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Neurobehavioral disorders among children born to mothers exposed to illicit substances during pregnancy

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Abstract

Background Exposure to illicit substances during pregnancy may have long-term impacts on children's neurodevelopment. This study explores subsequent risks for intellectual disability, autistic disorders, and attention deficit and hyperactivity disorders in children born to mothers exposed to illicit substances before or during pregnancy.

Methods We identified women with illicit drug use by linking the police records from the "Substance Abuse Control Databases" and Taiwan Birth Registration and Birth Notification records from 2004 to 2014. Children whose mothers that had exposed to illicit substances during pregnancy identified from the police records were the "substance-exposed cohort." A 1:1 ratio exact-matched comparison cohort based on child's gender, child's birth year, mother's birth year, and child's first use of the health insurance card, as well as a "propensity score (PS)-matched" comparison cohort of children born by substance-unexposed mothers, was established. Multivariate Cox regression analyses with competing risk models were performed.

Results Higher incidences of intellectual disability (adjusted hazard ratio (aHR) = 2.41, 95% confidence interval (CI): 1.15–5.03) and attention deficit and hyperactivity disorder (ADHD) (aHR = 2.35, 95% CI: 1.63–3.28) were found in children prenatally exposed to illicit substances during pregnancy compared to exact-matched non-exposed cohorts. Adjusted risks of ADHD were significantly higher in mothers exposed to substances during pregnancy (aHR = 1.77 (1.42–2.21)) and before pregnancy (aHR = 1.43 (1.14–1.80)) compared to PS-matched unexposed cohorts after adjusting for covariates.

Conclusions This is one of the first studies using large population-based data linked to criminal records to reveal increased risks of intellectual disability and ADHD in children with prenatal exposure to illicit substances compared to matched unexposed controls. Our results also highlight the importance of preventive measures and interventions for the well-being of both the mother and the child.

Keywords Pregnancy, Prenatal exposure, Illicit substance, Children, Intellectual disability, Attention deficit and hyperactivity disorders

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Background

Illicit substance misuse or dependence causes significant impacts on public safety, family functions, or individual physical or mental health conditions. Users of illicit substances may suffer damages on their circulatory, respiratory, digestive, immune, or nervous systems, leading to higher mortality rates compared to the general population [1, 2]. In 2015, an estimated 280 million people aged 15–64 in the world had used at least one illicit substance illegally (most prevalent ones are cannabis, amphetamine, and opioids) in the past year, accounting for 5% of this age group [3]. According to Taiwan's National Substance Abuse Survey, the lifetime prevalence of using any illicit substance among adults aged 18 to 64 was 1.33%, with amphetamines, ketamine, and cannabis being the most common [4].

Illicit substance users are predominantly male, but female users are mostly of childbearing age [5]. Literature shows that women aged 18 ~ 29 years have the highest risk of developing substance use disorder [6]. In Taiwan, 26.6% of indigenous pregnant women reported consuming alcohol after recognizing their pregnancy, with 52.5% continued to drink [7]. In a study of over 1 million pregnant women on Medicaid (a US government program that provides health insurance to low-income individuals and families), 21.6% were found to have filled an opioid prescription, and 2.5% received a supply of chronic opioid medication lasting more than 1 month [8]. From 1992 to 2012, the rate of pregnant women seeking treatments for opioid use (either medical or illegal use) in the US increased from 2 to 28% [6]. This rise may be attributed to increased opioid use among pregnant women, greater awareness, improved access to treatment facilities, and broader public health initiatives aimed at addressing substance use disorders. Among female inmates and patients in drug rehabilitation institutions in Taiwan, 56–64% reported using illicit substances during pregnancy [9]. Most illicit substances would affect embryos through the placenta and may cause obstetric complications, excess mortality, neonatal abstinence syndrome, abnormal physical problems, or neurodevelopment issues in both human and animal models [10, 11]. Prior research and our previous study have shown elevated risks of short-term neonatal outcomes, such as the abstinence syndrome, stillbirths, low birth weight [12], congenital heart defects, small head circumferences, or neural tube defects in children prenatally exposed to opioid, heroin, or amphetamine during pregnancy [13–15]. Few studies have mentioned the raised long-term risks of prenatal exposures of opioids (either legal or illegal use) or heroin on children's intellectual functions or neurobehavioral disorders, such as autistic disorder or attention deficit hyperactivity disorder (ADHD) after birth [16, 17]. The literature has described significantly lower scores on verbal, performance, or full intelligence quotient (IQ), as well as more school or behavioral problems among children with prenatal opioid exposures (either legal or illegal use) and followed at school ages of 3 to 15 years [14, 17, 18]. However, an overall nonsignificant trend of poorer outcomes on cognitive or behavioral problems (effect sizes of 0.18 and 0.38, respectively; confidence interval contains 0) was found among opioid exposed preschool children in a meta-analysis that included five studies [11]. They suggested that their results should be cautiously interpreted due to their stringent criteria of excluding intra-uterine exposures of multiple substances, and the findings of studies they included were assessed as moderate to weak quality. Previous studies on intra-uterine opioid exposure for school-aged children are limited [11], making comparable analysis challenging. Additionally, the analysis of rare outcomes such as autistic disorders or ADHD has been insufficient [11]. Research on amphetamine use in pregnant women, despite its high prevalence and association with increased risks of low birth weight, microcephaly, and hypotonicity in newborns [19], is sparse. Few studies have addressed the long-term effects, such as poorer academic achievements [20] and increased aggression among school-aged children with prenatal amphetamine exposure [21].

Due to the scarcity of existing research on the long-term effects of intra-uterine opioid and amphetamine exposure, this present study used a comprehensive, nationwide, population-based criminal database of illicit substance use [12] to provide a reliable identification source for substance exposure. With linkages to several governmental birth, household registrations, and data on health and medical utilizations in Taiwan, we aimed to investigate the risks of intellectual disability and relatively rarer neurobehavioral outcomes of autistic disorders and ADHD from birth to age of 13 among cohorts of children prenatally exposed or unexposed to heroin, amphetamine, ketamine, or other substances.

Methods

Study subjects

We conducted a cohort study comparing the risks of subsequent neurodevelopmental disorders between children with or without prenatal exposures to illicit drugs before or during pregnancy [12]. The study cohort was established by identifying pregnant women arrested by the police due to illicit substance use from the "Substance Abuse Control Databases" [12]. In Taiwan, illicit drugs are classified into schedules I to IV by the Ministry of Justice based on their potentials for addiction, abuse, and societal harm (Additional file 1: Table S1). The period of pregnancy was confirmed by

information using birth date and the number of gestational weeks recorded in the Birth Registration files. The rationale for selecting pregnant women arrested by police for illicit substance use is based on the need for accurate and reliable identification of substance exposure. Police records from the "Substance Abuse Control Databases" provide a comprehensive and verifiable source of data on illicit substance use. By linking these records with Taiwan Birth Registration and Birth Notification records, we can determine the timing of substance exposure relative to pregnancy, allowing for the analysis of the subsequent risks for neurodevelopmental conditions in children. Mothers arrested by the police between conception date and birthdates of children were defined as the "substance-exposed during pregnancy cohort (DP)." Mothers identified before the conception date were categorized as the "substance-exposed before pregnancy cohort (BP)."

The comparison cohort comprised children born by women who were not exposed to substances (substance-unexposed cohort) and were not in the "Substance Abuse Control Databases." Given the reason to select a comparison cohort that was representative of the population and has various characteristic parameters similar to the exposed group to be able to control for potential confounding factors, two stages of the exact- and propensity score (PS)-matching process were applied. In the first stage of exact- and PS-matching, unexposed subjects with similar demographic and comorbidities. However, there were still differences in various individual characteristics that might act as potential confounders (as indicated in Table 1, where between-group differences persisted even after exact matching) and it is challenging to select a subset from the comparison cohort that matches DP or BP exposed cohort across various parameters; hence, propensity scores were matched with the exposed cohort to address these confounding issues and achieve greater similarities between the exposed or unexposed groups. The propensity scores were calculated by entering all covariates into a logistic regression model to estimate the probability (propensity score) of each individual based on the selected covariates. To further mitigate the impact of confounders and ensure comparability between substance-exposed DP or BP groups and unexposed groups, we further categorized the exposed cohort into substance-exposed during or before pregnancy subgroups and selected exact- and PS-matched subjects from the unexposed cohort for comparisons in the second stage of matching (detailed flow chart of our matching process is demonstrated in our previous work [12]). To avoid choosing the extreme cases, children who did not use the health insurance in exposed and unexposed cohorts were not included.

Study database

This study linked the Household Registration files to obtain the mother's basic demographic data, the National Health Insurance Research Database (the NHIRD, a population-based and comprehensive healthcare database that contains de-identified registration files and claims data from the National Health Insurance program in Taiwan) to obtain the mother's and the child's health and medical utilizations and medical expenses from emergency visits, outpatient and hospitalization records, the "Substance Abuse Control Database" that contained crime records for information on illicit substance uses in women, the Nation's Birth Registration and Birth Notification files, and the Death Registration files. The whole research process was conducted in the "Statistic Science Center" (from now on referred to as the "Center") of the Statistics Department of the Ministry of Health and Welfare in Taiwan. The Science Center was responsible for integrating all the above databases and provided data to the research team after re-scrambling National Identification (ID) codes for de-identifications. All personal information, including ID numbers and other data, was encrypted, ensuring no specific identifications could be obtained. The research team went into the Science Center, performing statistical analyses only on the data the Center provided by the Center's regulations. Since no personal identifications are possible, informed consent was waived by the Institutional Review Board of National Taiwan Normal University (IRB number: 202002HM010).

Outcome variables

The starting point for each participant in this study was the date of birth (between 2004 and 2014); the endpoint for each participant was the first diagnoses of neurodevelopment disorders including intellectual disability, autistic disorders, or ADHD, death, immigration, or December 31, 2017 (i.e., the end of the study). Hence, the minimum age of the participants was 3 years, and the maximum was 13 years. Having at least three diagnoses from outpatient records, or one discharge diagnosis from hospitalization records of neurodevelopmental disorders, including intellectual disability (ICD-9-CM: 317–319; ICD-10: F70, F71, F72, F73, F78, F79), autistic disorders (ICD-9-CM: 299; ICD-10: F84), and attention deficit and hyperactivity disorders (ADHD, ICD-9-CM: 314; ICD-10: F90), between birth to the school age of 13, identified from the NHIRD among children born to mothers in the exposed before or during pregnancy or unexposed groups, were ascertained as our main outcome. Prior literature indicated that an over 74% of positive predictive value of a diagnosis is enhanced when it is confirmed

Table 1 Characteristics and covariates that were still significantly different after the exact matching (total $n = 7104$)

Variable	Exposed before pregnancy ($n = 1776$), *n* (%)	Exposed during pregnancy ($n = 1776$), *n* (%)	Unexposed ($n = 3552$), *n* (%)	*p* value
Mother, heroin use				
During pregnancy	0	863	0	
Before pregnancy	769	787	0	
Mother, amphetamine use				
During pregnancy	0	931	0	
Before pregnancy	815	775	0	
Mother, ketamine use				
During pregnancy	0	149	0	
Before pregnancy	85	71	0	
Mother, education				< 0.001
Elementary, junior high school	774 (43.58)	881 (49.61)	427 (12.02)	
Senior high school	873 (49.16)	831 (46.79)	1404 (39.53)	
College	129 (7.26)	64 (3.6)	1721 (48.45)	
Mother, marital status				< 0.001
Single	359 (20.21)	595 (33.5)	264 (7.43)	
Married	1146 (64.53)	814 (45.83)	3208 (90.32)	
Divorce, widowhood	271 (15.26)	367 (20.66)	80 (2.25)	
Mother, Charlson comorbidity index				< 0.001
0	1532 (86.26)	1511 (85.08)	3171 (89.27)	
1	189 (10.64)	185 (10.42)	342 (9.63)	
≥ 2	55 (3.1)	80 (4.5)	39 (1.1)	
Mother, levels of income				< 0.001
< 20,000 $NTD	955 (53.80)	1336 (75.22)	547 (15.40)	
20,000–39,999 $NTD	755 (42.51)	421 (23.7)	2216 (62.39)	
≥ 40,000$NTD	66 (3.72)	19 (1.07)	789 (22.21)	
Mother, residence				< 0.001
Rural	374 (21.06)	460 (25.9)	545 (15.34)	
Urban	1402 (78.94)	1316 (74.1)	3007 (84.66)	
Mother, hospital days during pregnancy				< 0.001
0	108 (6.08)	171 (9.63)	162 (4.56)	
1–3	795 (44.76)	699 (39.36)	1709 (48.11)	
> 3	873 (49.16)	906 (51.01)	1681 (47.33)	
Mother, outpatient visits during pregnancy				< 0.001
0–10	372 (20.95)	813 (45.78)	133 (3.74)	
11–20	489 (27.53)	494 (27.82)	1000 (28.15)	
> 20	915 (51.52)	469 (26.41)	2419 (68.1)	
Mother, medical expenditure				< 0.001
0–19,999 $NTD	205 (11.54)	333 (18.75)	234 (6.59)	
20,000–39,999 $NTD	897 (50.51)	758 (42.68)	2086 (58.73)	
≥ 40,000 $NTD	674 (37.95)	685 (38.57)	1232 (34.68)	
Mother, prescription used during pregnancy that are harmful to the fetus				< 0.001
No	985 (55.46)	1114 (62.73)	2081 (58.59)	
Yes	791 (44.54)	662 (37.27)	1471 (41.41)	
Mother, prescription used during pregnancy that are harmful to the fetus in an animal or human experiment				< 0.001
No	638 (35.92)	761 (42.85)	1274 (35.87)	
Yes	1138 (64.08)	1015 (57.15)	2278 (64.13)	
Children, order of this birth				0.135
1	1764 (99.32)	1758 (98.99)	3507 (98.73)	
≥ 2	12 (0.68)	18 (1.01)	45 (1.27)	

Table 1 (continued)

Variable	Exposed before pregnancy ($n=1776$), *n* (%)	Exposed during pregnancy ($n=1776$), *n* (%)	Unexposed ($n=3552$), *n* (%)	*p* value
Children, birth place				< 0.001
Hospital	1049 (59.07)	1078 (60.7)	2392 (67.34)	
Clinic	715 (40.26)	662 (37.27)	1156 (32.55)	
Other	12 (0.68)	36 (2.03)	4 (0.11)	
Children, cesarean section				< 0.001
No	1069 (60.19)	1148 (64.64)	2389 (67.26)	
Yes	707 (39.81)	628 (35.36)	1163 (32.74)	
Children, 5th minimum APGAR score				< 0.001
< 7	15 (0.84)	24 (1.35)	9 (0.25)	
≥ 7	1761 (99.16)	1752 (98.65)	3543 (99.75)	
Children, death				< 0.001
No	1766 (99.44)	1756 (98.87)	3543 (99.75)	
Yes	10 (0.56)	20 (1.13)	9 (0.25)	
Children, attention deficit hyperactivity disorder, ADHD				< 0.001
No	1660 (93.47)	1624 (91.44)	3445 (96.99)	
Yes	106 (5.97)	132 (7.43)	98 (2.76)	
Children, intellectual disability				< 0.001
No	1740 (97.97)	1708 (96.17)	3519 (99.07)	
Yes	26 (1.46)	48 (2.70)	24 (0.68)	
Children, autistic disorder				< 0.001
No	1753 (98.7)	1746 (98.31)	3519 (99.07)	
Yes	13 (0.73)	10 (0.56)	24 (0.68)	

ADHD attention deficit and hyperactivity disorder

The comparison cohort was selected by two stages of exact matching. The exact matching by mother's year of birth, child's gender, child's year of birth, and child's first use of health insurance card (all $p > 0.99$ after exact matching) of mothers exposed to substances before pregnancy ($n=1776$, the "substance-exposed before pregnancy cohort"), mothers exposed to substances during pregnancy ($n=1776$, the "substance-exposed during pregnancy cohort"), and the comparison cohort ("substance-unexposed mothers," $n=3552$). More details may be referred to our previous work [12]

through three to four separate outpatient visits from the NHIRD [22].

Covariates

Covariates included the age and health status of the parents, mothers' age at birth, education and income levels, marital status, the city where the mother is currently living, the number of births, the number of gestation weeks, Charlson's comorbidity index (CCI), health and medical utilizations, including days of hospitalization, outpatient or emergency visits, medical expenses during pregnancy, medications harmful to the fetus prescribed during pregnancy, the child's gender, the city of child's birth (as a proxy of levels of urbanization or accessibility of healthcare), birth weight, the method of delivery (cesarean or natural birth), the physical status of the baby at birth (fifth minute American Pediatric Gross Assessment Record (APGAR) score), and the child's year at first use of the health insurance card (as a proxy of how the child might be affected by his congenital conditions). The CCI provides a method to quantify the burden of comorbid diseases that may influence the health status of pregnant women and the risk of adverse pregnancy outcomes [23]. The APGAR score is used to evaluate a newborn's health condition. At a total of 10 points, an APGAR score of less than 7 requires clinical first-aid evaluation. These covariates were also used in the calculation of propensity scores. Other risk factors, including smoking status, body mass index, alcohol use, or postnatal socioeconomic environment, are not available in the dataset.

Statistical analyses

This is a retrospective cohort study which takes account of death as a competing risk. A chi-square test was used to compare subjects' characteristics, neurodevelopmental outcomes, and logistic regression model calculated propensity scores. Cox regression with a competing risk model was used to compare the hazards of neurodevelopmental disorders between substance-exposed and -unexposed cohorts. The starting point was the date of birth; the endpoints were the first diagnoses of neurodevelopmental disorders of intellectual disability, autistic

disorders, or attention deficit and hyperactivity disorders, death, immigration, or December 31, 2017. Since there were still some residual imbalances after the PS-matching, we performed a double adjustment, where covariates were included in the Cox regression model to remove any remaining confounding [24]. Two adjustment models were compared. Covariates adjusted in model 1 included the child's gender, birth year, the year that first used a health insurance card, mothers' year of birth, age at giving birth, education, income, and urbanization levels, marital status (from the Household Registration files), Charlson comorbidity index, medical utilization (including days of hospitalizations, or outpatient or emergency visits), medical expenses, medications proven harmful to fetus prescribed during pregnancy, and cesarean section. Covariates in model 2 included those adjusted in model 1 and whether the child had diagnoses of preterm, low birth weight, and fifth minute APGAR scores. Both adjustment models applied to exact- and PS-matched comparisons.

Results

Among the 1,969,040 newborns identified from the Birth Registration and Birth Notification files between 2004 and 2014, 34 did not have any records in the National Health Insurance Research Database. Among the remaining 1,969,006 newborns, 18,235 were identified as having mothers who were caught by police for illicit drug use through the "Substance Abuse control Databases" between 2001 and 2015. Of these 18,235 mothers, 2078 (11.4%) of them were found to have been exposed to and being caught with illicit drug use during pregnancy, and 8772 (48.11%) of them have been exposed to and caught with illicit drug use within the year before pregnancy. The majority of drug users apprehended by the police were using heroin, amphetamine, and ketamine and therefore we had Table 1 focused on these substances. Other illicit substances classified in the "Substance Abuse Control Database" were provided in Supplement Table S1 to illustrate the association between different types of substances exposed during pregnancy and ADHD. However, due to insufficient sample sizes, it was not possible to analyze the association by drug type for intellectual disability.

After the exact-matching, 1776 newborns from the substance-exposed before pregnancy cohort, 1776 newborns from the substance-exposed during pregnancy cohort, and 3552 unexposed cohort were selected and exact-matched by child's gender, birth year, mother's birth year, and child's first use of the health insurance card. Characteristics of child's gender, birth year, child's first use of the health insurance card, and mother's birth year were matched without significant differences (all $p > 0.99$). Characteristics and covariates that were not matched or still showed significant differences among the three cohorts are shown in Table 1. The substance-exposed mothers had significantly higher proportions of elementary or junior high school education levels, single, lives in rural places, higher Charlson comorbidity index, lower income, received cesarean section, being prescribed with medications possibly but not proven to be harmful to the fetus from animal or human trials, gave birth at clinics rather than hospitals, fewer outpatient visits during pregnancy, preterm birth, had low birth weight child, and had newborns with fifth minute APGAR score < 7 than substance-unexposed mothers (all $p < 0.001$). Under such exact matching, newborns from the substance-exposed cohort had significantly higher incidences of intellectual disability (2.70%, 1.46%, and 0.68% for exposed during pregnancy, before pregnancy, and unexposed, respectively; $p < 0.001$) and attention deficit and hyperactivity disorders (7.43%, 5.97%, and 2.76% for exposed during pregnancy, before pregnancy, and unexposed, respectively; $p < 0.001$) (Table 1). Autistic disorders did not reveal higher incidences in the exposed than the unexposed cohort (0.56%, 0.73%, and 0.68% for exposed during pregnancy, before pregnancy, and unexposed, respectively; $p < 0.001$).

Table 2 shows that 4156 newborns from the substance-unexposed cohort were selected, PS-matched to the substance-exposed cohort separated by the time of exposure (exposed before pregnancy, $n = 2078$; during pregnancy, $n = 2078$). Characteristics of child's gender, child's birth year, the year of child's first use of health insurance card, birth orders, birth place, mother's age at giving birth, mother's urbanization levels, mother's education level, mother's marital status, Charlson comorbidity index, mothers' levels of income, mother's days of hospitalization, outpatient visits, medication prescribed during pregnancy, and the method of delivery (cesarean or natural birth) showed similar distribution between 3 cohorts (Table 2).

Results from competing risk Cox regression analyses of unadjusted and adjusted hazards for neurodevelopmental disorders between substance-exposed and unexposed cohorts with exact match are shown in Table 3 and Fig. 1. The cumulative incidence of risks for ADHD and intellectual disability were higher in the exposure during pregnancy group than the exposure before pregnancy group (Fig. 1). Unadjusted hazards of intellectual disability (HR = 4.48, 95% confidence interval (CI): 2.75–7.30; 2.24 (1.29–3.91)) and ADHD (HR = 3.08, 95% CI: 2.37–3.99; 2.28, 1.73–3.00) were significantly higher in substance-exposed during pregnancy and before pregnancy cohorts than the unexposed cohorts, respectively. After adjusting for potential confounders,

Table 2 Characteristics and covariates that were not matched or were still significantly different after the propensity matching (total $n = 8312$)

Variable	Exposed before pregnancy ($n = 2078$), *n* (%)	Exposed during pregnancy ($n = 2078$), *n* (%)	Unexposed ($n = 4156$), *n* (%)	*p* value
Mother, age at this childbirth (year)				< 0.001
14–17	23 (1.11)	32 (1.54)	162 (3.9)	
18–34	1848 (88.93)	1829 (88.02)	3353 (80.68)	
≥ 35	207 (9.96)	217 (10.44)	641 (15.42)	
Mother, heroin use				
During pregnancy	0	1027	0	
Before pregnancy	991	902	0	
Mother, amphetamine use				
During pregnancy	0	1106	0	
Before pregnancy	1168	895	0	
Mother, ketamine use				
During pregnancy	0	153	0	
Before pregnancy	81	71	0	
Mother, education				0.012
Elementary, junior high school	1081 (52.02)	1052 (50.63)	2079 (50.02)	
Senior high school	930 (44.75)	953 (45.86)	1982 (47.69)	
College	67 (3.22)	73 (3.51)	95 (2.29)	
Mother, marital status				0.826
Single	654 (31.47)	678 (32.63)	1347 (32.41)	
Married	977 (47.02)	949 (45.67)	1941 (46.7)	
Divorce, widowhood	447 (21.51)	451 (21.7)	868 (20.89)	
Mother, Charlson comorbidity index				0.409
0	1824 (87.78)	1784 (85.85)	3590 (86.38)	
1	180 (8.66)	205 (9.87)	405 (9.74)	
≥ 2	74 (3.56)	89 (4.28)	161 (3.87)	
Mother, insurance premium				0.012
< 20,000 $NTD	1563 (75.22)	1564 (75.26)	3243 (78.03)	
20,000–39,999 $NTD	491 (23.63)	494 (23.77)	888 (21.37)	
≥ 40,000$NTD	24 (1.15)	20 (0.96)	25 (0.6)	
Mother, residence				0.352
Rural	515 (24.78)	531 (25.55)	1099 (26.44)	
Urban	1563 (75.22)	1547 (74.45)	3057 (73.56)	
Mother, hospital days during pregnancy				0.884
0	217 (10.44)	209 (10.06)	420 (10.11)	
1–3	846 (40.71)	820 (39.46)	1667 (40.11)	
> 3	1015 (48.85)	1049 (50.48)	2069 (49.78)	
Mother, outpatient visits during pregnancy				< 0.001
0–10	372 (20.95)	813 (45.78)	133 (3.74)	
11–20	489 (27.53)	494 (27.82)	1000 (28.15)	
> 20	915 (51.52)	469 (26.41)	2419 (68.1)	
Mother, medical expenditure				0.036
0–19,999 $NTD	979 (47.11)	992 (47.74)	1895 (45.6)	
20,000–39,999 $NTD	616 (29.64)	580 (27.91)	1156 (27.82)	
≥ 40,000 $NTD	483 (23.24)	506 (24.35)	1105 (26.59)	
Mother, prescription used during pregnancy that are harmful to the fetus				0.171
No	1313 (63.19)	1309 (62.99)	2704 (65.06)	
Yes	765 (36.81)	769 (37.01)	1452 (34.94)	
Mother, prescription used during pregnancy that are harmful to the fetus in an animal or human experiment				0.006

Table 2 (continued)

Variable	Exposed before pregnancy (*n* = 2078), *n* (%)	Exposed during pregnancy (*n* = 2078), *n* (%)	Unexposed (*n* = 4156), *n* (%)	*p* value
No	858 (41.29)	884 (42.54)	1882 (45.28)	
Yes	1220 (58.71)	1194 (57.46)	2274 (54.72)	
Children, order of this birth				0.154
1	2068 (99.52)	2060 (99.13)	4117 (99.06)	
≥ 2	10 (0.48)	18 (0.87)	39 (0.94)	
Children, birth place				0.004
Hospital	1209 (58.18)	1251 (60.2)	2530 (60.88)	
Clinic	850 (40.9)	787 (37.87)	1550 (37.3)	
Other	19 (0.91)	40 (1.92)	76 (1.83)	
Children, cesarean section				0.918
No	1345 (64.73)	1345 (64.73)	2708 (65.16)	
Yes	733 (35.27)	733 (35.27)	1448 (34.84)	
Children, 5th minimum APGAR score				< 0.001
< 7	31 (1.49)	32 (1.54)	57 (1.37)	
≥ 7	2047 (98.51)	2046 (98.46)	4099 (98.63)	
Children, death				0.023
No	2036 (97.98)	2030 (97.69)	4098 (98.6)	
Yes	42 (2.02)	48 (2.31)	58 (1.40)	
Children, ADHD				< 0.001
No	1911 (91.96)	1883 (90.62)	3916 (94.23)	
Yes	125 (6.02)	147 (7.07)	182 (4.38)	
Children, intellectual disability				0.009
No	2000 (96.25)	1971 (94.85)	4007 (96.41)	
Yes	36 (1.73)	59 (2.84)	91 (2.19)	
Children, autistic disorder				0.103
No	2023 (97.35)	2019 (97.16)	4073 (98)	
Yes	13 (0.63)	11 (0.53)	25 (0.60)	

ADHD attention deficit and hyperactivity disorder. The comparison cohort was selected by two stages of propensity score (PS) matching. The propensity matching by mother's year of birth, child's gender, child's year of birth, and child's first use of health insurance card (all $p > 0.99$ after exact matching) of mothers exposed to substances before pregnancy ($n = 2078$, the "substance-exposed before pregnancy cohort"), mothers exposed to substances during pregnancy ($n = 2078$, the "substance-exposed during pregnancy cohort"), and the comparison cohort ("substance-unexposed mothers," $n = 4156$). More details may be referred to our previous work [12]

risks of intellectual disability (aHR = 2.41, 95% CI: 1.15–5.03) and ADHD (aHR = 2.35, 95% CI: 1.68–3.28) were significantly higher in the exposed during pregnancy than unexposed groups. The risk of ADHD remained higher in the exposed before pregnancy than unexposed groups (aHR = 1.92, 95% CI: 1.41–2.62). The increased risk of ADHD was found in the heroin (aHR: 2.00, 1.47–2.72), amphetamine (aHR: 2.01 (1.46–2.76)), and cannabis (aHR: 4.48, 1.20–16.68) exposed during pregnancy than unexposed groups.

Table 4 shows results from competing risk Cox analysis propensity score matched data. The significance results were similar with the previous exact match data analysis. However, the strength of association (HR) was reduced after potential confounders being further controlled.

Discussion

This is one of the first studies to date that used nationwide criminal records linked with population-based birth registrations and health utilization datasets to compare the risks of neurobehavioral disorders, including intellectual disability, autistic disorders, and ADHD, from birth to 13 years of age among children prenatally exposed or unexposed to illicit substances. We found overall increased risks of intellectual disability in children exposed to intrauterine illicit substances and increased risks of ADHD in children prenatally exposed to illicit substances during and before pregnancy compared to those exact- and PS-matched unexposed controls. Our findings showed that the risks of ADHD and intellectual disability were higher in the exposure during pregnancy group than the exposure before

Table 3 Competing risk adjusted Cox regression analysis of intellectual disability, autistic disorder, and attention deficit and hyperactivity disorder (exact matching by child's gender, child's birth year, mother's birth year, and the year of child's first use of health insurance card, total $n = 7104$)

Variable	Exposed period	Unadjusted analysis		Adjusted analysis model 1		Adjusted analysis model 2	
		Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
ADHD	Unexposed	1.00		1.00		1.00	
	During pregnancy	3.08 (2.37–3.99)	< 0.001	2.43 (1.75–3.38)	< 0.001	2.35 (1.68–3.28)	< 0.001
	Before pregnancy	2.28 (1.73–3.00)	< 0.001	1.97 (1.45–2.68)	< 0.001	1.92 (1.41–2.62)	< 0.001
Intellectual disability	Unexposed	1.00		1.00		1.00	
	During pregnancy	4.48 (2.75–7.30)	< 0.001	2.64 (1.29–5.39)	0.008	2.41 (1.15–5.03)	0.019
	Before pregnancy	2.24 (1.29–3.91)	0.004	1.53 (0.76–3.08)	0.236	1.45 (0.71–2.94)	0.307
Autistic disorder	Unexposed	1.00		1.00		1.00	
	During pregnancy	0.90 (0.43–1.88)	0.776	0.95 (0.39–2.31)	0.916	0.99 (0.92–1.07)	0.827
	Before pregnancy	1.11 (0.56–2.17)	0.769	1.10 (0.49–2.45)	0.814	1.00 (0.93–1.06)	0.923

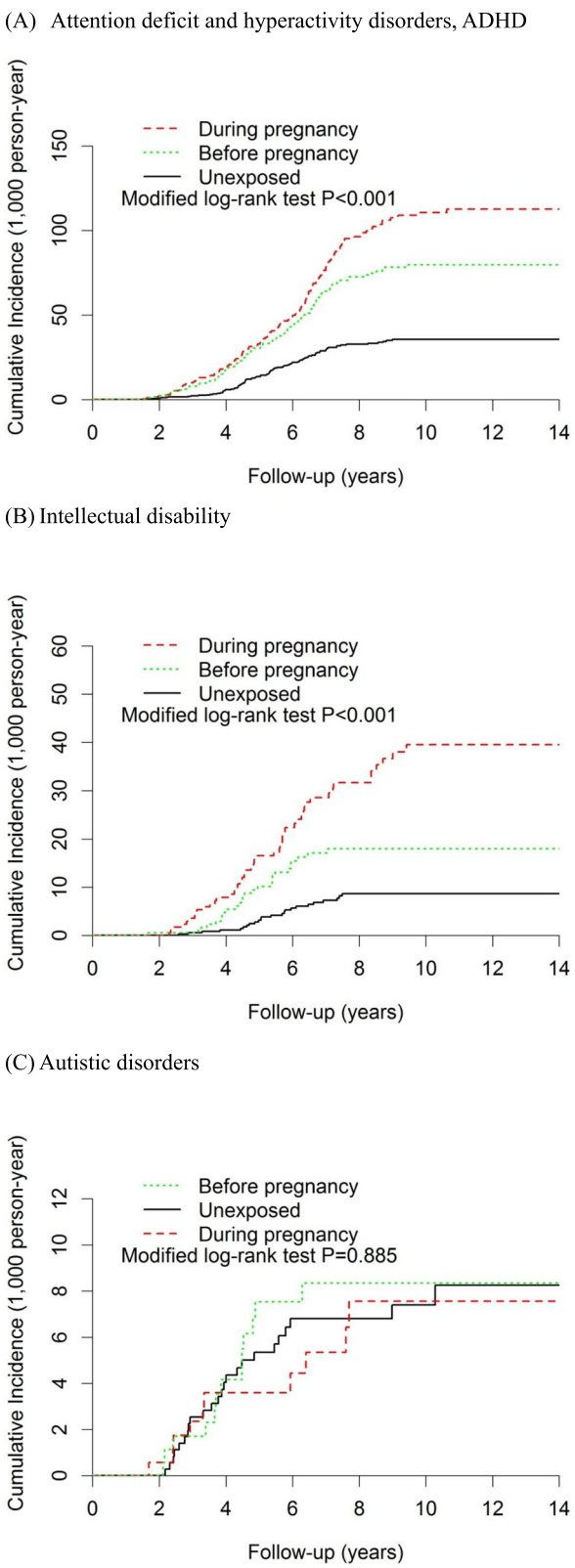
Adjusted analysis model 1: adjusted for child's gender, child's birth year, the year of child's first use of health insurance card, birth orders, birth place, mother's age at giving birth, mother's urbanization levels, mother's education level, mother's marital status, Charlson comorbidity index, mothers' levels of income, mother's days of hospitalization, outpatient visits, medication prescribed during pregnancy, the method of delivery (cesarean or natural birth), and mortality

Adjusted analysis model 2: model 1 + the fifth minute APGAR score, premature birth, and low birth weight

pregnancy group, and such results may indicate the need to detect and intervene before and during pregnancy. While adjusting for covariates, such as preterm birth, low birth weight, and fifth minute APGAR score slightly attenuated the risks for intellectual disability, our study does not separate the effects of substance exposure from those of poor birth outcomes. Therefore, enhancing antepartum screening and addressing the negative effects of social determinants of health remain crucial.

The finding that increased risks of ADHD occurred among children prenatally exposed to illicit substances before or during pregnancy was in line with previous literature reporting higher rates of inattention, hyperactivity [17, 21], psychiatric comorbidities, aggressiveness, externalizing behavioral problems, or poorer academic performances in children with prenatal opioid, heroin, or amphetamine exposures compared with unexposed controls [25, 26]. The neuronal toxic effects of prenatal illicit substance exposures to the fetus' developing brain may partly explain [27]. As shown in human and animal data, exposures to amphetamine or opioid may lead to alterations in brain structure, particularly in white matter microstructure and connectivity in regions like the frontal and limbic areas [28]. These changes might result in cognitive impairments, behavioral issues, and increased risk of ADHD [29, 30]. Genetic heritability should also be taken into account. The comorbidity of ADHD in women with illicit substance use is generally higher than that in the general population [31]. Adoption study showed that the presence of behavioral problem was still higher after adoption in children with prenatal illicit substance exposures than unexposed controls [17]. It is still necessary to consider the interplays of genetic and environmental factors. Reasons for neurobehavioral outcomes among children with prenatal illicit substance exposures might be multifactorial and may also be influenced by parental psychological, socioeconomic status, education, housing, or access to adequate nutrition or medical care of postpartum caregivers [11, 26]. Hence, improving the care quality of families, providing resources and support for substance use treatment and mental health services, increasing identifications for affected teens, and providing medical or social interventions for high-risk individuals may help modify social adaptations or learning conditions in these ADHD children [16, 25].

Our finding of increased risk of intellectual disability in children prenatally exposed to illicit substances during pregnancy was in agreement with past studies describing children with intra-uterine exposures of cocaine, heroin, or opiate having intellectual impairments at preschool or school age [32, 33]. While Baldacchino et al. reported a trend of poorer cognitive level in pre-school children prenatally exposed to opioid than non-exposed in their meta-analysis, they commented that the non-significance may be because of small numbers and sample sizes of primary studies available [11]. Impacts of intrauterine exposures to opioid might be related to dosages, durations, or co-ingestions of other substances. The child's condition may also worsen or improve with age. Comparing outcomes on the same basis may be difficult since various neurobehavioral assessment tools have been applied for different ages among previous studies [34]. Regarding possible mechanisms, where the fetus is



◀ **Fig. 1** Exposure to illicit substances before or during pregnancy and associations with child's ADHD, intellectual disability, and autistic disorders. Exact match data by child's gender, child's birth year, mother's birth year, and child's first use of the health insurance card; during pregnancy exposed ($n=1776$), before pregnancy exposed ($n=1776$), and unexposed ($n=3552$)

exposed to methadone, opioids, heroin, or amphetamine, there is a higher risk of prematurity, and prematurity has been found to be negatively correlated with cognitive, language, visual-spatial developments, or memory [35]. Animal and brain imaging studies have also revealed structural and metabolic abnormalities in the offspring of pregnant rats or humans with intra-uterine exposures of methadone or methamphetamine [15]. Small brain sizes or striatal structures were also observed, and these are all possible risk factors related to intellectual ability [36]. In addition, methadone or amphetamine may increase the releases of serotonin, acetylcholine, norepinephrine, or dopamine in the developing brain [25, 37]. The neurodevelopmental effects observed in animal models might further explain how substances may be toxic to neuronal proliferation, differentiation, or myelination associated with cognitive impairments [15, 25, 38]. These may also be related to impairments of children's cognitive developments, including visual, spatial, attentional, or working memory processes [31]. Some previous studies suggest that the intellectual disability in children prenatally exposed to heroin or opioid was more associated with education or socioeconomic levels of their parents or postnatal caregivers and not to the degree of perinatal complications or comorbidities [17]. However, in Ornoy's study, even cared by adoptive families after births, children with intra-uterine exposures of heroin still performed significantly poorer than that of the unexposed controls [14]. Moe also pointed out that substance-exposed children had weaker visual-motor and perceptual abilities than unexposed controls, and this may still be related to the influences of prenatal adversity [39]. In any case, if adverse effects from prenatal exposures are difficult to prevent, perhaps efforts may be made to support and optimize the postnatal family environment or caregivers' quality after the baby is born to ensure positive effects on the neurocognitive development of these children [14, 17, 39].

We found that after adjusting for obstetric conditions of low birth weight, preterm birth, and fifth minute APGAR scores, in addition to maternal demographic and medical utilizations, the risk of intellectual disability was no longer significantly higher in children exposed to illicit substances compared to unexposed controls. While our findings suggest that improving antenatal physical exams and managements could potentially mitigate

Table 4 Competing risk adjusted Cox regression analysis of intellectual disability, autistic disorder, and attention deficit and hyperactivity disorder (propensity score matched, total $n = 8312$)

Variable	Espoused period	Unadjusted analysis		Adjusted analysis model 1		Adjusted analysis model 2	
		Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
ADHD	Unexposed	1.00		1.00		1.00	
	During pregnancy	1.78 (1.44–2.22)	< 0.001	1.80 (1.45–2.24)	< 0.001	1.77 (1.42–2.21)	< 0.001
	Before pregnancy	1.42 (1.13–1.79)	0.002	1.45 (1.16–1.82)	0.001	1.43 (1.14–1.80)	0.002
Intellectual disability	Unexposed	1.00		1.00		1.00	
	During pregnancy	1.41 (1.01–1.95)	0.041	1.41 (1.01–1.96)	0.042	1.35 (0.97–1.88)	0.077
	Before pregnancy	0.81 (0.55–1.19)	0.274	0.82 (0.56–1.2)	0.298	0.79 (0.54–1.16)	0.233
Autistic disorder	Unexposed	1.00		1.00		1.00	
	During pregnancy	0.93 (0.46–1.90)	0.851	0.93 (0.46–1.89)	0.834	0.88 (0.42–1.83)	0.733
	Before pregnancy	1.06 (0.54–2.07)	0.869	1.05 (0.54–2.06)	0.881	1.05 (0.53–2.05)	0.893

Unexposed and exposed groups distinguished by time were propensity score matched by covariates included child's gender, child's birth year, the year of child's first use of health insurance card, birth orders, birth place, mother's age at giving birth, mother's urbanization levels, mother's education level, mother's marital status, Charlson comorbidity index, mothers' levels of income, mother's days of hospitalization, outpatient visits, medication prescribed during pregnancy, and the method of delivery (cesarean or natural birth)

Adjusted analysis model 1: without regression controlling of fifth minute APGAR score, premature birth, and low birth weight

Adjusted analysis model 2: regression controlling of fifth minute APGAR score, premature birth, and low birth weight

ADHD attention deficit and hyperactivity disorder

some risks, it is important to note that our study does not distinguish between the modifiable effects of substance exposure and confounding by poor birth outcomes. Therefore, early detection of women and pregnant mothers' exposure status and better access to antenatal care remain crucial. Insufficient prenatal care in pregnant women using substances has been associated with delayed managements of obstetric complications [15, 19, 40], which may contribute to poorer fetal health outcomes. Fear of legal repercussions may cause pregnant women who use substances to avoid essential antepartum care [9]. Additionally, a significant proportion of women treated for substance abuse also suffer from depressive or anxiety disorders. Literature showed that among women who received treatment for cocaine and alcohol abuse, 30–70% also had some forms of depressive or anxiety disorder [9, 41]. Our results indicate that adequate prenatal care and interventions, including substance use treatment programs [42] or efforts to reduce comorbidities, may help mitigate long-term adverse outcomes in children. However, focusing on interventions before pregnancy, such as preconception care and early substance use treatment, may also help reducing the risk of neurodevelopmental disorders. Comprehensive antepartum checkups, routine screenings for maternal substance use, early identifications of at-risk pregnancies, and timely psychosocial interventions could further reduce the incidence of these disorders [43–45]. Collaborative efforts among healthcare systems, social services, child welfare, and judicial systems to address unmet health and social needs [46] have been shown to improve child neurodevelopment. Enhancing early identification of pregnant women with substance exposures, reducing barriers to adequate antepartum care, and providing long-term postpartum follow-ups with appropriate psychosocial interventions to high-risk families, children, and their teachers [16] may also be beneficial [44, 45, 47].

Strengths and limitations

Major strengths of this study included the large population-based records that linked mother's and child's data and the follow-up cohorts that assist statistical capabilities and further adjustments of potential confounders. Our propensity score matched multivariate analyses further allow different demographic or comorbid conditions be compared on more equal basis. The multi-dimensional linkages to various population-based datasets provided reliable and detailed information regarding substance exposure, medical diagnoses, and health care utilizations.

Key limitations are that, first, there are still some residual confounders cannot be completely matched even with propensity score matching. Second, possibilities of misclassification bias for outcome ascertainment or selection bias for exposure ascertainment cannot be completely ruled out. For instance, not all individuals using illicit substances would be arrested by the police thus missing some of the exposed. Arrested individuals for substance use during pregnancy may have poorer health, more mental health issues, more severe substance use, weaker social support networks, or face more socioeconomic challenges that complicated their ability to seek help or avoid legal issues compared to those unarrested [44, 45].

However, there is no exact ratio for the ones being prosecuted among pregnant women that used substances, and many cases may not be reported or recorded in official statistics. It is important to note that what is being analyzed is not drug use and developmental outcomes, rather arrest for drugs and developmental outcomes. Nonetheless, this study excluded children who did not have any records of utilizing the health insurance and included dates of the child's first use of health insurance card as one of the matching variables in order to reduce selection biases from the comparison cohort. Third, although we have controlled and matched several covariates, there are still other risk factors, including smoking status, body mass index, alcohol use, or postnatal socioeconomic environment, that were not available in the dataset. One important consideration is the lack of data on alcohol use associated with the potential presence of fetal alcohol spectrum disorder (FASD) among the children studied. FASD encompasses a range of physical, behavioral, and cognitive impairments resulting from prenatal alcohol exposure, including growth deficiencies, central nervous system dysfunction, and neurodevelopmental disorders. Given that alcohol use is often associated with illicit substance use, it is plausible that some of the children in our study may also have been exposed to alcohol in utero. This co-exposure could confound our findings, as the neurodevelopmental outcomes observed might be influenced by both illicit substance use and alcohol exposure. Unfortunately, our study did not have access to data on alcohol use, which limits our ability to fully disentangle the effects of these exposures. Future research should consider including comprehensive data on alcohol use during pregnancy to better understand its impact on neurodevelopmental outcomes. Fourth, this study only included live births, and not stillbirths or miscarriages, into analyses; health hazards in children prenatally exposed to illicit substances use before or during pregnancy may be underestimated. Similarly, under-identification is still possible when there might be pregnant women with illicit substances use not caught by the police and were not included into our study subjects. Generalizations of our finding may be restricted. Finally, this is an observational study to examine whether risks of neurodevelopmental disorders were elevated comparing pregnant women with or without illicit substance use. Possible biological mechanisms still require further investigations.

Conclusions

In this large nationwide cohort study, increased risks of intellectual disability and ADHD were found in children prenatally exposed to illicit substances during or before pregnancy. This change underscores the importance of preventive measures and interventions for the well-being of both the mother and the child. Early detections of pregnant mothers' exposure status and better access to antenatal care remain crucial. Focusing on interventions before and during pregnancy may be helpful in reducing the risk of neurodevelopmental disorders.

Abbreviations

PS-matched	Propensity score-matched
aHR	Adjusted hazard ratio
CI	Confidence interval
ADHD	Attention deficit and hyperactivity disorder
US	United States
IQ	Intelligence quotient
DP	Substance-exposed during pregnancy cohort
BP	Substance-exposed before pregnancy cohort
NHIRD	National Health Insurance Research Database
Center	The "Statistic Science Center"
ID	Identification
IRB	Institutional Review Board
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
CCI	Charlson's comorbidity index
APGAR	American Pediatric Gross Assessment Record

Supplementary Information

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Additional file 1: Table S1 Competing risk adjusted Cox regression analysis of attention deficit and hyperactivity disorder by drug type during pregnancy.

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None.

Authors' contribution

Authors Vincent Chin-Hung Chen and Charles Tzu-Chi Lee designed the study and wrote the protocol. Author Charles Tzu-Chi Lee conducted and checked the statistical analyses. Author Shu-I Wu wrote the first draft. All authors contributed to the writing and have approved the final manuscript.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

This study linked the Household Registration files to obtain the mother's basic demographic data, the National Health Insurance Research Database (the NHIRD, a population-based and comprehensive healthcare database that contains de-identified registration files and claims data from the National Health Insurance program in Taiwan) to obtain the mother's and the child's

health and medical utilizations and medical expenses from emergency visits, outpatient and hospitalization records, the "Substance Abuse Control Database" that contained crime records for information on illicit substance uses in women, the Nation's Birth Registration and Birth Notification files, and the Death Registration files. All personal information, including ID numbers and other data, was encrypted, ensuring no specific identifications could be obtained. The research team went into the Science Center, performing statistical analyses only on the data the Center provided by the Center's regulations. Since no personal identifications are possible, informed consent was waived by the Institutional Review Board of National Taiwan Normal University (IRB number: 202002HM010).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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