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ORIGINAL RESEARCH

Exposure to anesthesia during delivery and risk of autism spectrum disorder: A retrospective cohort study

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Abstract

Introduction: Despite the growing use of pain management during delivery, evidence regarding the association between different modes of obstetric anesthesia and autism spectrum disorder in offspring is mixed.

Material and Methods: We conducted a retrospective cohort study of 98 630 singleton live births at a single hospital (2011–2019), with follow-up through January 2023. Participants were grouped by delivery and anesthesia type: (1) vaginal delivery without analgesia, (2) vaginal delivery with epidural, (3) cesarean with neuraxial anesthesia, and (4) cesarean with general anesthesia. Autism spectrum disorder (ASD) diagnosis was the primary outcome. Kaplan–Meier plots and Cox regression were used to assess cumulative incidence and hazard ratios.

Results: Of the cohort (51.2% male, 62.0% Bedouin), 21.2% were born by vaginal delivery with epidural, 3.8% by cesarean with neuraxial anesthesia, and 11.4% by cesarean with general anesthesia. Cumulative ASD incidence was higher in all exposure groups (vaginal delivery with epidural: 1.25%, cesarean with neuraxial anesthesia: 1.56%, cesarean with general anesthesia: 1.50%) than in vaginal delivery without analgesia (0.55%). Nevertheless, after adjustment for covariates, only cesarean with general anesthesia was significantly associated with increased ASD risk (aHR = 1.571; 99% CI: 1.12–2.22).

Conclusions: These findings suggest that general anesthesia during cesarean delivery, but not neuraxial anesthesia or epidural use, might be associated with ASD risk. Further studies are needed to understand the underlying mechanisms.

KEYWORDS
autism spectrum disorder, cesarean section, epidural anesthesia, general anesthesia, neuraxial anesthesia

Abbreviations: ASD, autism spectrum disorder; EVD, vaginal delivery with epidural; GACD, cesarean with general anesthesia; NACD, cesarean with neuraxial anesthesia; VD, vaginal delivery without analgesia.

Aviv Ben Kish and Yair Binyamin equal contribution for this article.

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1 | INTRODUCTION

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition that is characterized by impairment of social communication, along with restricted, repetitive patterns of behavior or activities.[1] ASD has become a major public health concern in the past few decades, with a substantial increase in the prevalence of ASD worldwide,[2] including Israel.[3]

The etiology of ASD is multifactorial, involving complex interactions between genetic and environmental factors.[4] While genetic factors contribute significantly to ASD risk, they do not fully account for the recent rises in prevalence.[5] In attempts to delineate non-genetic ASD risk factors, a significant body of research has focused on possible contributing factors in the prenatal and perinatal period, which represents a critical window of neurodevelopmental vulnerability.[6]

In the past few years, attention has been drawn to a possible association between pain management during birth and a later diagnosis of ASD in the offspring, since some studies have suggested that exposure to general or epidural anesthesia during labor is associated with an increased risk of ASD,[7–11] while other studies have not found any such association.[12,13] Whereas general anesthesia is used exclusively for cesarean deliveries, neuraxial anesthesia (e.g. spinal, epidural) for pain management may be administered for both vaginal and cesarean deliveries. Data on links between cesarean anesthesia types and ASD remain limited and inconsistent. Some studies reported greater ASD risk with general vs. neuraxial anesthesia,[8,14] while others found no clear correlations.[8,15]

Given both the conflicting data and the substantial knowledge gaps about the linkage between pain management during labor and a later diagnosis of ASD, we conducted a historical cohort study to systematically investigate the associations between different types of analgesia administered during labor and ASD risk in the offspring. Knowledge about these relationships will inform clinical guidelines and prevention strategies.

Key message

In this retrospective cohort study, cesarean delivery under general anesthesia, but not under neuraxial anesthesia, was associated with a higher risk of a later diagnosis of autism spectrum disorder compared to natural delivery.

2 | MATERIAL AND METHODS

2.1 | Participants

This retrospective cohort study included 98 630 single live-born infants delivered at Soroka University Medical Center (SUMC) between January 2011 and December 2019 and followed up until January 2023. SUMC is the sole major medical center in the southern region of Israel, known as the Negev, and is the referral center for patients with mild to complex conditions from the entire region. Importantly, it is the largest birth facility in Israel, with over 15 000 births per year. The population of the Negev region, which consists of approximately 1 million citizens, has a unique ethnic composition in that more than 25% of the citizens are Bedouin Arabs. This population sector contributes to >50% of the births at SUMC.

A flowchart depicting study cohort ascertainment is given in Figure 1. The study cohort included only members of Clalit Health Services (CHS), the largest health maintenance organization in Israel to which over 75% of the Negev population belong. Excluded from the cohort were infants with congenital abnormalities and genetic syndromes including drug withdrawal syndrome in the newborn, Marfan syndrome, Parder-Willi syndrome fragile X syndrome, Angelman syndrome, and Tuberous sclerosis complex that are associated with an increased risk of ASD.

2.2 | Study variables

The study cohort was divided into four groups: three exposure groups, based on the mode of delivery and the type of intrapartum anesthesia, and a reference group of vaginal delivery without analgesia (VD) (Figure 1). The characteristics delineating the three exposure groups were: (1) Vaginal delivery with epidural analgesia (EVD), (2) cesarean delivery with neuraxial anesthesia (spinal, epidural or combined spinal-epidural anesthesia) (NACD), and (3) cesarean delivery with general anesthesia (GACD). The primary outcome variable was a diagnosis of ASD in the offspring, established on the basis of DSM-5 criteria[16] that was determined by a child psychiatrist or a pediatric neurologist following a comprehensive assessment by a specialized multidisciplinary team, as described previously.[17] ASD cases were ascertained from the database of the Azrieli National Centre for Autism and Neurodevelopmental Research (ANCAN)[18] Additional prenatal, perinatal, and postnatal variables that have been associated with either the exposure factors or the outcome were included as covariates and potential confounders (Appendix S1).

2.3 | Data sources

Data on exposure variables and potential covariates was obtained from the database of the Obstetrics and Gynecology Division at SUMC, which includes detailed prenatal, perinatal, and postnatal information on deliveries at the hospital since 1990. This data was cross-referenced with data from the ANCAN database, which contains comprehensive information on all children diagnosed with ASD according to DSM-5 criteria at SUMC since 2015.[17,18]

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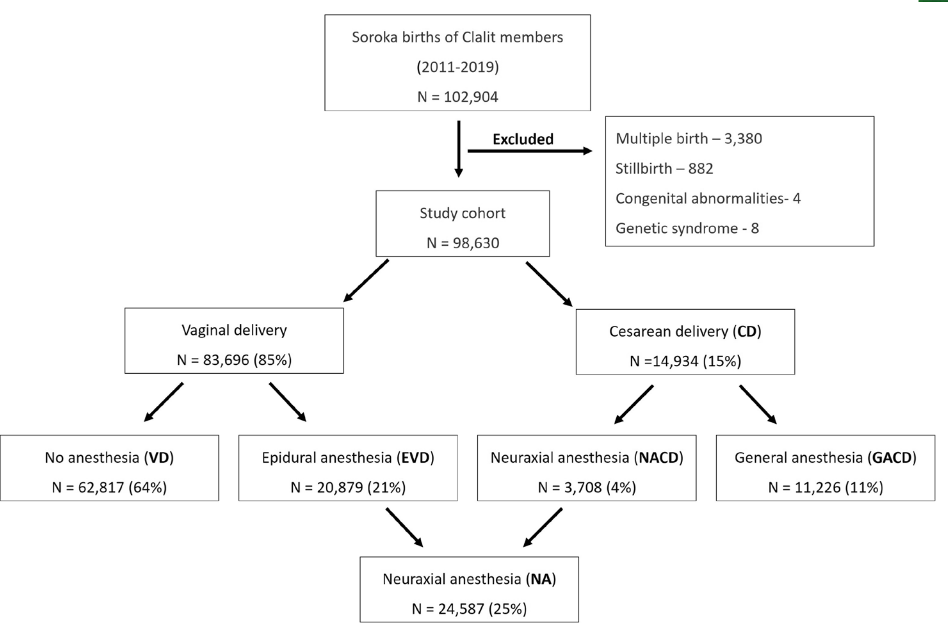

FIGURE 1 Flowchart depicting the ascertainment of the study groups.

2.4 | Statistical analysis

We used standard univariate statistical tests to assess the association between the exposure groups and the different prenatal, perinatal, and postnatal variables as well as between ASD and the same covariates. Associations between categorical variables were assessed using the χ^2 test or Fisher's exact test when more than 20% of the cells had expected counts below five. Associations between categorical and continuous variables were evaluated using independent *t*-tests for normally distributed variables or Mann–Whitney tests for non-normally distributed variables. Variables that were significantly associated with at least one of the exposure groups and with ASD were considered potential confounders and were, consequently, included in the multivariable regression models. Kaplan-Meir plots were used to compare the cumulative incidence of ASD between the four study groups with time-to-event (ASD diagnosis) being capped at 10 years of age. In addition, a series of Cox regression models were constructed using the same follow-up time and with sequential adjustment for prenatal, perinatal, and postnatal confounders to assess the hazard ratios of ASD independently associated with different types of obstetric anesthesia. Furthermore, sensitivity analyses were performed by reapplying the above-mentioned regression models to the study cohort stratified according to infant sex and ethnicity.

We also performed a subgroup analysis within the GACD group, dividing it into "urgent" and "non-urgent" surgeries.

Statistical analyses were conducted using SPSS version 26 (IBM, Armonk, NY). The threshold for statistical significance was defined as a two-sided alpha of 0.05 for the univariate analyses. A more stringent threshold of 0.01 was used in the Cox regression analyses to adjust for the analysis of multiple exposure groups.

3 | RESULTS

The study cohort comprised 98 630 newborns; of these 62 817 (64%) were natural births without any anesthetic procedure (VD; reference group), 20 879 (21%) were vaginal deliveries with epidural analgesia (EVD group), and 14 934 (15%) were cesarean deliveries with either neuraxial anesthesia (NACD group; 3708 [24.8%]) or general anesthesia (GACD group; 11 226 [75.2%]) (Figure 1).

All the prenatal, perinatal, and neonatal factors examined showed statistically significant differences between the exposure groups and the reference (VD) group (Table 1). Among the most notable factors was maternal age, which was approximately 2 to 4 years higher for cesarean versus vaginal deliveries (30.7 (6.02) and 32.2 (5.5) mothers in the GACD and NACD groups, respectively vs. 28.5 (5.8) and 28.7 (5.2) for the VD and EVD groups, respectively). Furthermore, women in all three exposure groups exhibited higher rates of gestational diabetes, polyhydramnios, and oligohydramnios than women in the VD group. In addition, the rates of amniocentesis and pregnancies conceived through assisted reproductive technology were also higher in the three exposure groups (Table 1). In addition, we found a higher proportion of vaginal deliveries without anesthesia among Bedouin women compared with Jewish women (73.3% vs. 26.7%, respectively).

A total of 535 (0.54%) children in the study cohort were diagnosed with ASD during the study period. A comparison of prenatal, perinatal, and neonatal factors between the ASD and non-ASD groups revealed a threefold lower rate of Bedouin infants in the ASD group compared to the non-ASD group (24.4% vs. 62.2%; $p < 0.001$) (Table 2). In addition, the ASD group was characterized by a higher maternal age at birth (30.3 (5.8) vs. 28.9 (5.7) years), and higher rates of gestational diabetes (5.0% vs. 2.7%), preterm deliveries (17.0% vs. 13.0%), malpresentation

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TABLE 1 Characteristics of the study groups.

Characteristic, mean ± SD or % (N)	VD (Ref.) (N = 62 817)	EVD (N = 20 879)	NACD (N = 3708)	GACD (N = 11 226)
Maternal and prenatal characteristics				
Mother's age at birth (years)[a]	28.52 ± 5.84	28.71 ± 5.28	32.2 ± 5.51	30.77 ± 6.02
Ethnicity (Bedouin)[a]	73.3% (46023)	32.7% (6834)	24.6% (914)	65.6% (7363)
Gestational diabetes[a]	2% (1251)	3.1% (654)	6.8% (252)	4.8% (539)
Polyhydramnios	9.4% (5930)	1.2% (260)	2.9% (109)	3.2% (361)
Oligohydramnios	1.4% (877)	2.5% (519)	2.7% (100)	3.2% (358)
Amniocentesis[a]	1.4% (901)	3.7% (781)	7.2% (267)	3.1% (348)
Assisted reproductive technology[a]	0.9% (552)	2.5% (514)	5.1% (189)	3.4% (385)
Recurrent miscarriage[a]	2.7% (1707)	2.1% (438)	2.9% (106)	4.4% (491)
Past cesarean delivery[a]	7.8% (4905)	7.2% (1496)	52.1% (1932)	51.1% (5733)
Preeclampsia[a]	1.8% (1140)	3.1% (639)	3.6% (133)	3.7% (416)
Labor and perinatal characteristics				
Gestational age (days)[a]	274.12 ± 3.68	274.51 ± 12.83	268.14 ± 15.02	265.73 ± 19.17
Pre-term delivery (<37 weeks)[a]	10.3% (6491)	10.3% (2151)	21.9% (811)	29.8% (3340)
Post-term delivery (≥42 weeks)	2.4% (1485)	1.2% (255)	0.7% (27)	1.9% (217)
Vacuum delivery	2.1% (1320)	5.7% (1199)	<0.1% (0)	<0.1% (3)
Malpresentation of fetus[a]	0.4% (273)	0.1% (31)	22.3% (828)	20.6% (2318)
Placental abruption[a]	0.1% (36)	<0.1% (7)	0.6% (21)	2.5% (278)
Meconium[a]	7.3% (4609)	7.4% (1545)	7.2% (266)	10.4% (1170)
Labor dystocia[a]	<0.1% (17)	0.1% (13)	7.1% (260)	6.3% (705)
Placenta previa	<0.1% (19)	<0.1% (3)	2.4% (89)	2.8% (316)
Preterm prelabor rupture of membranes	0.4% (229)	0.6% (134)	1.1% (39)	1.1% (123)
Umbilical cord around the neck[a]	24.7% (15498)	28.2% (5882)	12.9% (480)	11.3% (1264)
Oxytocin induction[a]	5.2% (3260)	10.9% (2285)	4.2% (155)	3.8% (429)
Pethidine[a]	2.0% (1234)	0.3% (65)	0.2% (9)	0.2% (19)
Umbilical cord prolapse	0.2% (145)	0.3% (57)	0.8% (31)	2.1% (241)
Fetal distress[a]	2.7% (1703)	6.6% (1376)	12.1% (447)	19.2% (2156)
Fever during labor	<0.1% (19)	0.1% (14)	0.1% (5)	0.4% (40)
Infant characteristics				
Birthweight (g)[a]	3202 ± 478	3243 ± 475	3168 ± 588	3045 ± 694
Infant's gender (male)[a]	50.5% (31714)	52.1% (10870)	52.2% (1935)	53.2% (5968)
Small for gestational age[a]	2.1% (1304)	2.0% (411)	3.4% (127)	4.2% (475)
Large for gestational age[a]	3.8% (2385)	4.3% (900)	7.6% (281)	7.4% (829)
1-min abnormal Apgar score (<7)[a]	1.0% (648)	1.4% (283)	3.6% (132)	13.6% (1525)
5-min abnormal Apgar score (<7)[a]	0.4% (275)	0.3% (72)	0.8% (28)	1.8% (203)

Abbreviations: EVD, vaginal delivery with epidural analgesia; GACD, cesarean delivery under general anesthesia; NACD, cesarean delivery with neuraxial anesthesia (spinal, epidural, or combined spinal-epidural anesthesia); VD, vaginal delivery without anesthesia (Reference group).
[a]Characteristics statistically significant differences ($p < 0.001$) between VD and exposure groups.

(5.2% vs. 3.5%), cesarean deliveries (23.4% vs. 15.1%), preeclampsia (4.1% vs. 2.4%), oxytocin induction (8.4% vs. 6.2%), fetal distress (9.5% vs. 5.7%), and male sex of the newborn (79.% vs. 51.0%). All these differences were statistically significant at $p < 0.05$ (Table 2).

The cumulative incidence of ASD was approximately twice as high in all the exposure groups as in the VD group: EVD 1.25%, NACD 1.56%, GACD 1.50% vs. 0.55% in VD (Figure 2). To assess the independent association of the different anesthesia modes with ASD risk, we applied Cox regression analysis while progressively adjusting the models for potential confounders. A univariate (unadjusted) analysis (Model 0; Table 3) revealed an increased ASD hazard associated with all anesthesia exposures, with the highest hazard ratio being associated with NACD (HR = 2.69; 99% CI 1.89–3.84). Adjustment for maternal prenatal (Model 1; Table 3) and perinatal (Model 2; Table 3) factors reduced the hazard ratio of ASD in all exposure groups, but it still remained statistically significant. Adding fetal variables to the Cox model (Model 3; Table 3) rendered the association of ASD with NACD non-significant, while the associations

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TABLE 2 Comparison of characteristics between infants diagnosed with ASD and non-ASD infants.

Characteristic, mean ± SD or % (*N*)	ASD (*N* = 535)	Non-ASD (*N* = 98 095)	*p*-value
Maternal and prenatal characteristics			
Mother's age at birth (years)	30.37 ± 5.82	28.94 ± 5.70	**<0.001**
Ethnicity (Bedouin)	24.4% (136)	62.2% (60998)	**<0.001**
Gestational diabetes	5.0% (27)	2.7% (2669)	**<0.001**
Polyhydramnios	2.2% (12)	1.3% (1311)	0.074
Oligohydramnios	3.0% (16)	1.9% (1838)	0.066
Amniocentesis	4.9% (26)	2.3% (2271)	**<0.001**
Assisted reproductive technology	5.2% (28)	1.6% (1612)	**<0.001**
Recurrent miscarriage	3.9% (21)	2.8% (2721)	0.119
Past cesarean section	15.1% (81)	14.3% (13985)	0.563
Preeclampsia	4.1% (22)	2.4% (2306)	0.007
Labor and perinatal characteristics			
Gestational age (days)	271.46 ± 16.13	273.02 ± 14.53	**0.031**
Pre-term delivery (<37 weeks)	17.0% (91)	13.0% (12702)	**0.005**
Post-term delivery (≥42 weeks)	1.7% (9)	2.0% (1975)	0.592
Vacuum delivery	3.0% (16)	2.5% (2506)	0.528
Malpresentation of fetus	5.2% (28)	3.5% (3422)	**0.038**
Cesarean delivery	23.4% (125)	15.1% (14809)	**<0.001**
Placental abruption	0.6% (3)	0.3% (339)	0.402
Meconium	9.0% (48)	7.7% (7542)	0.276
Labor dystocia	1.7% (9)	1% (986)	0.121
Placenta previa	0.4% (2)	0.4% (425)	0.842
Preterm prelabor rupture of membranes	0.7% (4)	0.5% (521)	0.498
Umbilical cord around the neck	25% (134)	23.4% (22990)	0.382
Oxytocin induction	8.4% (45)	6.2% (6084)	**0.041**
Pethidine	0.6% (3)	1.3% (1324)	0.113
Fetal distress	9.5% (51)	5.7% (5631)	**<0.001**
Fever during delivery	0.2% (1)	0.1% (77)	0.378
Umbilical cord prolapse	0.4% (2)	0.5% (472)	0.724
Infant characteristics			
Birthweight (g)	3165 ± 567	3191 ± 514	0.239
Infant's gender (male)	79.8% (427)	51.0% (50060)	**<0.001**
Small for gestational age	2.4% (13)	2.3% (2304)	0.706
Large for gestational age	4.3% (23)	4.5% (4372)	0.701
1-min abnormal Apgar score (<7)	3.2% (17)	2.7% (2571)	0.442
5-min abnormal Apgar score (<7)	0.4% (2)	0.6% (576)	0.513

Note: Statistically significant differences are shown in bold.

of EVD and GACD with ASD remained statistically significant (aHR = 1.30; 99% CI 1.03–1.64 and aHR = 1.571; 99% CI 1.12–2.22).

To further explore the association between GACD and ASD, we applied the fully adjusted Cox model (Model 3) only to women who had cesarean delivery while comparing the risk of ASD in the GACD group vs. the NACD group (Table S1). The results of this analysis revealed that children born in cesarean delivery with general anesthesia had a 1.12 higher hazard to have ASD than children born in cesarean delivery with neuraxial anesthesia (aHR = 1.12; 99% CI 1.04–1.37). Further stratification of the GACD group into urgent and non-urgent surgeries based on known medical indications revealed no significant differences in the adjusted hazard ratios of ASD associated with each of these subgroups (Table S2). These findings suggest that the association between GACD and ASD may be attributed largely to the type of anesthesia rather than to factors related to the surgery itself.

Finally, to assess the robustness of our findings, we also applied the fully adjusted Cox model (Model 3) to the study cohort stratified by ethnicity and sex (Jewish/Bedouin, Male/female, Tables S3 and S4). The insignificant Breslow-Day results ($p > 0.05$) for all these comparisons suggest no effect modification of ethnicity on the association between any type of obstetric anesthesia and ASD. Nevertheless, it should be noted that the aHR of ASD among Bedouin children in the EVD group was more than twice that of their Jewish counterparts, suggesting a potential confounding effect of ethnicity on our results.

4 | DISCUSSION

In the present study, we performed a comprehensive investigation of the association between pain-relief anesthetic techniques during delivery and the risk of ASD. Our analyses show that ASD was associated with cesarean deliveries conducted under general anesthesia, without substantial distinction between cesarean deliveries conducted with or without a medical indication. The observed 1.571-fold increased ASD risk associated with cesarean deliveries conducted under general anesthesia aligns with the results of a case–control study from our own group[9] and with the results of a Taiwanese retrospective cohort study.[8] Importantly, to the best of our knowledge, to date those two studies and the current study are the only ones that have examined the association between cesarean delivery conducted under general anesthesia and ASD. Thus, although the results are remarkably consistent, further studies in additional populations are required to establish this disturbing association.

There was a substantial reduction in the hazard ratio associated with all exposures between Model 2 and Model 3. The variables that mostly contributed to this reduction were "Small for gestational age" and "1-min abnormal Apgar score," two variables that are known to be associated with both cesarean delivery[19,20] and ASD.[21,22]

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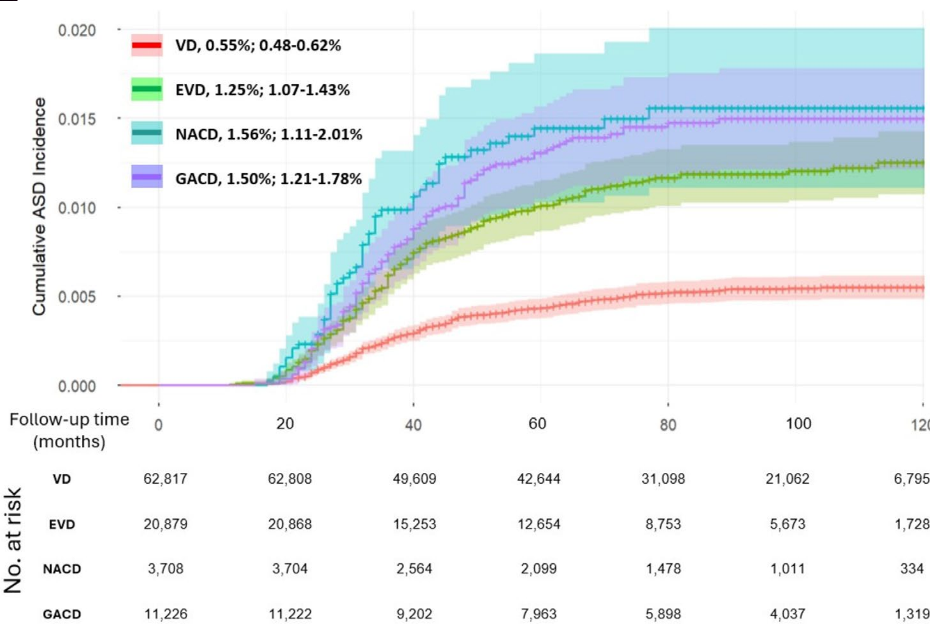

FIGURE 2 Kaplan–Meier plots of the cumulative incidence (with 99% confidence intervals) of ASD onset for the four study groups of delivery types: Vaginal delivery without analgesia (VD), vaginal delivery with epidural analgesia (EVD), cesarean delivery with neuraxial anesthesia (NACD), and cesarean delivery under general anesthesia (GACD). The *x*-axis is labeled as Follow-up time (months) with numeric month values shown at 20-month intervals. The median follow-up time for the entire study population was 77 months.

TABLE 3 Multivariate analysis for the risk of ASD.

		Model 0		Model 1		Model 2		Model 3	
Variable	ASD (*N* (%))	HR	99% CI	HR	99% CI	HR	99% CI	HR	99% CI
VD (*N* = 62 814)	235 (0.4%)	Reference							
EVD (*N* = 20 879)	175 (0.8%)	2.344	1.91–2.84	2.231	1.83–2.71	2.166	1.72–2.62	1.301	1.03–1.64
NACD (*N* = 3708)	34 (0.9%)	2.692	1.89–3.84	2.308	1.54–3.50	2.046	1.48–3.32	1.253	0.75–1.96
GACD (*N* = 11 226)	91 (0.8%)	2.131	1.75–2.75	2.064	1.62–2.71	1.801	1.30–2.47	1.571	1.12–2.22

Note: Model 0: Only the exposure variable. Model 1: adjustment for maternal and prenatal characteristics: Model 0 + mother's age at birth, gestational diabetes, assisted reproductive technology, recurrent miscarriage, past cesarean section, ethnicity preeclampsia, and amniocentesis. Model 2: adjustment for labor and perinatal characteristics: Model 0 + Model 1, gestational age, pre-term delivery, malpresentation of fetus, placental abruption, labor dystocia, umbilical cord around neck, oxytocin induction, fetal distress, meconium, and cesarean delivery. Model 3: adjustment for infant characteristics: Model 0 + Model 1 + Model 2, infant's weight at birth, infant's gender, small for gestational age, large for gestational age, 1-min abnormal Apgar score, 5-min abnormal Apgar score.

Abbreviations: EVD, vaginal delivery with epidural analgesia; GACD, cesarean delivery under general anesthesia; NACD, cesarean delivery with neuraxial anesthesia (spinal, epidural, or combined spinal-epidural anesthesia); VD, vaginal delivery without anesthesia.

Interestingly, the largest reduction in hazard ratio between the models was in the association with the EVD exposure. In recent years, an association between "1-min abnormal Apgar score" and epidural anesthesia has been reported[23,24] as well as "Small for gestational age" and EVD exposure.[25]

The association between exposure to general anesthesia during birth and a later diagnosis of ASD in the infants is in line with the findings of several studies that performed on animals that have found that neonatal exposure to anesthetics may influence fetal brain development.[26–29] Other studies that performed on human fetuses found such neurological damage predominantly affects areas responsible for synaptogenesis, apoptosis, neurogenesis, and myelination.[30,31]

In contrast, other studies that examined early-life exposure to procedures performed under general anesthesia suggested that a single brief exposure to general anesthesia is not associated with any long-term neurodevelopmental deficits in children's brains.[32] However, those studies focused on cognitive functioning as their main outcome and did not directly test a diagnosis of ASD or autistic symptoms. Nonetheless, in light of the inconclusive evidence regarding the potential link between neurotoxic changes during critical periods of brain development and subsequent neurodevelopmental alterations, the FDA has issued warnings about the potential risks of neurodevelopmental damage associated with the exposure of newborns and young children to general anesthesia.[33]

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We also found a weak association between vaginal deliveries with epidural anesthesia and ASD. However, the fact that this association was evident only for vaginal/epidural but not for cesarean/epidural deliveries implies a confounding effect of this association, possibly by the large ethnic differences in the use of epidural anesthesia. Indeed, there were large differences between Jewish and Bedouin women in the hazard ratios of ASD associated with the EVD and NACD groups (Table S4), thus supporting the possibility of such confounding by ethnicity. A similar marginal association of ASD with epidural anesthesia was found in a large cohort study in British Columbia.[34] There, too, the authors reported a marginal association of ASD with epidural anesthesia, which they attributed to residual confounding. Two additional large cohort studies also found no association between epidural anesthesia and ASD,[35,36] thereby providing further support for the notion that epidural anesthesia during birth is not associated with an increased risk of ASD in the offspring.

Given the suggested association between cesarean sections performed under general anesthesia and the risk of ASD, together with the FDA recommendation to limit the use of gestational general anesthesia, the relatively high prevalence of cesarean deliveries conducted under general anesthesia in our study is quite alarming. This trend can be attributed to the preference of the large local Bedouin population to decline epidural pain management for both vaginal and cesarean deliveries due to cultural beliefs and perceptions. Consequently, when a cesarean section is needed in this population sector, general anesthesia is usually preferred over neuraxial anesthesia. Additionally, many of these women require multiple cesarean sections, which increases the risk of delivery-related complications, and in such cases, obstetricians may prefer general anesthesia, as it provides better surgical conditions compared to neuraxial anesthesia. Despite these ethnic differences in anesthetic use during birth, no significant difference in the hazard ratio of ASD associated with exposure to general anesthesia was seen between Bedouin and Jewish offspring, thus negating the possibility that such an observed association between general anesthesia and ASD is confounded by these ethnic differences. We note here that, importantly and regardless of the above findings, a significant shift towards spinal anesthesia for cesarean delivery occurred at SUMC in 2020 following an extensive effort on the part of the staff to communicate the risks associated with general anesthesia to women about to undergo cesarean procedures.

Our study has several limitations. First, the relatively limited ASD cases included in the study cohort and the stringent significance level of $\alpha = 0.01$ in our regression models (accounting for the multiple exposures in this study) restricted the power of our regression models to identify low-effect statistically significant exposure-outcome associations. The low number of cases is consistent with previous reports of ASD prevalence from this population,[37,38] although it is still possible that some cases were lost to follow up due to death or relocation to other healthcare service providers. Second, the relatively higher prevalence of general anesthesia for cesarean deliveries in our cohort compared to global standards could potentially introduce regional bias and therefore results may not extrapolate to other populations with different obstetric practices or anesthesia use patterns. Third, our data lacks information regarding the duration of the neuraxial or general anesthesia during delivery, a factor that could moderately influence the risk associated with ASD. Finally, the adjustment models omit potential key confounders such as maternal psychiatric history, socioeconomic status, education, parity, and medication use. These unmeasured variables may be correlated with both anesthesia choice and ASD risk and hence could underlie additional confounding to the results of our models.

5 | CONCLUSION

Our study suggests that exposure to general anesthesia during delivery is associated with ASD diagnosis in the offspring, whereas neuraxial anesthesia is not. Ongoing research is imperative to further elucidate the mechanisms underlying the relationship between general anesthesia and ASD, especially in light of the paucity of research on this relationship and its critical public health consequences.

AUTHOR CONTRIBUTIONS

A.B.K. and Y.B. performed analyses and wrote the first draft of the manuscript. A.M. and G.M. collected the data and provided the study resources. I.M. was responsible for the study conception, supervision, and editing of the final manuscript's draft. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

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.

ETHICS STATEMENT

The study protocol was approved on March 13th, 2022, by the Institutional Review Board at SUMC (#SOR-237-21) in accordance with the Declaration of Helsinki guidelines for ethical research involving human subjects. Informed consent was waived due to the retrospective nature of the study.

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