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# Maternal risk factors associated with offspring biliary atresia: population-based study

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**BACKGROUND:** Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of the intra and extrahepatic biliary tree. If untreated, it results in severe liver injury and death. The etiology and pathogenesis of BA remain unclear. Few studies have investigated the association between maternal illness/drug use and the occurrence of BA in offspring.
**METHODS:** We used the data from the Birth Certificate Application of Taiwan and linked to National Health Insurance Research Database and Taiwan Maternal and Child Health Database for the years 2004 to 2017 ($N = 1,647,231$) on 2022/03, and identified BA cases according to diagnosis and procedure code. A total of 285 BA cases were identified.
**RESULTS:** Mothers with type 2 diabetes mellitus and non-dependent drug abuse had higher rates having BA children than non-BA children, with an odds ratio of 2.17 (95% confidence interval [CI] = 1.04–4.53) and OR: 3.02 (95% CI = 1.34–6.78), respectively.
**CONCLUSION:** These results support the notion that BA occurrence is related to maternal reasons. Further studies should be designed to identify additional maternal and pregnancy risk factors and to understand the underlying pathophysiology.

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**IMPACT:**

1. The occurrence of offspring biliary atresia may be related to maternal illness/drug use.
2. Maternal drug abuse and type 2 diabetes mellitus pose a high risk for offspring biliary atresia.
3. If maternal etiology is found, biliary atresia might be a preventable disease.

## INTRODUCTION

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of the intra and extrahepatic biliary tree[1]. Ten to twenty percent of the BA patients show associated heart and/or gastrointestinal defects[2]. Although the overall incidence is low (approximately 1 in 10,000 to 20,000 live births)[3–5], BA is a very serious condition; if left untreated, it results in severe liver injury and death in all cases. Despite the successful introduction of portoenterostomy (Kasai procedure), approximately half of adolescent survivors with normal biochemical parameters show histological cirrhosis[6] and potential for decompensation, portal hypertension, and even malignancy[7]. At present, BA is the most common cause of liver transplantation in children;[8] however, successfully treated patients are required to remain pharmacologically immunosuppressed, which increases the risk of infection and malignancy in the form of post-transplant lymphoproliferative disorders[9].

Previously, many studies have focused on various aspects to improve the outcomes with BA such as early diagnosis, surgery, prevention of irreversible liver damage, and liver transplantation. It is also important to focus on elucidating the etiology of this devastating disease and prevent its occurrence[10]. Although several mechanisms have been implicated, including the alteration of the ductal plate during the first trimester of fetal life[11], viral infections[12,13], immune-related mechanisms[14], and changes in the vascular system[15], the etiology and pathogenesis of BA remain unclear.

BA can be classified as congenital or acquired. Congenital BA has been thought to emerge during the first trimester of pregnancy where the bile duct development and BA laterality defects are observed. Although acquired BA appears to begin post-birth, observations such as elevated direct bilirubin levels at birth, biliary abnormalities during fetal ultrasound, and abnormal gamma-glutamyl transferase levels in the amniotic fluid suggest that the acquired BA also initiates before birth[16]. Hence, most, if not all, forms of BA may originate before birth making it a disease beginning in utero. Furthermore, if maternal etiology is involved, BA might be a preventable disease[10]. In this study, we used the Taiwan National Health Databases to investigate the link of

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maternal risk factors such as illness and drug use to BA occurrence.

## METHODS

### Data source

The healthcare system in Taiwan, known as the National Health Insurance (NHI) implemented in 1995, is a compulsory social insurance program. This system is extremely accessible and covers over 99% of the total population. The National Health Insurance Research Database (NHIRD), derived from the NHI and the records of public health research, contains administrative and health claim data that can be analyzed. First of all, we used the data from the Taiwan Maternal and Child Health Database (MCHD, 2004–2017), a nationwide population-based data set established, updated, and supervised by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan[17]. Information from the database was validated with a high level of completeness for most of its components[18,19]. By using the identification numbers of children and their parents in MCHD, we linked several registration data sets, including the birth certificate application, multiple causes of death, and medical claims of NHIRD through encrypted personal identification numbers. Next, we used the Registry of Catastrophic Illness Patients Database (RCIPD) to search for the patients diagnosed with BA. The RCIPD enrolls every patient affected by catastrophic illness confirmed through laboratory, imaging, pathology, and clinical diagnosis by NHI administration experts. The data set comprises the medical records and information of patients, such as sex, age, date of birth, medical care facilities utilized, date of outpatient clinical visit or admission, management, procedures and treatment, identification number of transfer, and the major diagnosis according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, before 2016) codes or Tenth revision (ICD-10-CM, from 2016) codes. This study was approved by the Institutional Review Board of Kaohsiung Chang-Gung Memorial Hospital (IRB Permit No 202001508B0), Taiwan.

### Sampled patients

First, 1,815,692 live births from 1,282,863 women with Taiwanese citizenship were retrieved from the Birth Certificate Application of Taiwan from 2009 to 2017. 5,582 women were excluded since they could not be linked to the NHIRD. We then had 1,809,625 live births from 1,277,281 women. After excluding cases of multiple births ($N = 59,760$) and those where birth records were not linked to MCHD ($N = 102,634$), the study cohort included 1,647,231 live births from 1,201,775 women. We chose the patients as BA patients if the patients had the diagnosis of BA (ICD-9-CM code 751.61, ICD-10 CM Q 44.2) as per the RCIPD, or had the diagnosis of BA and ever receiving Kasai portoenterostomy (51.37) or liver transplantation (50.5) or had the diagnosis of BA but never receiving Kasai portoenterostomy or liver transplantation but expired before two years-old though not identifying catastrophic illness ($N = 285$). Those who ever had the diagnosis of BA without receiving Kasai portoenterostomy or liver transplantation but survived more than two years-old ($N = 340$) or had ever received liver transplantation without the diagnosis of BA ($N = 32$) were excluded to clean the non-BA data. In total, the number of non-BA cases were 1,646,574.

To improve data accuracy, we selected that maternal illness was diagnosed at least once during hospitalization or two times in the outpatient department in the year before giving birth (Supplemental Table 1). For maternal medication-related selection, antidepressants (N06A_ATD), olytics (N05B_ANX), and Z-drug (sleeping pills for insomnia) (N05CF_Zdrug) needed to be prescribed at least four times in the outpatient department in the year before giving birth. BA case having a diagnosis of 745-47 or 759.3 excluding 747.0 (ICD-9) or Q20-28 or Q89.3 excluding Q25.0 (ICD-10) was considered having a major congenital malformation of the heart or vessels and regarded as congenital BA in this study.

### Statistical analysis

The annual incidence rates of BA for each calendar year from 2009 to 2017 were calculated. Demographic and clinical characteristics were given as numbers and percentages, and numbers less than or equal to 3 were not presented according to the policy of Health and Welfare Data Science Center. Each item was assessed with Pearson's chi-squared test or Fisher's exact test. We used multivariable logistic regression model to investigate the risk factors associated with BA. In our study, women could contribute multiple deliveries, so generalized estimating equation with exchangeable correlation structure was used to evaluate the effects of model parameters. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC). Statistical significance was set at $P < 0.05$ as 2-tailed tests were considered statistically significant.

## RESULTS

In total, 285 and 1,646,574 patients were identified in the BA and non-BA groups, respectively. The details of the patient selection methods are shown in Fig. 1. The incidence of BA was 21–36 cases per year with an incidence of 12.48–21.18/100000 (Table 1). Table 2 shows the demographic characteristics of children with

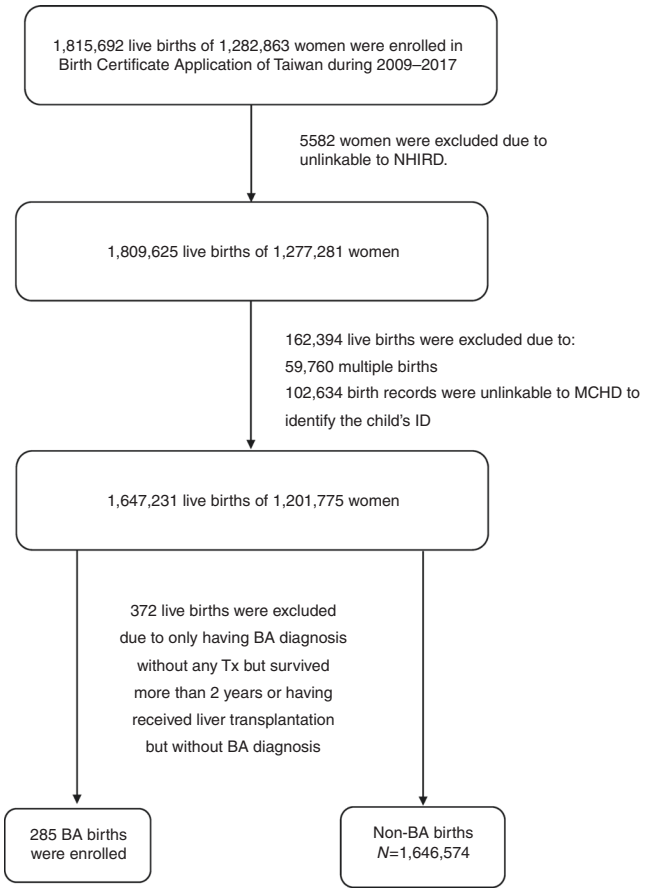


**Fig. 1** Flow chart of cases selection.

**Table 1.** The annual incidence of biliary atresia (BA), 2009–2017.

| Year | BA cases | Live births | Incidence* | 95% CI |
|---|---|---|---|---|
| 2009 | 29 | 180,293 | 16.08 | 11.18–23.15 |
| 2010 | 31 | 146,341 | 21.18 | 14.90–30.12 |
| 2011 | 34 | 176,870 | 19.22 | 13.74–26.90 |
| 2012 | 35 | 199,252 | 17.57 | 12.61–24.47 |
| 2013 | 30 | 185,387 | 16.18 | 11.31–23.14 |
| 2014 | 36 | 191,050 | 18.84 | 13.59–26.12 |
| 2015 | 34 | 203,098 | 16.74 | 11.96–23.43 |
| 2016 | 35 | 196,274 | 17.83 | 12.80–24.84 |
| 2017 | 21 | 168,294 | 12.48 | 8.14–19.14 |

*No. of BA cases per 100,000 live births.
*CI* confidence interval.

**Table 2.** Demographic characteristics of children with congenital, acquired BA and non-BA and their mothers.

| Variables | Congenital BA ($N = 48$) | | Acquired BA ($N = 237$) | | non-BA ($N = 1,646,574$) | | *P* value |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | |
| Children | | | | | | | |
| Sex | | | | | | | |
| Male | 19 | 39.6 | 105 | 44.3 | 854,796 | 51.9 | 0.0148 |
| Female | 29 | 60.4 | 132 | 55.7 | 791,778 | 48.1 | |
| Born prematurely | 9 | 18.8 | 31 | 13.1 | 119,206 | 7.2 | <0.0001 |
| Maternal | | | | | | | |
| Age at pregnancy | | | | | | | 0.3018 |
| <25 | 8 | 16.7 | 30 | 12.7 | 185,097 | 11.2 | |
| 25–29 | 18 | 37.5 | 77 | 32.5 | 473,821 | 28.8 | |
| 30–34 | 13 | 27.1 | 86 | 36.3 | 660,342 | 40.1 | |
| ≥35 | 9 | 18.8 | 44 | 18.6 | 327,314 | 19.9 | |
| Urbanization | | | | | | | 0.5743 |
| 1 (City) | 8 | 16.7 | 52 | 21.9 | 358,230 | 21.8 | |
| 2 | 27 | 56.3 | 122 | 51.5 | 872,992 | 53.0 | |
| 3 | 7 | 14.6 | 36 | 15.2 | 276,947 | 16.8 | |
| 4 (Village) | 6 | 12.5 | 27 | 11.4 | 138,405 | 8.4 | |
| Family income | | | | | | | 0.0002 |
| 0–15840 | 8 | 16.7 | 47 | 19.8 | 183,621 | 11.2 | |
| 15841–25000 | 24 | 50.0 | 87 | 36.7 | 679,498 | 41.3 | |
| >25000 | 16 | 33.3 | 103 | 43.5 | 783,455 | 47.6 | |
| History of abortion | 6 | 12.5 | 22 | 9.3 | 175,717 | 10.7 | 0.7233 |
| History of infertility | 7 | 14.6 | 32 | 13.5 | 244,587 | 14.9 | 0.8414 |
| History of stillbirth | ≤3 | | ≤3 | | 18,380 | 1.1 | 0.7535 |
| Number of pregnancies | | | | | | | 0.4272 |
| 0 | 29 | 60.4 | 133 | 56.1 | 890,270 | 54.1 | |
| 1 | 13 | 27.1 | 79 | 33.3 | 607,513 | 36.9 | |
| ≥2 | 6 | 12.5 | 25 | 10.5 | 148,791 | 9.0 | |
| Season of conception | | | | | | | 0.2154 |
| Spring | 10 | 20.8 | 70 | 29.5 | 390,549 | 23.7 | |
| Summer | 12 | 25.9 | 48 | 20.3 | 397,560 | 24.1 | |
| Autumn | 17 | 35.4 | 58 | 24.5 | 416,780 | 25.3 | |
| Winter | 9 | 18.8 | 61 | 25.7 | 441,685 | 26.8 | |
| Maternal comorbidities | | | | | | | |
| Hypertension | ≤3 | | ≤3 | | 21,241 | 1.3 | 0.5832¶ |
| DM, type 2 | ≤3 | | 5 | 2.1 | 23,094 | 1.4 | 0.0238¶ |
| Gestational DM | ≤3 | | 6 | 2.5 | 56,999 | 3.5 | 0.8268¶ |
| Thyroid disease | ≤3 | | 7 | 3.0 | 64,067 | 3.9 | 0.7870¶ |
| Anemia | ≤3 | | 23 | 9.7 | 156,019 | 9.5 | 0.5186¶ |
| UTI | 17 | 35.4 | 68 | 28.7 | 424,842 | 25.8 | 0.1871 |
| Mood disorders | ≤3 | | ≤3 | | 23,398 | 1.4 | 0.2040¶ |
| Anxiety[a] | 4 | 8.3 | 22 | 9.3 | 98,508 | 6.0 | 0.0797 |
| Nondependent abuse of drugs | ≤3 | | 4 | 1.7 | 8,952 | 0.5 | 0.0034¶ |
| Sleep disorders | ≤3 | | 7 | 3.0 | 27,592 | 1.7 | 0.1758¶ |
| Depressive disorder | ≤3 | | 5 | 2.1 | 12,785 | 0.8 | 0.0850¶ |
| DM type 1 | ≤3 | | ≤3 | | 1,389 | 0.1 | 1.0000¶ |
| CHD | ≤3 | | ≤3 | | 4,065 | 0.2 | 0.5036¶ |
| CTD | ≤3 | | ≤3 | | 20,462 | 1.2 | 0.6454¶ |
| Epilepsy | ≤3 | | ≤3 | | 4,850 | 0.3 | 0.5672¶ |
| Nephritis[b] | ≤3 | | ≤3 | | 6,736 | 0.4 | 0.7000¶ |
| Obesity | ≤3 | | ≤3 | | 7,273 | 0.4 | 0.4192¶ |
| OCPD | ≤3 | | ≤3 | | 210 | 0.0 | 1.0000¶ |

**Table 2.** continued

| Variables | Congenital BA ($N = 48$) | | Acquired BA ($N = 237$) | | non-BA ($N = 1,646,574$) | | $P$ value |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | |
| Drug dependence | ≤3 | | ≤3 | | 1,398 | 0.1 | 1.0000¶ |
| Adjustment reaction | ≤3 | | ≤3 | | 12,534 | 0.8 | 0.3786¶ |
| Alcohol disorder | ≤3 | | ≤3 | | 3,433 | 0.2 | 0.1718¶ |
| Maternal medication | | | | | | | |
| Antidepressants | ≤3 | 3.9 | 8 | 3.4 | 42,450 | 2.6 | 0.1336¶ |
| Anxiolytics | 4 | 12.6 | 32 | 13.5 | 166,936 | 10.1 | 0.2107 |
| Z-drug (sleeping pills for insomnia) | ≤3 | 4.2 | 10 | 4.2 | 41,075 | 2.5 | 0.1124¶ |

[a] including anxiety, dissociative and somatoform disorders; [b] including Nephritis, Nephrotic syndrome, and nephrosis; ¶Fisher's exact test; *CHD* congenital heart disease, *CTD* connective tissue disease, *DM* diabetes mellitus, *OCPD* obsessive–compulsive personality disorder, *UTI* urinary tract infection

congenital, acquired BA and non-BA and their mothers. There were 124 male and 161 female BA children with significant higher incidence in female than male. Forty-eight (16.8%) children were classified as having congenital BA. One hundred and thirty (45%) BA patients were diagnosed before 60 days-old. There was a statistically significant higher rate of premature birth for BA children. Family income also influenced the occurrence of BA. There were no significant differences on urbanization, age at pregnancy, number of pregnancies, season of conception and previous history of abortion, infertility or stillbirth. Mothers having type 2 DM or non-dependent abuse of drugs had higher rates to have BA children.

Logistic regression analysis showed that there was a significant difference between children of BA and non-BA patients in sex and premature birth, between mothers of BA and non-BA patients in family income, type 2 DM, anxiety, dissociative and somatoform disorders, non-dependent abuse of drugs. After multivariate adjusted analysis, there were significant differences in sex and premature birth in children, family income, type 2 DM and non-dependent abuse of drugs in mothers of BA to non-BA patients. If we only considered maternal factors, family income, type 2 DM and non-dependent abuse of drugs were still risk factors. If we excluded the premature cases, family income, type 2 DM and non-dependent abuse of drugs in addition to sex were still different statistically (Table 3 and Supplemental Table 2).

We further analyzed whether there was any difference in risk factors about the occurrence of congenital and acquired BA. For congenital BA to non-BA, there were significant differences in born prematurely in children, type 2 DM and non-dependent abuse of drugs in mothers after multivariate adjusted analysis. If only considered maternal factors, type 2 DM and non-dependent abuse of drugs were still risk factors. If we excluded the premature cases, non-dependent abuse of drugs was still significant (Table 4 and Supplemental Table 3). For acquired BA to non-BA, there were significant differences in sex and born prematurely in children, family income in mothers. If we only considered maternal factors, family income was still significant. If we excluded the premature cases, children sex and family income had the significant difference (Supplemental Table 4).

## DISCUSSION

This is a nationwide population-based study that utilized a large database to identify children/maternal risk factors associated with BA. The results suggested that female, born prematurely in children and family low income, type 2 DM and non-dependent drug abuse in mothers pose a high risk for BA. The maternal risk factors between congenital and acquired BA were quite different: type 2 DM and non-dependent abuse of drugs in congenital BA while family income in acquired BA.

In this study, we enrolled the BA patients mostly from the RCIPD. Because, BA leads to death by age 2 years if untreated[20], we also enrolled any patient who had the diagnosis of BA but never receiving Kasai portoenterostomy or liver transplantation but expired before two years-old though not ever identified as catastrophic illness. We excluded those who ever had the diagnosis of BA but never receiving any procedure but survived more than two years-old because the discrimination between definite and suspected BA cases is not possible by ICD code. The incidence of BA and percentage of congenital BA in this study was similar to previous reports from our country[21,22]. The relatively low percentage (45%) of BA patients diagnosed before 60 days-old, cannot be fully explained based on our present data.

We found that premature birth was associated with a higher risk for BA with an OR of 2.05. These results were consistent with previous large-scale studies from Sweden[8], Taiwan[22], and the Netherlands[23], where the incidences of BA were also reportedly higher in premature infants than in term infants with an OR of 1.65–2.9. Interestingly, the factor of prematurity was significant statistically in both congenital and acquired BA in this study. The possible mechanism of premature birth acting as a risk factor may be related to biliary obstruction leading to fetal distress and a higher likelihood of preterm birth. Another possibility is the weak immune system in premature births leading to disorganized reactions to infectious and/or toxic insults, and triggering progressive inflammatory responses of the biliary tract.

Previous study reported that there is a positive correlation between hyperglycemia during embryogenesis and congenital malformations in infants of diabetic mothers[24]. Correa et al., stated that pregestational DM was associated with a wide range of birth defects while GDM was associated with a limited group of birth defects[25]. Our finding about type 2 DM mother had a higher rate to have congenital BA baby that was consistent with their report that pregestational DM had an OR 3.14 for isolated biliary atresia and OR 18.40 for BA with multiple defects which hint that congenital BA might be related to diabetic embryopathy[25].

An interesting epidemic of BA in over 200 lambs and 9 calves was attributed to maternal grazing and ingestion of a toxic weed known as red crumbweed, growing on the newly exposed silt foreshores of Burrinjuck Dam, New South Wales, Australia[26]. Howley et al.[27] studied the relationship between asthma medication use and birth defects and found an elevated OR of 3.02 for BA. A stronger association OR 3.60 was noticed during the use of anti-inflammatory as well as asthma medications during pregnancy. In a Quebec Pregnancy Cohort study, the use of tricyclic antidepressants during the pregnancy increased the risk of digestive system defects in fetuses (OR 2.55)[28]. Furthermore, alterations in the serotonin levels by antidepressants have been thought to impact fetal morphogenesis and organogenesis[29]. Given that most antidepressants used during the first trimester of

**Table 3.** Logistic regression analysis for characteristics of children with BA versus non-BA and their mothers.

| Variables | Crude | | | | Model 1* | | | |
|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | | *P* value | OR | 95%CI | | *P* value |
| Children | | | | | | | | |
| Sex | | | | | | | | |
| Male | 0.71 | 0.56 | 0.90 | 0.0047 | 0.70 | 0.56 | 0.89 | 0.0033 |
| Female | 1.00 | Ref | | | 1.00 | Ref | | |
| Born prematurely | 2.09 | 1.50 | 2.92 | <0.0001 | 2.05 | 1.47 | 2.87 | <0.0001 |
| Maternal | | | | | | | | |
| Age at pregnancy | | | | | | | | |
| <25 | 1.02 | 0.70 | 1.49 | 0.9019 | 0.91 | 0.63 | 1.32 | 0.6287 |
| 25–29 | 1.00 | Ref | | | 1.00 | Ref | | |
| 30–34 | 0.75 | 0.56 | 0.99 | 0.0430 | 0.77 | 0.58 | 1.02 | 0.0715 |
| >=35 | 0.81 | 0.58 | 1.13 | 0.2128 | 0.80 | 0.56 | 1.14 | 0.2122 |
| Urbanization | | | | | | | | |
| 1 (City) | 0.70 | 0.46 | 1.07 | 0.1032 | 0.81 | 0.53 | 1.24 | 0.3262 |
| 2 | 0.72 | 0.49 | 1.04 | 0.0823 | 0.80 | 0.55 | 1.18 | 0.2607 |
| 3 | 0.65 | 0.41 | 1.02 | 0.0638 | 0.71 | 0.45 | 1.12 | 0.1366 |
| 4 (Village) | 1.00 | Ref | | | 1.00 | Ref | | |
| Family income | | | | | | | | |
| 0–15840 | 1.00 | Ref | | | 1.00 | Ref | | |
| 15,841–25,000 | 0.55 | 0.39 | 0.75 | 0.0002 | 0.59 | 0.43 | 0.82 | 0.0017 |
| >25,000 | 0.51 | 0.37 | 0.70 | <0.0001 | 0.59 | 0.43 | 0.81 | 0.0013 |
| History of abortion | 0.91 | 0.62 | 1.35 | 0.6433 | 0.92 | 0.61 | 1.40 | 0.7045 |
| History of infertility | 0.91 | 0.65 | 1.27 | 0.5788 | 0.97 | 0.68 | 1.37 | 0.8494 |
| History of stillbirth | 0.94 | 0.30 | 2.94 | 0.9186 | 0.89 | 0.26 | 3.02 | 0.8526 |
| Number of pregnancies | | | | | | | | |
| 0 | 1.00 | Ref | | | 1.00 | Ref | | |
| 1 | 0.83 | 0.64 | 1.07 | 0.1595 | 0.88 | 0.68 | 1.15 | 0.3511 |
| ≥2 | 1.15 | 0.78 | 1.68 | 0.4897 | 1.08 | 0.72 | 1.61 | 0.7103 |
| Season of conception | | | | | | | | |
| Spring | 1.29 | 0.94 | 1.78 | 0.1013 | 1.29 | 0.94 | 1.78 | 0.1170 |
| Summer | 0.95 | 0.67 | 1.34 | 0.7812 | 0.95 | 0.67 | 1.34 | 0.7782 |
| Autumn | 1.14 | 0.82 | 1.57 | 0.4446 | 1.13 | 0.81 | 1.56 | 0.4801 |
| Winter | 1.00 | Ref | | | 1.00 | Ref | | |
| Maternal comorbidities | | | | | | | | |
| Hypertension | 1.09 | 0.41 | 2.92 | 0.8654 | 0.82 | 0.30 | 2.22 | 0.6898 |
| DM, type 2 | 2.03 | 1.01 | 4.10 | 0.0483 | 2.17 | 1.04 | 4.53 | 0.0380 |
| Gestational DM | 0.70 | 0.33 | 1.49 | 0.3557 | 0.65 | 0.30 | 1.38 | 0.2606 |
| Thyroid disease | 0.71 | 0.35 | 1.44 | 0.3463 | 0.69 | 0.34 | 1.40 | 0.3020 |
| Anemia | 0.92 | 0.61 | 1.38 | 0.6852 | 0.87 | 0.57 | 1.32 | 0.5110 |
| UTI | 1.22 | 0.95 | 1.58 | 0.1213 | 1.18 | 0.91 | 1.53 | 0.2148 |
| Mood disorders | 0.99 | 0.37 | 2.65 | 0.9801 | 0.51 | 0.16 | 1.63 | 0.2539 |
| Anxiety | 1.58 | 1.05 | 2.36 | 0.0267 | 1.33 | 0.80 | 2.22 | 0.2645 |
| Nondependent abuse of drugs | 3.93 | 1.75 | 8.83 | 0.0009 | 3.02 | 1.34 | 6.78 | 0.0075 |
| Sleep of nonorganic origin | 1.69 | 0.84 | 3.42 | 0.1414 | 1.11 | 0.47 | 2.62 | 0.8206 |
| Depressive disorder | 2.28 | 0.94 | 5.53 | 0.0675 | 1.61 | 0.50 | 5.16 | 0.4250 |
| Maternal medication | | | | | | | | |
| Antidepressants | 1.52 | 0.83 | 2.77 | 0.1754 | 0.94 | 0.35 | 2.49 | 0.8952 |
| Anxiolytics | 1.28 | 0.90 | 1.82 | 0.1642 | 1.05 | 0.69 | 1.59 | 0.8362 |
| Z-drug | 1.72 | 0.96 | 3.06 | 0.0665 | 1.25 | 0.61 | 2.56 | 0.5482 |
| Depressive disorder | 2.28 | 0.94 | 5.53 | 0.0675 | 1.61 | 0.50 | 5.16 | 0.4250 |
| Maternal medication | | | | | | | | |
| Antidepressants | 1.52 | 0.83 | 2.77 | 0.1754 | 0.94 | 0.35 | 2.49 | 0.8952 |
| Anxiolytics | 1.28 | 0.90 | 1.82 | 0.1642 | 1.05 | 0.69 | 1.59 | 0.8362 |
| Z-drug | 1.72 | 0.96 | 3.06 | 0.0665 | 1.25 | 0.61 | 2.56 | 0.5482 |

*Adjusted for all covariates in Table 2

**Table 4.** Logistic regression analysis for characteristics of children with congenital BA versus non-BA and their mothers.

| Variables | Crude | | | | Model 1* | | | |
|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | | *P* value | OR | 95% CI | | *P* value |
| Children | | | | | | | | |
| Sex | | | | | | | | |
| Male | 0.61 | 0.34 | 1.08 | 0.0906 | 0.59 | 0.33 | 1.06 | 0.0757 |
| Female | 1.00 | Ref | | | 1.00 | Ref | | |
| Born prematurely | 2.96 | 1.43 | 6.10 | 0.0034 | 2.82 | 1.33 | 5.95 | 0.0066 |
| Maternal | | | | | | | | |
| Age at pregnancy | | | | | | | | |
| <25 | 1.14 | 0.49 | 2.62 | 0.7614 | 1.00 | 0.45 | 2.21 | 0.9965 |
| 25–29 | 1.00 | Ref | | | 1.00 | Ref | | |
| 30–34 | 0.52 | 0.25 | 1.06 | 0.0709 | 0.56 | 0.26 | 1.19 | 0.1317 |
| >=35 | 0.72 | 0.33 | 1.61 | 0.4285 | 0.74 | 0.33 | 1.71 | 0.4863 |
| Urbanization | | | | | | | | |
| 1 (City) | 0.52 | 0.18 | 1.48 | 0.2194 | 0.64 | 0.22 | 1.83 | 0.4041 |
| 2 | 0.71 | 0.29 | 1.73 | 0.4544 | 0.83 | 0.35 | 1.99 | 0.6828 |
| 3 | 0.58 | 0.20 | 1.73 | 0.3322 | 0.63 | 0.21 | 1.88 | 0.4053 |
| 4 (Village) | 1.00 | Ref | | | 1.00 | Ref | | |
| Family income | | | | | | | | |
| 0–15,840 | 1.00 | Ref | | | 1.00 | Ref | | |
| 15,841–25,000 | 0.81 | 0.36 | 1.80 | 0.6072 | 0.95 | 0.41 | 2.21 | 0.9005 |
| >25,000 | 0.47 | 0.20 | 1.10 | 0.0802 | 0.62 | 0.25 | 1.56 | 0.3094 |
| History of abortion | 1.20 | 0.51 | 2.81 | 0.6820 | 1.17 | 0.43 | 3.21 | 0.7626 |
| History of infertility | 0.98 | 0.44 | 2.18 | 0.9579 | 1.05 | 0.47 | 2.35 | 0.9116 |
| History of stillbirth | 1.88 | 0.26 | 13.66 | 0.5306 | 1.45 | 0.15 | 13.82 | 0.7473 |
| Number of pregnancies | | | | | | | | |
| 0 | 1.00 | Ref | | | 1.00 | Ref | | |
| 1 | 0.66 | 0.34 | 1.26 | 0.2081 | 0.71 | 0.36 | 1.40 | 0.3226 |
| ≥2 | 1.24 | 0.51 | 2.98 | 0.6341 | 1.14 | 0.48 | 2.69 | 0.7649 |
| Season of conception | | | | | | | | |
| Spring | 1.26 | 0.51 | 3.09 | 0.6191 | 1.25 | 0.51 | 3.08 | 0.6265 |
| Summer | 1.48 | 0.62 | 3.52 | 0.3729 | 1.46 | 0.61 | 3.49 | 0.3900 |
| Autumn | 2.00 | 0.89 | 4.49 | 0.0923 | 1.95 | 0.87 | 4.40 | 0.1060 |
| Winter | 1.00 | Ref | | | 1.00 | Ref | | |
| Maternal comorbidities | | | | | | | | |
| Hypertension | 1.63 | 0.22 | 11.80 | 0.6296 | 0.95 | 0.10 | 8.92 | 0.9661 |
| DM, type 2 | 4.69 | 1.46 | 15.08 | 0.0096 | 5.20 | 1.50 | 18.06 | 0.0094 |
| Gestational DM | 0.59 | 0.08 | 4.30 | 0.6055 | 0.41 | 0.06 | 2.60 | 0.3404 |
| Thyroid disease | 0.53 | 0.07 | 3.81 | 0.5244 | 0.52 | 0.07 | 3.78 | 0.5151 |
| Anemia | 0.42 | 0.10 | 1.71 | 0.2239 | 0.37 | 0.09 | 1.45 | 0.1528 |
| UTI | 1.58 | 0.87 | 2.85 | 0.1312 | 1.55 | 0.83 | 2.87 | 0.1679 |
| Mood disorders | 3.02 | 0.73 | 12.43 | 0.1264 | 1.86 | 0.32 | 10.64 | 0.4876 |
| Anxiety | 1.43 | 0.51 | 3.98 | 0.4946 | 1.11 | 0.36 | 3.37 | 0.8591 |
| Nondependent abuse of drugs | 7.95 | 1.93 | 32.76 | 0.0041 | 5.94 | 1.30 | 27.19 | 0.0217 |
| Sleep of nonorganic origin | 1.25 | 0.17 | 9.05 | 0.8262 | 0.60 | 0.03 | 10.70 | 0.7312 |
| Maternal medication | | | | | | | | |
| Antidepressants | 2.52 | 0.78 | 8.11 | 0.1213 | 2.25 | 0.42 | 12.13 | 0.3436 |
| Anxiolytics | 0.81 | 0.29 | 2.24 | 0.6792 | 0.44 | 0.14 | 1.37 | 0.1566 |
| Z-drug | 1.70 | 0.41 | 7.00 | 0.4629 | 1.06 | 0.12 | 9.24 | 0.9600 |

*Adjusted for all covariates in Table 2

pregnancy are from inadvertent exposure, exposure occurs during the early phase of gestation when women are unaware that they are pregnant. In our study, maternal non-dependent abuse of drugs had an elevated OR in congenital but not in the acquired BA even more emphasized the importance of drug use in the first trimester. It was difficult to ascertain if a disease, other health problems, and/or medication was responsible for the increased risk for BA. Although the absolute risk is relatively small, the findings support the need to regulate the use of drugs before and after the pregnancy.

Several studies suggested that rates of BA are higher among girls[21,30]. Our study was also consistent with this association. Evidence concerning differences in prevalence by sex of infant and the possible causes is inconclusive. Some studies revealed that there may be some association between economic development and BA[31]. The overall socioeconomic improvement may result in better health services and possibly fewer exposures to infections during pregnancy, thereby reducing the incidence of BA. In our study, mothers with lower family income have higher rate to have acquired BA baby but not in congenital BA that seemed to be consistent with their opinion.

There have been inconsistent reports regarding the association of the seasons in which mothers were conceived and the BA occurrence in infants. In our study, we did not find significant difference about seasonality as a risk for BA. Jimenez-Rivera and colleagues also had the same conclusion by systematic review[32]. Fischler et al.[8] stated that a high maternal age and parity of at least 4 represented a higher risk of BA occurrence in children. In the current study, we did not observe a difference in BA occurrence in children for various maternal ages or number of pregnancies. There have been very few P4 births in the last ten years in the country, yet the incidence of BA has not changed significantly.

The current study has a few limitations: (1) the BA subtypes was classified chiefly by whether combination of congenital heart anomalies or not; (2) detailed drug history was not available; and (3) the diagnoses of non-dependent abuse of drugs were established by physicians and the differences in diagnoses could not be controlled by different healthcare providers. Nevertheless, to prevent this bias, we included only those cases where at least 2 illness-related ambulatory claims or one inpatient claim and at least 4 drug use-related ambulatory claims were made in one year before giving birth.

The major strength of this study is the high number of participants from a nationwide population-based database that contained numerous cases of BA. The design of the national databases used in this study does not allow access to the charts of individual patients. However, the sensitivity and specificity of methods employed in this study detected BA patients, as judged from the comparison of data with previous reports by other groups in the country. This suggests that access-related limitations had no significant effect on the results of the study. To understand the detailed pathophysiology of the relationship between BA patients and maternal illness/drug use, further studies are required.

## CONCLUSIONS

We conclude that the BA occurrence is related to maternal factors that include type 2 DM and drug abuse. The results provide crucial evidence to support the notion based on preventable risk factors for BA. Further studies should be conducted to obtain more information about BA pathophysiology.

## DATA AVAILABILITY

The data underlying this study is from the National Health Insurance Research Database, which has been transferred to the Health and Welfare Data Science Center (HWDC). Requests for data can be sent as a formal proposal to the HWDC, Department of Statistics, Ministry of Health and Welfare, Taiwan (https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html) with an IRB approval for research purpose only. To access the data, please contact the HWDC (stsung@mohw.gov.tw; stpeicih@mohw.gov.tw).

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## AUTHOR CONTRIBUTIONS

C.C.M. and K.K.C. wrote the first draft of the manuscript. C.W.H., and S.C.H., reviewed and edited the subsequent drafts. L.C.P and C.K.J. performed formal analyses. Y.Y.H validated the statistical analyses. Y.J.B. and S.J.M. supervised and critically reviewed the manuscript. All authors approved the final version of the manuscript.

## PATIENT CONSENT

Because this was a secondary data analysis, all identifications of patients and institutions were removed before data release, so patient consent was not required.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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