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Association between general anesthesia for cesarean delivery and subsequent developmental disorders in children: a nationwide retrospective cohort study

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Abstract

Background Exposure to general anesthetics (GA) in early childhood is associated with developmental disorders. However, few studies have addressed in-utero exposure to anesthetics during delivery and subsequent developmental disorders in the offspring. This study aimed to investigate whether GA for cesarean delivery is associated with developmental disorders in children.

Methods Using data retrieved from the National Health Insurance Research Database linked to the Birth Reporting Database and the Maternal and Child Health Database between 2015 and 2020, this nationwide retrospective cohort study compared the incidence of developmental disorders following cesarean delivery under GA with that under neuraxial anesthesia (NA). Developmental disorders were diagnosed using the corresponding International Classification of Diseases codes traced 2–6 years after delivery.

Results After excluding twins, children born with congenital anomalies or diseases and those with missing data, 325,309 eligible singleton pregnancies delivered through cesarean section under either GA or NA were enrolled. Of the total, 6973 of them were delivered under GA and 318,336 under NA. After propensity score-based fine stratification weighting with a model including age, socioeconomic deprivation, gestational status, infant sex, preterm delivery, low birth weight, and cesarean delivery duration, children delivered under GA were associated with a higher risk of developmental disorders diagnosed within 2 years (adjusted odds ratio [aOR], 1.17; 95% confidence interval [CI], 1.07–1.28), 3 years (aOR, 1.12; 95% CI, 1.04–1.21), and 4 years (aOR, 1.12; 95% CI, 1.04–1.21) compared with those under NA. This association was no longer present when the confounding effect of Apgar scores was included in the propensity-score model.

Conclusions GA for cesarean delivery may be associated with developmental disorders diagnosed within 2–4 years after birth manifested through poorer 1- and 5-min Apgar scores. There is no evidence of a direct relationship between GA-related neurotoxicity and subsequent developmental disorders.

Keywords Anesthesia, Apgar scores, Developmental disorders, Neurotoxicity

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Background

The global rate of cesarean section delivery has continuously risen from about 7% in 1990 to 21% in 2021 [1]. While neuraxial technique has been widely accepted as the optimal anesthesia for cesarean delivery, general anesthesia (GA) could be useful and inevitable in certain situations, particularly in emergency situations or patients with contraindications to neuraxial anesthesia (NA) [2]. In-utero exposure to general anesthetics raises a concern on potential neurotoxicity to the fetus. The United States Food and Drug Administration issued a warning in 2016 that exposure to general anesthetics at an early age or during the third trimester of pregnancy may affect the development of the brains of children [3].

Preclinical evidence shows that general anesthetic exposure during the rapid synaptogenesis period could result in neurodegeneration and long-term neurological impairment in animals, including primates, by accelerating apoptosis [4, 5]. Current evidence shows that almost every anesthetic, either inhalational or intravenous, could lead to dose-dependent neuroapoptosis [6]. A systematic review supported that children with multiple GA exposure before 4 years of age might have an increased risk of neurodevelopmental delay [7]. Since most anesthetics are poorly ionized and can cross the placenta, pregnant women who require surgical intervention under GA may expose the fetus to potentially neurotoxic agents. Nevertheless, human studies on the long-term neurodevelopmental effects of perinatal exposure to anesthetics have shown mixed results. While some observational studies have reported associations between anesthesia during pregnancy and autism spectrum disorders, a systematic review and meta-analysis concluded that these associations could not be confirmed because of varying controls for confounding factors and the limited number of studies available [8]. Accumulation of evidence in this field is necessary to further clarify the relationship. Given that GA is sometimes required for cesarean delivery, it is crucial to determine whether anesthetic exposure during delivery is related to subsequent developmental disorders.

In this retrospective cohort study, we aimed to investigate whether GA for cesarean delivery is associated with subsequent developmental disorders in the offspring by analyzing a nationwide registry and claims database. We hypothesized that children delivered through cesarean section under GA might be associated with a higher risk of developing developmental disorders in the following years than those delivered under NA.

Methods

Data source

The data analyzed in this study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD), Birth Reporting Database (BRD), and Taiwan Maternal and Child Health Database (TMCHD) from 2015 to 2020. The NHIRD is based on the National Health Insurance Program that was implemented in 1995 and covers 99% of the Taiwanese population. It contains information on age, socioeconomic status, International Classification of Diseases (ICD) codes for diagnoses and procedures, dates of admission and discharge, and insurance claims. The BRD collects information of all live births and stillbirths that were delivered in Taiwan with a weight of > 500 g or a gestational age of > 20 weeks. This dataset provides information on birth weight, gestational age, delivery method, Apgar score, and maternal age at delivery. The TMCHD provides a link between mothers and their offspring. All identifiers were encrypted before the data were released by the Ministry of Health and Welfare to ensure privacy. This study was exempt from full review by the Institutional Review Board of Chi Mei Medical Center (11,105-E02), and a waiver of the requirement for obtaining patient consent was granted due to the use of anonymized data. This research was conducted in accordance with the Helsinki Declaration [9].

Study design

In this population-based retrospective cohort study, women who delivered via cesarean section between 2015 and 2020 in Taiwan were identified using diagnosis-related group codes (370, 371). Patient data was traced back to 1 year before the delivery for demographic characteristics and underlying diseases, and living singletons were followed up until 2021 for the diagnosis of developmental disorders. Participants with missing or incomplete data were excluded. Children with congenital syphilis, epilepsy, cerebral palsy, extreme immaturity, mental retardation, or chromosomal anomalies were excluded to focus on the relationship between anesthesia during cesarean delivery and subsequent developmental disorders (Fig. 1).

The participants were divided into GA and NA groups. Anesthesia for cesarean delivery was recognized using payment codes: 96020C–96022C for GA and 96005C–96008C for NA, including spinal and epidural techniques.

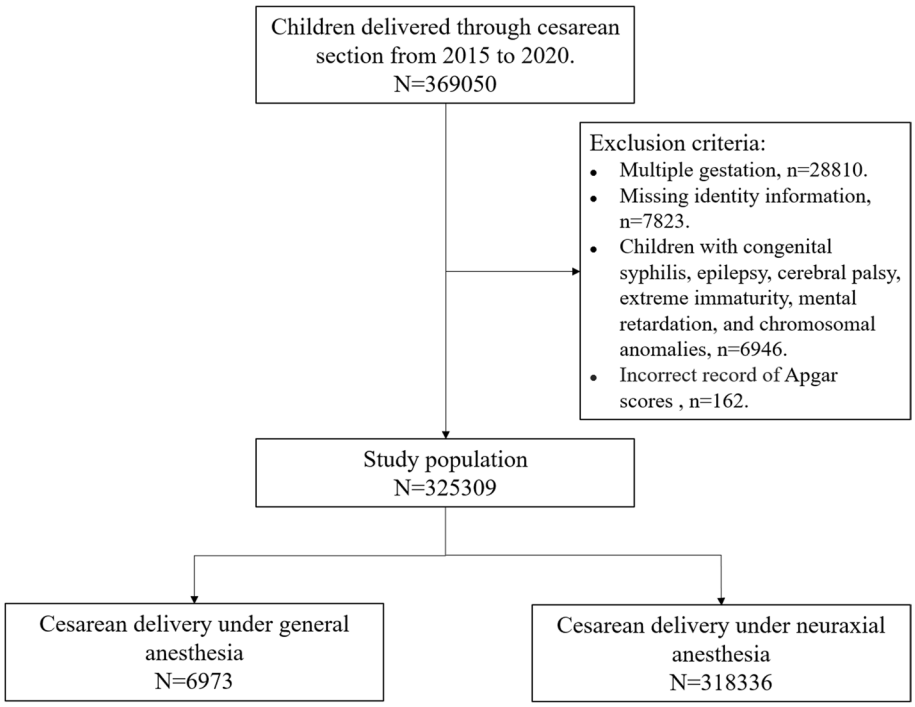

Fig. 1 Flow diagram of the study

Outcomes

The primary outcome was the first diagnosis of any developmental disorder, including pervasive and specific developmental disorders, attention-deficit hyperactivity disorder, conduct disorder, emotional disorders, selective mutism, Tourette's disorder, hearing loss, speech disturbances, alexia, delayed milestones, and lack of expected normal physiological development. Developmental disorders were identified using the ICD, 9th or 10th Revision, Clinical Modification (ICD-9 CM or ICD-10 CM) codes (see Additional file 1) assigned to outpatient clinic visits or admissions. Developmental disorders were further categorized into emotional disorder, lack of expected normal physiological development, psychomotor issue, hearing impairment, reading disorder, and speech disturbance. The definitions, incidences, and risk differences of each developmental disorder category between children in the general and neuraxial anesthesia groups were presented in Additional file 2.

Covariates

The covariates included maternal age at delivery, socioeconomic deprivation, maternal comorbidities, obstetric conditions, and fetal status at birth (Table 1). Age was stratified into four categories: < 30, 30–34, 35–39, and ≥ 40 years. Individuals certified by the authority as low income and socioeconomic vulnerable were marked as experiencing socioeconomic deprivation in the dataset. Gestational status, including coagulopathy or thrombocytopenia, hypertension or gestational hypertension, preeclampsia or eclampsia, diabetes mellitus or gestational diabetes mellitus, obesity, fetal distress, congenital anomalies, premature rupture of membranes, placenta previa, placental abruption, antepartum hemorrhage, and late pregnancy, was identified using the ICD-9 CM codes before 2016 and ICD-10 CM codes thereafter (see Additional file 3). According to the definition of the ICD-10-CM code, late pregnancy, including post-term (O48.0) and prolonged pregnancy (O48.1), refers to pregnancy extending beyond 40 completed weeks of gestation. Gestational age, preterm delivery, birth weight, low birth weight, 1-min and 5-min Apgar score, duration of cesarean delivery, length of hospital stay of the infant, and infant sex were also included as covariates. This study was conducted in accordance with the following guidelines: Strengthening the Reporting of Observational Studies in Epidemiology, and Reporting of Studies Conducted Using the Observational Routinely Collected Health Data [10, 11].

Statistical analyses

The demographic characteristics of the children in the GA and NA groups are shown as numbers (%) for categorical variables and median (Q1–Q3) for continuous variables in Table 1. Differences in demographic characteristics between the groups were tested using Pearson's

Table 1 Demographic information of children delivered via cesarean section in Taiwan from 2015 to 2020

	GA, *n* (%)	NA, *n* (%)	*P*-value[a]
Overall, *n*	6973	318,336	
Maternal age at delivery (years)			
< 30	1797 (25.77)	84,525 (26.55)	< 0.001
30–34	2403 (34.46)	119,849 (37.65)	
35–39	2224 (31.89)	93,194 (29.28)	
≥ 40	549 (7.87)	20,768 (6.52)	
Socioeconomic deprivation	37 (0.53)	875 (0.27)	< 0.001
Gestational status			
Coagulopathy or thrombocytopenia	187 (2.68)	1218 (0.38)	< 0.001
Hypertension or gestational hypertension	503 (7.21)	11,134 (3.50)	< 0.001
Preeclampsia or eclampsia	634 (9.09)	10,038 (3.15)	< 0.001
Diabetes mellitus or gestational diabetes mellitus	1057 (15.16)	23,521 (7.39)	< 0.001
Obesity	28 (0.40)	457 (0.14)	< 0.001
Fetal distress	651 (9.34)	5893 (1.85)	< 0.001
Congenital anomalies	349 (5.01)	3477 (1.09)	< 0.001
Premature rupture of membranes	624 (8.95)	11,946 (3.75)	< 0.001
Placenta previa	783 (11.23)	14,920 (4.69)	< 0.001
Placental abruption	456 (6.54)	3176 (1.00)	< 0.001
Antepartum hemorrhage	230 (3.30)	4290 (1.35)	< 0.001
Late pregnancy	513 (7.36)	11,006 (3.46)	< 0.001
Delivery status			
Gestational age (weeks), median (Q1–Q3)	38 (36–39)	38 (37–39)	< 0.001
Preterm delivery (< 37 weeks)	1976 (28.34)	27,281 (8.57)	< 0.001
Birth weight (g), median (Q1-Q3)	2930 (2496–3260)	3065 (2810–3340)	< 0.001
Low birth weight (< 2,500 g)	1749 (25.08)	23,275 (7.31)	< 0.001
1-min Apgar score	8 (7–9)	8 (8–9)	< 0.001
< 7	1553 (22.27)	6598 (2.07)	< 0.001
≧7	5420 (77.73)	311,738 (97.93)	
5-min Apgar score	8 (7–10)	8 (8–10)	< 0.001
< 7	1523 (21.84)	6496 (2.04)	< 0.001
≧7	5450 (78.16)	311,840 (97.96)	
Surgery duration (hours)			
< 2	6215 (89.13)	312,727 (98.24)	< 0.001
2–4	623 (8.93)	5508 (1.73)	
> 4	135 (1.94)	101 (0.03)	
NICU admission	884 (12.68)	5444 (1.71)	< 0.001
Length of hospital stay of the infant (days)			
0	5551 (79.61)	306,789 (96.37)	< 0.001
1–6	471 (6.75)	5294 (1.66)	
≧7	951 (13.64)	6253 (1.96)	
Infant sex			
Male	3807 (54.60)	167,370 (52.58)	0.001
Female	3166 (45.40)	150,966 (47.42)	

GA general anesthesia, *NA* neuraxial anesthesia, *NICU* neonatal intensive care unit

[a] *P*-value was derived from Pearson's chi-square test for categorical variables and Wilcoxon's rank sum test for continuous variables

chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The enrolled children were followed up from 2 to 6 years after birth for the diagnosis of developmental disorders. The incidences of developmental disorders were compared between the groups using Pearson's chi-square test. The categories of

developmental disorders and risk differences between the two groups are presented in Additional file 2.

Because there were obvious differences in the sample sizes and underlying conditions between children exposed to GA and NA during cesarean delivery, we introduced propensity score-based fine stratification weighting (PS-FSW) to reduce residual bias and to estimate the average treatment effect of anesthesia exposure during delivery on subsequent developmental disorders in the following years [12, 13]. The propensity score was assigned as the probability of exposure to GA or NA, with the covariates included in the logistic regression model. To control for potential confounding effects, the adjusted covariates were delineated across three models as follows: (1) Model A accounted for perinatal factors, including maternal age at delivery, socioeconomic deprivation, gestational status, infant sex, preterm delivery, low birth weight, and the duration of cesarean delivery. (2) Model B included these perinatal factors and also incorporated neonatal conditions at birth, adding Apgar scores at 1 and 5 min. (3) Model C further included short-term neonatal conditions, integrating the covariates from Model B with NICU admission and the length of hospital stay of the infant. These models were developed by sequentially adding covariates to address confounding factors at different stages—during pregnancy, at birth, and after birth—to control for variables that might affect the outcomes more comprehensively.

After trimming participants from non-overlapping regions of the propensity score distribution, there were 100 equally sized strata based on the distribution [12]. By using the weighted generalized linear models with logic link function, the estimated effect of anesthesia on the occurrence of developmental disorders was calculated using robust variance estimates to account for weighting odds ratios (OR) with 95% confidence intervals (CIs). CIs that did not overlap with the value of one were considered statistically significant. The c-statistic was used to measure the overall covariate balance achieved through PS-FSW. A c-statistic of 0.5 suggests no predictive power, implying that the two groups are similar in terms of the covariates being considered. Before applying the PS-FSW approach, the c-statistics was up to 0.7, which indicates a certain level of imbalance or difference in the covariate distribution between the GA and NA groups. After applying the PS-FSW approach, the c-statistic decreased to close to 0.5, demonstrating that the covariate effects were now balanced between the two groups (Additional file 4). The balance achieved through the PS-FSW approach means that any associations observed between the type of anesthesia (GA or NA) and developmental disorders were not confounded by the covariates included in the models. In other words, the PS-FSW approach successfully controlled for potential confounding variables, allowing for a clearer assessment of the relationship between anesthesia type and developmental disorders [13–15].

A subgroup analysis was conducted to assess whether the results remained consistent or varied for children with 5-min Apgar scores <7 and ≥ 7, serving as a sensitivity analysis to evaluate robustness [16]. The interaction term was assessed using the Type III test and is detailed in Additional File 5. The significance of an interaction term was tested to assess its contribution to the model using a Wald chi-squared test. The Type III (Wald) test employed here is a chi-square statistics used to test the null hypothesis that the interaction term is equal to 0. A p-value less than 0.05 rejects this null hypothesis, indicating that the interaction term is statistically significant and not equal to 0 [17–19]. All statistical analyses were performed using the SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

A total of 325,309 singleton pregnancies delivered via cesarean section between 2015 and 2020 that met the eligibility criteria were retrieved from this dataset. Of the total, 6973 (2.14%) were delivered under GA and 318,336 (97.86%) under NA. For the GA group, 6842 (98.12%) patients were maintained with volatile agents, while 131 (1.88%) received total intravenous anesthesia (TIVA). In the NA group, 223,730 (70.28%) received spinal anesthesia, and 94,606 (29.72%) received epidural anesthesia. The demographic characteristics of the enrolled participants are shown in Table 1. Participants in the GA group exhibited a higher proportion of socioeconomic deprivation (0.53% vs. 0.27%, $p<0.001$) and gestational status, including coagulopathy or thrombocytopenia, hypertension or gestational hypertension, preeclampsia or eclampsia, diabetes mellitus or gestational diabetes mellitus, obesity, fetal distress, congenital anomalies, premature rupture of membranes, placenta previa, placental abruption, antepartum hemorrhage, and late pregnancy. In addition, infants in the GA group experienced worse delivery outcomes, characterized by preterm delivery, extended cesarean delivery duration, lower birth weight, worse Apgar scores at 1 and 5 min, and a prolonged length of hospital stay of the infant. The proportion of male newborns was higher in the GA group than in the NA group (54.6% vs. 52.58%, $p=0.001$).

The numbers and incidences of developmental disorders are shown in Table 2. The incidences of developmental disorders diagnosed within 2, 3, 4, 5, and 6 years after birth were higher in children exposed to GA during delivery than in those exposed to NA. The estimated effect sizes were calculated after balancing confounders

Table 2 The number of enrollees and incidences of developmental disorders in children delivered via cesarean section under GA or NA

	Total		General anesthesia		Neuraxial anesthesia		*P*-value
	Enrollees, *n*	Developmental disorders, *n* (%)	Enrollees, *n*	Developmental disorders, *n* (%)	Enrollees, *n*	Developmental disorders, *n* (%)	
Total enrollees, *n*	325,309		6973		318,336		
Years of follow-up							
2 years	284,468	17,935 (6.30)	6336	642 (10.13)	278,132	17,293 (6.22)	< 0.001
3 years	237,854	26,784 (11.26)	5617	897 (15.97)	232,237	25,887 (11.15)	< 0.001
4 years	188,044	28,168 (14.98)	4752	962 (20.24)	183,292	27,206 (14.84)	< 0.001
5 years	129,569	24,474 (18.89)	3291	796 (24.19)	126,278	23,678 (18.75)	< 0.001
6 years	65,960	14,847 (22.51)	1614	456 (28.25)	64,346	14,391 (22.37)	< 0.001

[a] *P*-value was derived from Pearson's chi-square test for categorical variables and Wilcoxon's rank sum test for continuous variables

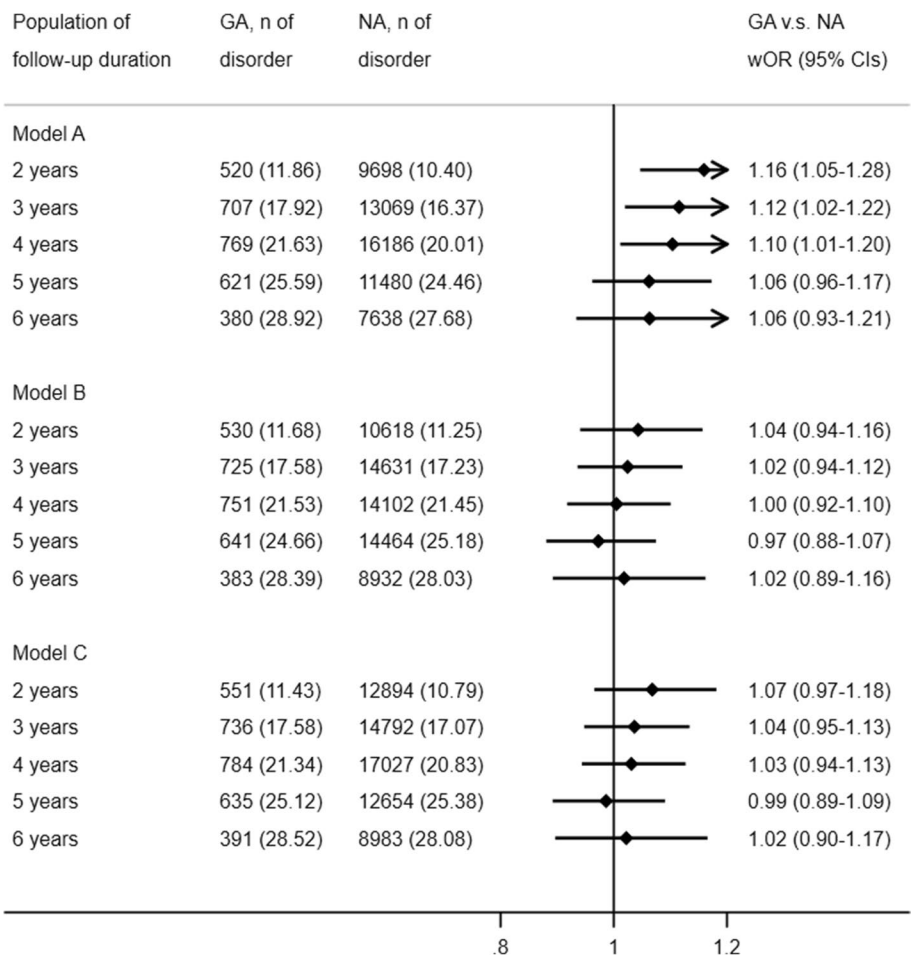

Fig. 2 Estimated effect of GA for cesarean delivery on the development of developmental disorders in children compared with NA

with PS-FSW (Fig. 2). When the propensity score was derived from Model A, GA for cesarean delivery was associated with a higher risk of developmental disorder within 2 years (OR, 1.16; 95% CI, 1.05–1.28), 3 years (OR, 1.12; 95% CI, 1.02–1.22), and 4 years (OR, 1.10; 95% CI, 1.01–1.20) than NA. For follow-up periods extending to 5 and 6 years, no significant association was found between GA for cesarean delivery and subsequent developmental

disorders. The observed associations between GA for cesarean delivery and subsequent developmental disorders disappeared upon incorporating Apgar scores as one of the covariates to achieve balance through PS-FSW with Model B and Model C.

To examine whether the association between anesthesia for cesarean delivery and subsequent developmental disorders could be modified by neonatal condition at birth, we performed a subgroup analysis of the 5-min Apgar score that was < 7 or ≥ 7 as a sensitivity test. No significant association was found between anesthesia for cesarean delivery and subsequent developmental disorders in either subgroup (Fig. 3). We also checked the interaction terms of 5-min Apgar score and anesthesia and found it significant with follow-up timeframes of 2, 3, 4, 5, and 6 years after birth.

Discussion

In this nationwide retrospective cohort study, we found that children delivered via cesarean section under GA had a higher risk of developmental disorders within 2, 3, and 4 years of birth compared to those delivered under NA. However, this association diminished after balancing the confounding effect of Apgar score through PS-FSW.

Early exposure to potentially neurotoxic anesthetics and related consequences has long been a concern for both clinical practitioners and parents. Substantial preclinical studies indicate that anesthesia neurotoxicity may harm the neonatal brain, causing neuronal cell apoptosis and deficits in long-term cognitive function in animals, including non-human primates [4, 20]. Despite cumulative evidence from animal research, it remains inconclusive whether exposure to GA in early childhood could harm the immature brain and neurodevelopment [21, 22]. Three large population-based studies reported that a single brief anesthesia exposure in early childhood might not be associated with any long-term neurodevelopmental deficits [23–25]. Similar conclusions were drawn by the GAS trial, which showed no evidence of an increased risk of adverse neurodevelopmental outcome at 2 and 5 years of age when comparing children who underwent less than an hour of GA in infancy with those who underwent regional anesthesia [26, 27]. While limited exposure to anesthetics seemed to be safe, another population-based cohort study revealed that children exposed to GA before 2 years old were associated with a higher risk of developmental delay, particularly for those with multiple exposures and longer durations [28]. Besides the amount of exposure, studies evaluating a wide range of outcomes might have contributed to mixed results in this field. A systematic review and meta-analysis examined the associations between exposure to GA and domain-specific neurodevelopmental outcomes in children. It found that children with any exposure had worse behavioral problem scores and higher incidences of neurodevelopmental disorder; furthermore, the associations could differ based on the neurodevelopmental domain [29]. Another review pooling results from prospective studies concluded that single GA exposure was associated with increased behavioral problems without a difference in general intelligence [30].

Because most general anesthetics readily cross the placenta and reach the fetus [31], fetuses of pregnant women undergoing surgery with GA may expose the immature brain to potentially neurotoxic agents, resulting in long-term consequences. Similarly, studies on fetal exposure to anesthetics during pregnancy, comparable to exposure in early childhood, have yielded mixed results regarding associations with long-term neurodevelopmental outcomes. A secondary analysis of a randomized controlled trial showed no significant association between GA for cesarean delivery and overall neurodevelopmental delay except for higher odds of developing severe motor delay [32]. Huberman Samuel et al. investigated 347 children with autism spectrum disorder and suggested that the disorder could be attributed to GA exposure during cesarean delivery [33]. However, in a subsequent meta-analysis, the authors reported that there was no solid evidence supporting an association between anesthesia during labor and autism spectrum disorder [8]. The mixed results across different studies may be attributed to variations in the control of confounding factors. In our study, the incidences of any developmental disorders and each of the six categories were found significantly higher for children in the GA group compared to those in the NA group. To minimize the confounding effects of perinatal factors, we first balanced demographic factors, gestational status, preterm delivery, low birth weight, and the duration of cesarean delivery using PS-FSW (Model A). We found that GA for cesarean delivery was associated with a higher risk of developmental disorders in children up to 4 years after birth, even after balancing confounders through PS-FSW with Model A.

While direct neurotoxicity from anesthetics reported in pre-clinical models might not be sufficiently extrapolated to human patients [34], previous literature consistently links poor fetal condition to higher risks of subsequent developmental vulnerabilities [35–37]. To address this, we incorporated Apgar scores into the propensity score model B. After balancing confounding factors through fine stratification weighting in Model B, the association between anesthesia and developmental disorders diminished. Including the length of hospital stay of the infant and NICU admission in Model C yielded consistent results. Low Apgar score can be attributed to a myriad of risk factors in addition to GA [38], making it challenging

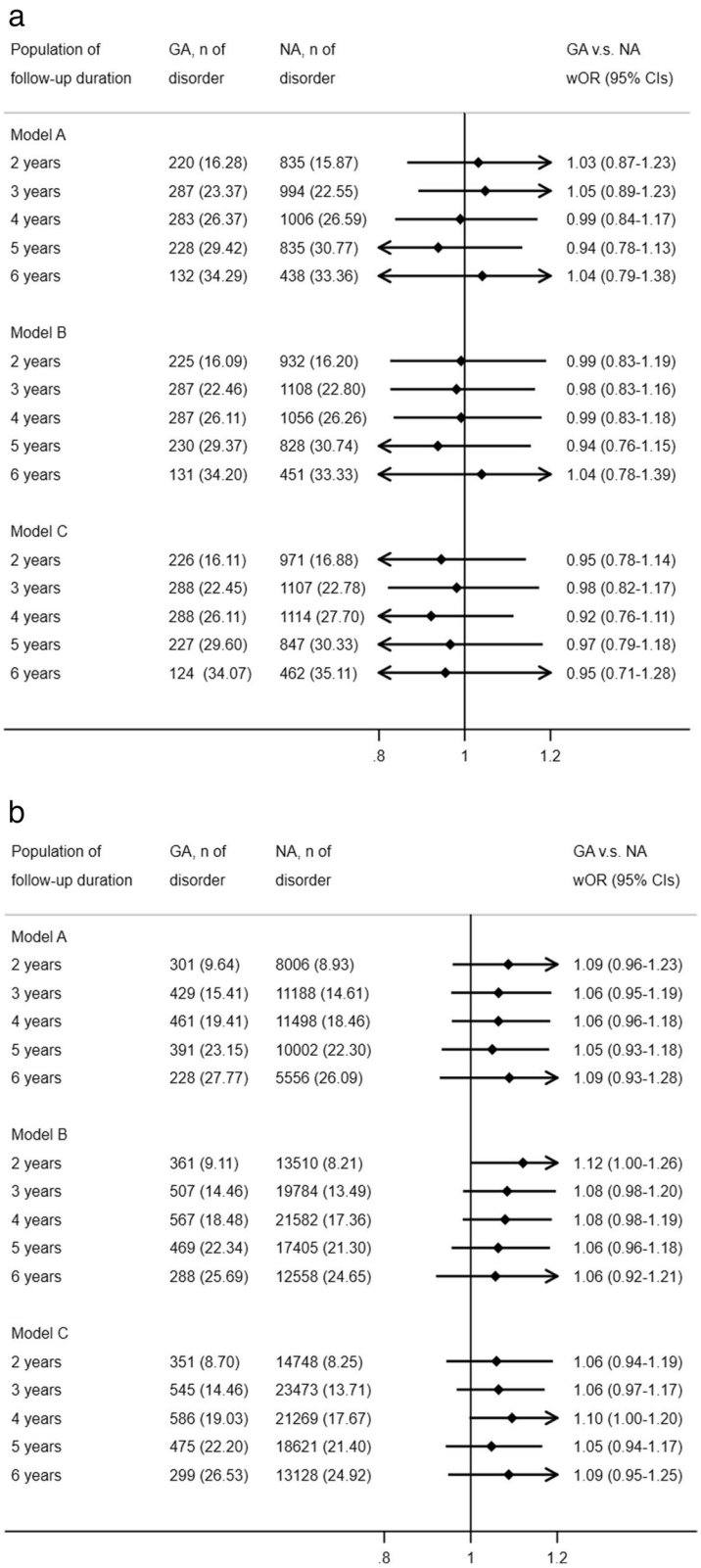

Fig. 3 Subgroup analysis of the risk of developing developmental disorders comparing children delivered through cesarean section under GA and children delivered under NA with a 5-min Apgar score of (**a**) < 7 or (**b**) ≥ 7

to elucidate its role in the relationship between anesthesia exposure and subsequent developmental disorders. Since a low Apgar score has been well-established as an effective predictor of developmental disorders [36, 37], it is reasonable that balancing for Apgar score might mitigate the association between anesthesia and subsequent developmental disorders.

To further clarify the role of Apgar score, we performed a subgroup analysis using a 5-min Apgar score threshold of 7 and found no significant association between anesthesia for delivery and developmental disorders. It appears that if we could ensure infants were born with similar 5-min Apgar scores, the differences between general and neuraxial anesthesia for cesarean delivery on the occurrence of subsequent developmental disorders might be negligible; nevertheless, it is unlikely to manipulate Apgar scores in a clinical scenario. Children delivered via cesarean section under GA are more likely to present with a low 5-min Apgar score [39]. This is often due to emergency cesarean delivery necessitated by fetal distress or the effects of general anesthetics crossing the placenta, which can impair respiratory function and result in poor Apgar scores at birth. Considering the complexity of this relationship, a conservative conclusion should be drawn when determining the association between anesthesia exposure, Apgar scores, and developmental disorders.

Limitations

Despite the resilience to sampling errors in the analysis of a nationwide database, a few limitations need to be mentioned. First, baseline imbalances may be a concern. Compared to NA, the proportion of patients who underwent GA for cesarean delivery was much lower, and the population could be quite different from that of children delivered under NA. As a result, we balanced the confounders using PS-FSW, which is advantageous in circumstances where the exposure prevalence is low, to cope with confounding effects [13]. Although we balanced numerous confounders using PS-FSW, there may still be discrepancies due to some unmeasured confounding factors not recorded in the NHIRD, such as the involvement of reproductive procedures and the time from induction to delivery. Further studies are needed to evaluate the influence of these unmeasured covariates. Second, this database only allowed us to trace the enrollees for up to 6 years. Although developmental disorders diagnosed more than 6 years after birth could not be detected, the current data implied no significant effect of anesthesia over 4 years. Adverse events occurring after 6 years may not be attributable to a single anesthetic exposure during delivery. Third, misclassification bias due to incorrect coding could be a concern. Since clinical practitioners may occasionally make errors in entering correct ICD codes when managing heavy workloads, the accuracy and validity of the data might be questioned. Nevertheless, the codes recorded in the claims database were reviewed and validated by auditors to ensure claim accuracy. The ICD codes used to identify the primary outcome had been validated in a previous study using a two-step consensus development technique with a panel of five experts, including medical doctors specializing in early rehabilitation, psychiatry, and medical informatics [40]. Several validation studies conducted to assess the accuracy of diagnosis codes in the NHIRD have demonstrated modest to high sensitivity and positive predictive values for these codes [41]. In addition, a literature review of 50 published validation studies of diagnosis codes and related algorithms for a wide range of health outcomes in Taiwan reported positive predictive values ranging from 80 to 99% [42]. Fourth, inherently limited by the observational design, an association instead of a causal relationship could be concluded among anesthesia exposure during delivery and subsequent developmental disorders. Additionally, whether poor Apgar scores were a consequence of GA or a factor that led to the decision of GA for cesarean delivery remains uncertain. Nevertheless, the results of this study may help illuminate how GA for cesarean delivery could be related to developmental disorders in children and reveal the moderating effect of Apgar scores. Fifth, there was heterogeneity within both the GA and NA group. GA techniques can be further classified into those maintained with volatile agents or propofol infusion, while NA techniques include spinal anesthesia, epidural anesthesia, and combined spinal–epidural anesthesia. We acknowledge that investigating each technique in further detail would be valuable and contribute significantly to the field. However, our primary objective was to clarify the differences between GA and NA for cesarean delivery regarding the occurrence of subsequent developmental disorders from a broader perspective. Comparing each technique within a single study might be distracting. Further research with appropriate study designs is needed to focus on different techniques specifically. Finally, the results derived from this national database may not be directly generalizable to other countries with differing economic conditions, social structures, and racial demographics. Further studies from various countries are needed to clarify the relationship between anesthesia for cesarean delivery, Apgar scores at birth, and subsequent developmental disorders.

Conclusions

In conclusion, GA for cesarean delivery was associated with a higher risk of subsequent developmental disorders in children aged 2–4 years than NA after PS-FSW for demographic characteristics, gestational status, and

cesarean delivery duration. However, when balancing Apgar score as one of the covariates, the association between GA for cesarean delivery and subsequent developmental disorders was no longer present. It is unclear whether this represents an effect of GA on neonatal Apgar scores or, more likely, represents the compromised in-utero status leading to GA for urgent or emergent cesarean delivery. There is no evidence of a direct relationship between GA-related neurotoxicity and subsequent developmental disorders. Although a causal relationship between anesthetic exposure during delivery and long-term developmental disorders in children cannot be inferred, the results of this study may guide further studies for clinical decision-making.

Abbreviations

NHIRD	National Health Insurance Research Database
BRD	Birth Reporting Database
TMCHD	Taiwan Maternal and Child Health Database
ICD	International Classification of Diseases
ICD-9 CM	International Classification of Diseases 9th Revision, Clinical Modification
ICD-10 CM	International Classification of Diseases 10th Revision, Clinical Modification
OR	Odds ratios
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03886-6.

Additional file 1. The diagnostic criteria for developmental disorders.

Additional file 2. The definitions, incidences, and risk differences of each developmental disorder category between children in the general and neuraxial anesthesia group.

Additional file 3. The diagnostic criteria for the covariates.

Additional file 4. Balance of the covariates between the general and neuraxial anesthesia group before and after propensity score based fine stratification weighting approach. [a] Before balancing covariates by using PS-FSW approach, the c-statistic derived from logistic regression by adjusted all covariates.; [b] C-statistic close to 0.5 indicates that there was balance in covariate effects between the GA and NA groups.; Model A includes maternal age at delivery, socioeconomic deprivation, gestational status, infant sex, preterm delivery, low birth weight, and cesarean delivery duration as covariates in the weighting score. Model B includes maternal age at delivery, socioeconomic deprivation, gestational status, infant sex, preterm delivery, low birth weight, cesarean delivery duration, and Apgar score as covariates in the weighting score. Model C includes maternal age at delivery, socioeconomic deprivation, gestational status, infant sex, preterm delivery, low birth weight, cesarean delivery duration, Apgar score, NICU admission, and length of hospital stay of the infant as covariates in the weighting score.; PS-FSW: propensity score-based fine stratification weighting.

Additional file 5. The interaction effect between the anesthesia group and 5-minute Apgar score. [a]aOR (adjusted odds ratio): The interaction effect between anesthesia group and Apgar score 5 mins derived from logistic regression and adjusted by maternal age, socioeconomic deprivation, gestational status, infant sex, preterm delivery, low birth weight, cesarean delivery duration, NICU admission, and length of hospital stay of the infant as covariates.; [b] Type III test employed here is Wald Chi-square statistics used to test the null hypothesis that the interaction term is equal to zero. A p-value less than 0.05 rejects this null hypothesis, indicating that the interaction term is statistically significant and not equal to zero.

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Authors' contributions
YCC, PHT, and CHY were responsible for the study conception and design. YCC, FWL, and CHH were responsible for data collection, management, and analyses. All authors were involved in data interpretation. YCC and CHY drafted the initial manuscript, which was reviewed and critically revised by all authors. All authors approved the final manuscript as submitted.

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Data availability
The data that support the findings of this study are available from the Collaboration Center of Health Information Application, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Ministry of Health and Welfare.

Declarations

Ethics approval and consent to participate
This study was exempt from full review by the Institutional Review Board of Chi Mei Medical Center (11105-E02), and a waiver of the requirement for obtaining patient consent was granted due to the use of anonymized data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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