (0·75–1·43)
Sensitivity analysis				
≥2 prescriptions dispensed	82/3413	45259/2625422	1·40 (1·13–1·75)	1·04 (0·78–1·40)
Inpatient diagnosis	95/8599	23355/2625422	1·24 (1·02–1·52)	0·97 (0·73–1·28)
1-year follow-up	324/8599	87845/2625422	1·13 (1·01–1·26)	1·01 (0·88–1·17)
Positive control (diabetes)	658/10016	46382/2704109	4·03 (3·72–4·36)	3·14 (2·84–3·48)
Positive control (VPA use)	40/1019	47000/2713106	2·32 (1·69–3·18)	1·38 (0·86–2·23)

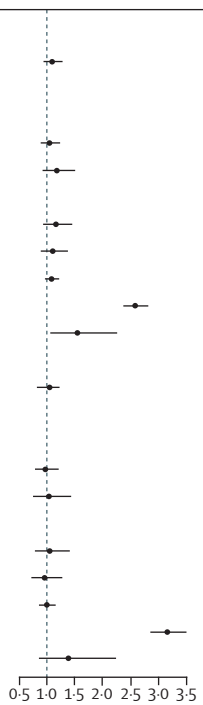


Figure 3: **Subgroup analyses and sensitivity analyses**
PS=propensity score. VPA=valproic acid.

	Exposed		Unexposed		Odds ratio	
	Events (n)	Risk/100 births	Events (n)	Risk/100 births	Unadjusted	PS-adjusted
Antidepressants	**n=14463**		**n=2693849**			
Overall malformations	522	3·61	77537	2·88	1·26 (1·16–1·38)	1·03 (0·92–1·15)
Nervous system	51	0·35	7325	0·27	1·30 (0·98–1·17)	1·00 (0·72–1·40)
Heart defects	300	2·07	46615	1·73	1·20 (1·07–1·35)	0·98 (0·85–1·14)
Respiratory system	40	0·28	4974	0·18	1·50 (1·10–2·05)	0·93 (0·61–1·42)
Oral cleft	22	0·15	3321	0·12	1·23 (0·81–1·88)	0·96 (0·56–1·64)
Digestive system	62	0·43	7594	0·28	1·52 (1·19–1·96)	1·12 (0·81–1·56)
Urinary system	53	0·37	7229	0·27	1·37 (1·04–1·79)	1·21 (0·84–1·73)
Genital system	20	0·14	2450	0·09	1·52 (0·98–2·36)	1·22 (0·71–2·09)
Limb	18	0·12	3379	0·13	0·99 (0·62–1·58)	0·97 (0·57–1·65)
Benzodiazepines	**n=50272**		**n=2632733**			
Overall malformations	1704	3·39	75526	2·87	1·19 (1·13–1·25)	1·03 (0·98–1·09)
Nervous system	154	0·31	7154	0·27	1·13 (0·96–1·32)	0·88 (0·74–1·04)
Heart defects	1032	2·05	45397	1·72	1·19 (1·12–1·27)	1·03 (0·96–1·11)
Respiratory system	129	0·26	4836	0·18	1·40 (1·17–1·67)	1·04 (0·84–1·29)
Oral cleft	77	0·15	3242	0·12	1·24 (0·99–1·56)	1·17 (0·91–1·49)
Digestive system	184	0·37	7361	0·28	1·31 (1·13–1·52)	1·18 (1·01–1·38)
Urinary system	146	0·29	7053	0·27	1·08 (0·92–1·28)	1·06 (0·88–1·27)
Genital system	56	0·11	2385	0·09	1·23 (0·94–1·60)	1·13 (0·84–1·52)
Limb	64	0·13	3300	0·13	1·02 (0·79–1·30)	0·93 (0·70–1·24)

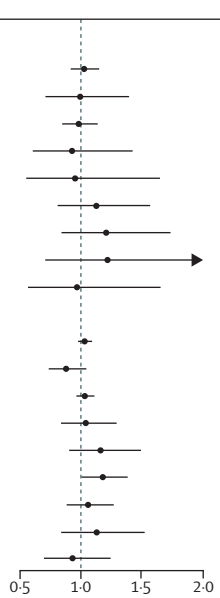


Figure 4: **Confirmatory analyses**
PS=propensity score.

to antidepressants or benzodiazepines only during pregnancy was not associated with increased risk of overall malformations and heart defects.

Compared with existing studies, this study is the largest study, consisting of 8599 pregnant people concomitantly using antidepressants and benzodiazepines during the first trimester as compared with 359 pregnant women in a Canadian study,[21] 1932 in a Swedish study,[22] and 5461 in a South Korean study.[12] We used Taiwan's nationwide database, which covers 99% of the population and allows for thorough longitudinal tracking. In addition, our study was specifically designed to address risks of congenital malformations associated with concomitant use of these medications, enabling a more precise definition of concomitant medication use. In contrast to previous studies reporting an increased risk of congenital malformations associated with maternal use of antidepressants and benzodiazepines,[11,12] our analyses did not report such a risk after addressing potential confounding by indication and genetic and environmental factors.

A cohort study conducted in South Korea[12] found that maternal use of benzodiazepines in combination with antidepressants was associated with an increased risk for heart defects (adjusted relative risk 1·26, 95% CI 1·08–1·46), but not for overall malformations (1·04, 0·93–1·18) in their subgroup analysis. Within the same study, an increased risk associated with maternal benzodiazepine use was observed only in specific heart defect types, such as cardiac septal defect and defects of the great arteries. These findings suggest that the increased risk might be specific to heart defects associated with prematurity. As maternal benzodiazepine use was reported to be associated with a potential increased risk of preterm birth in previous studies,[23,24] the inclusion of anomalies that are not genuinely congenital in origin (eg, patent ductus arteriosus and patent foramen ovale) could lead to an overestimate of the risk associated with benzodiazepine use.[25,26] Therefore, in our analyses, we deliberately excluded such congenital malformations that are likely to spontaneously resolve after birth in premature infants. This approach could explain the discrepancies between our study and previous research findings.

Additionally, this study assessed the risks of organ-specific congenital malformations associated with the concomitant use of benzodiazepines and antidepressants during the first trimester. Previous studies have not adequately addressed the risks of concomitant use of antidepressants and benzodiazepines during pregnancy, as they have only treated such concomitant use as subgroup analyses, with low sample sizes hindering their ability to report risks of organ-specific congenital malformations. The increased risk for digestive system defects (weighted OR 1·63, 95% CI 1·06–2·51) associated with concomitant use of benzodiazepines and antidepressants in this study therefore warrants further investigation. Notably, previous analyses of individual medications have reported a link between maternal benzodiazepine use and digestive system defects.[22,27] Regarding antidepressants, a Quebec Pregnancy Cohort study of 18 487 pregnant women found an increased risk of digestive system defects (adjusted OR 2·55, 95% CI 1·40–4·66) associated with tetracyclic antidepressant use.[9]

According to previous FDA pregnancy categories, which range from A (lowest risk) to X (highest risk), most benzodiazepines are listed as category D, with a few categorised as category X (such as estazolam). Antidepressants are primarily category C, with some categorised as category D (such as paroxetine) or B (such as maprotiline). Therefore, in analyses examining the distribution of different types of antidepressants and benzodiazepines among the concomitant users, we specifically targeted medications within higher-risk categories (appendix p 7). Our findings suggested an increased risk when the benzodiazepine taken as part of a combination was classified as category X. This finding highlights that, despite the FDA discontinuing the use of pregnancy risk categories, the use of medications classified as higher risk might still require careful evaluation for pregnant people.

The absolute risk observed in our study was 3·81 per 100 pregnancies in concomitant users and 2·87 per 100 pregnancies in those not exposed to antidepressants or benzodiazepines. The prevalence of birth defects in Taiwan has previously been reported as 2·72 per 100 pregnancies,[9] which is similar to that identified in this study. However, the crude associations found here were weaker compared with findings from earlier studies based on point estimates,[11,12] indicating misclassification of the potential concern of exposure and outcome in this study. We addressed these concerns through multiple sensitivity analyses that redefined the exposures and outcomes, such as extending the follow-up period to 1 year after delivery. The association between congenital malformations and firmly established risk factors (such as diabetes, and maternal use of valproic acid)[20,28] was reaffirmed in the positive analyses, strengthening the validity of the outcomes captured in this study.

The confirmatory analyses also provide additional data regarding the risk of congenital malformations associated with exposure to antidepressants or benzodiazepines. In our analysis of 14 463 pregnant women exposed to antidepressants during the first trimester, such use was not linked to an increased risk for overall malformations (weighted OR 1·03, 95% CI 0·92–1·15) or heart defects (0·98, 0·85–1·14), after considering the underlying conditions. This finding aligns with a previous study,[10] which suggested that the elevated association between antidepressant use and specific heart defects was largely attenuated by comparing the population with women who were exposed to antidepressants only outside of early pregnancy. Similar findings were reported for maternal

use of benzodiazepines and risk of congenital malformation among 50 272 pregnant people who were exposed to benzodiazepines during the first trimester in this study. Our findings were also consistent with a previous systematic review,[11] which found that benzodiazepine exposure during pregnancy is not associated with congenital malformations or with cardiac malformations specifically.

Certain limitations inherent in the study design need to be acknowledged. First, misclassification of exposure is a potential concern, as filling a prescription does not guarantee the medication was actually used. However, the sensitivity analysis requiring pregnant people to have filled at least two prescriptions during the first trimester did not affect findings. Second, the cohort was limited to livebirths, which might introduce selection bias if the probability of livebirth varies between concomitant users and non-users. Since severe malformations that result in termination of the pregnancy would not be captured, the strength of the association might be underestimated. Therefore, we conducted a quantitative bias analysis to assess the potential for selection bias, which suggested that even under the most extreme assumption the effect of such bias on estimates was expected to be minimal. Third, residual confounding cannot be completely ruled out, despite the adjustment for a broad range of covariates. Nonetheless, the likelihood of confounding resulting in a downward bias associated with concomitant use of these agents is minimal, and it is improbable that confounding could explain the null findings in our analyses. Fourth, our study is constrained by sample size, which prevents a detailed analysis of specific combinations of medications. Given the potential for distinct interactions between individual drugs, future research should explore the risks associated with specific medications. Finally, our study did not include individuals with lived experience in shaping the research question, study design, or choosing outcome measures.

Considering that maternal depression and anxiety are associated with adverse neonatal outcomes, the decision-making process for treatment becomes intricate for both clinicians and patients. Our findings suggest that if treatment is necessary, the use of antidepressants, benzodiazepines, or the concomitant use of both might be an option. However, the effects of medication use might extend beyond congenital malformations to other risks, such as preterm birth, respiratory distress at birth, and developmental disorders during growth. These potential adverse effects have not been thoroughly explored in the context of concomitant use, underscoring the necessity for a comprehensive assessment of individual risks and benefits before proceeding with the concomitant use of benzodiazepines and antidepressants during pregnancy.

This study provides insights for future drug safety communications regarding the concomitant use of antidepressants and benzodiazepines during pregnancy. The findings suggest that the concomitant use of antidepressants and benzodiazepines during the first trimester is not associated with a substantial increase in risk of most malformation subtypes. However, as there might be other potential adverse effects to using both medications concomitantly, a thorough assessment of the risks and benefits is crucial for clinical decision making.

Contributors

All authors contributed to clinical interpretation, drafted the Article, revised it critically for important intellectual content, and approved the final version for publication. H-MC, L-CM, C-WL, and F-YH designed the research. H-MC, L-CM, C-WL, W-WC, Y-YC, C-YS, L-KC, and F-YH drafted and prepared the manuscript. H-MC and F-YH accessed, verified, and analysed the data. H-MC, L-CM, C-WL, and F-YH provided methodological and statistical input. All authors had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

Data sharing

The birth certificate application and population health insurance data used in this study were provided by the Taiwan National Health Insurance Administration and the Health and Welfare Data Science Center. Data with potential identifying information were encrypted, and restricted access is provided exclusively to investigators who obtain approval from the Taiwan National Health Insurance Administration and the Health and Welfare Data Science Center.

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