Journal of Autism and Developmental Disorders
https://doi.org/10.1007/s10803-020-04415-5

RESPONSE

False Interpretation of Scientific Data Leads to Biased Conclusions About the Association Between Cesarean Deliveries Under General Anesthesia and Risk of Autism Spectrum Disorder

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In their recent letter to the editor, Sagi-Dain et al. severely criticized our recent study entitled "Exposure to general anesthesia may contribute to the assocation between cesarean delivery and autism spectrum disorder" by Huberman et al. Here, we respond point-by-point to their criticism, clarify several false statements and interpretations, and explain the importance and validity of our study.

One major point of criticism by Sagi-Dain et al. was apparent in their statement: "The evidence exploring the effects of general anesthesia and subsequent neurodevelopmental deficits is conflicting and prone to bias. A recent large randomized controlled trial has found no difference in neurodevelopmental outcomes at age 5 years in infants undergoing general anesthesia vs. awake-regional anesthesia (McCann et al. 2019)". We invite Sagi-Dain et al. to read the paper in depth and see that McCann actually reported the opposite with respect to ASD. When specifically assessing ASD outcomes in a subset of their sample (in Table 5 of their paper), they found that the rates of ASD in the general anesthesia (GA) group was twice higher than those in the regional anesthesia (RA) group (4% vs. 2%; RR 1.88). This is in agreement with the results of our study where the risk of ASD associated with GA was similar (i.e. OR 1.63). The reason that Sagi-Dain et al. miss-interpreted the McCann paper is that they only acknowledged the first analysis where McCann reported that full-scale intelligence quotient (FSIQ) did not differ across GA and RA groups. However, FSIQ is not a criteria for ASD diagnosis (American Psychiatric 2013) and, therefore, not relevant to the current discussion.

Furthermore, note that the McCann study examined the effects of postnatal exposure to general anesthesia (GA) up to a year after birth, in contrast to the perinatal exposure to GA that was evaluated in our study. While this difference might seem insignificant, it involves a critical period for brain development where even tiny alterations might lead to significant developmental consequences (Piven et al. 2017). Importantly, another study that explicitly examined the effect of perinatal exposure to anesthesia on the risk of ASD, found that only CS + GA was associated with the risk of ASD (adjusted Hazard ratio 1.52; P = 0.001), while CS + RA did not (Chien et al. 2015). These results that are strikingly similar to the ones published in our study, despite remarkable differences in the studied population, study design, adjusted confounders, provide additional support to the relationship between perinatal exposure to GA and risk of ASD.

Another major point of criticism by Sagi-Dain et al. was: "The main and crucial limitation of the statistical analysis is lack of referral to multiple possible confounders. One of the most important parameters, which could have severely affected the conclusions is the presence of fetal distress, associated both with higher need for general anesthesia, as well as the increased risk of neurodevelopmental disorders. Indeed, higher rates of non-reassuring fetal monitor (NRFM) are noted in children with DD (13.7% vs. 6.7% in the controls, P = 0.045). The authors do not mention this important association in the discussion, nor do they include the parameter of NRFM in multivariate analysis of risk factors".

Here again, Sagi-Dain et al. confuse between ASD and other types of developmental delays (DD), which were one

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Published online: 19 February 2020

Table 1 Birth complications that are associated with Cesarean Section (CS) operation

Variable	All births N	Vaginal birth N (%)	Birth with CS N (%)	Odds ratio (OR)	95% CI of OR
Total	2002[a]	1614	388		
Previous CS	296	100 (0.2%)	196 (50.5%)	15.5	11.6–20.5
Nonreassuring monitor	133	65 (4.0%)	68 (17.5%)	5.1	3.5–7.3
Preeclampsia	87	45 (2.8%)	42 (10.8%)	4.2	2.7–6.5
Malpresentation	75	9 (0.6%)	66 (17.0%)	37.0	18.1–77.0
Labor dystocia	50	10 (0.6%)	40 (10.30%)	18.4	9.1–37.2
Macrosomia	14	6 (0.4%)	8 (2.1%)	5.6	1.9–16.4
Placenta abruption	9	1 (0.1%)	8 (2.1%)	34.0	4.2–272.2
Umbilical prolapse	9	0 (0%)	9 (2.3%)	–	–
Rupture of uterus	1	0 (0%)	1 (0.3%)	–	–

[a]This sample comprises of the births of 347 children with ASD and 1655 children with typical development who were matched to cases on the basis of their age (±3 months), sex and ethnicity (Bedouin/Jewish)

of the comparison groups in our study. A closer look at Table 1 of our paper (Huberman Samuel et al. 2019), reveals that NRFM was significantly associated with DD but not with ASD and therefore is less relevant as a potential confounder in our regression models regarding ASD risk. Nevertheless, we did consider NRFM as one of the indications for an 'indicated' surgery in our stratification analysis as described below.

Sagi-Dain et al. also criticized our assignment of the study groups into cesarean deliveries that were 'indicated' versus 'non-indicated'. We agree that other classification approaches of Cesarean deliveries could be used (e.g. "elective" vs. "non-elective" or "emergency" vs. non-emergency"), however these classifications would not necessarily improve the ability to account for confounding factors. Nevertheless, to address these concerns, we identified specific birth and pregnancy complications associated with CS in our data (Table 1) and present new data demonstrating the rates of ASD for each of these complications while separating the three groups of birth modalities: (1) CS + GA; (2) CS + RA; (3) Vaginal delivery. The results of this analysis (Table 2) show that the odds ratio (OR) of ASD that is associated with CS + GA (compared with vaginal deliveries) is consistently higher than the OR of ASD associated with CS + RA. Furthermore, when all of these confirmed indications for CS are aggregated into one category (termed in Table 2 as "indicated" surgeries), the OR of ASD compared to vaginal deliveries was 1.82 (95% CI 1.12–2.94) while the OR of all other ("non-indicated") surgeries was slightly higher(although not significant due to a small sample size, OR 2.02 95% CI 0.92–4.45). These new results are strikingly similar to the results published in our original study (Huberman Samuel et al. 2019) and again demonstrate the robustness of our results and conclusions.

A final point raised by Sagi-Dain et al. was about the considerably high rate of GA in our sample. Indeed, the rates of CS + GA at Soroka University Medical Center (SUMC) are relatively high. The main reason for this is the unique population of parturients at SUMC who usually prefer to give birth without any kind of anesthesia (O'Hana et al. 2008; Sidelnick et al. 2009). Indeed, the rate of vaginal deliveries with epidural anesthesia in our study was only 29.4%. Thus, if an unplanned CS is required during labor in one of the remaining ~ 70% unanesthetized parturients, the use of GA is usually preferred. Consequently, the majority of CS births at SUMC are conducted with GA. It is important to note however, that the high rate of CS + GA in our study, do not influence the conclusions regarding the association between GA and ASD risk.

To conclude, current data from our study and others suggest that there is indeed a robust association between exposure to GA during CS and risk of ASD. Our additional analyses (Table 2) further attest to this relationship.

Table 2 Risk of ASD associated with different modes of anesthesia

Variable	N	Birth with CS + GA	Birth with CS + RA	Vaginal Delivery	Odds Ratio CS + GA[a] (95% CI)	Odds Ratio CS + RA[b] (95% CI)
All						
ASD	347	67 (19%)	14 (4%)	266 (77%)	1.52 (1.12–2.05)	0.90 (0.49–1.57)
Control	1655	224 (13%)	81 (5%)	1350 (82%)		
Previous CS						
ASD	58	38 (65%)	5 (9%)	15 (26%)	1.81 (0.93–3.50)	0.83 (0.28–2.47)
Control	238	119 (50%)	34 (14%)	85 (36%)		
Non-reassuring monitor						
ASD	26	13 (50%)	3 (12%)	10 (38%)	2.10 (0.83–5.32)	0.92 (0.23–3.70)
Control	107	34 (32%)	18 (17%)	55 (51%)		
Preeclampsia						
ASD	24	8 (33%)	5 (21%)	11 (46%)	1.30 (0.45–3.80)	1.29 (0.37–4.47)
Control	65	19 (29%)	12 (19%)	34 (52%)		
Malpresentation						
ASD	13	11 (84%)	1 (8%)	1 (8%)	2.38 (0.27–21.15)	0.47 (0.03–8.52)
Control	62	37 (60%)	17 (27%)	8 (13%)		
Labor dystocia						
ASD	11	8 (73%)	1 (9%)	2 (18%)	1.23 (0.22–7.01)	0.80 (0.06–11.30)
Control	39	26 (67%)	5 (13%)	8 (21%)		
Macrosomia						
ASD	2	1 (50%)	0 (0%)	1 (50%)	0.83 (0.04–17.0)	–
Control	12	6 (50%)	1 (8%)	5 (42%)		
Placenta abruption						
ASD	2	2 (100%)	0 (0%)	0 (0%)	–	–
Control	7	6 (86%)	0 (0%)	1 (14%)		
Umbilical cord prolapse						
ASD	1	1 (100%)	0 (0%)	0 (0%)	–	–
Control	8	6 (75%)	2 (25%)	0 (0%)		
Rapture of uterus						
ASD	0	0 (0%)	0 (0%)	0 (0%)	–	–
Control	1	1 (100%)	0 (0%)	0 (0%)		
Indicated[c]						
ASD	103	58 (56%)	15 (15%)	30 (29%)	1.82 (1.12–2.94)	1.38 (0.69–2.71)
Control	461	202 (44%)	69 (15%)	190 (41%)		
Non indicated[d]						
ASD	245	9 (4%)	2 (1%)	234 (96%)	2.02 (0.92–4.45)	0.76 (0.17–3.40)
Control	1193	22 (2%)	13 (1%)	1158 (97%)		

[a]Odds ratio of the risk of ASD associated with Cesarean section (CS) conducted with general anesthesia (GA) compared to vaginal delivery

[b]Odds ratio of the risk of ASD associated with Cesarean section (CS) conducted with regional anesthesia (RA) compared to vaginal delivery

[c]Births with at least one complication listed in this table. Some births might have more than one complication

[d]Births with no complications considered in this table

Acknowledgments Idan Menashe, Public Health Department, and The National Autism Research Center of Israel, Ben-Gurion University of the Negev, Beer Sheva, Israel, Ilan Dinstein, Psychology Department, and The National Autism Research Center of Israel, Ben-Gurion University of the Negev, Ben-Gurion University of the Negev, Beer Sheva, Israel, Hagit Flusser, MD, and Analiya Michaelovski, MD, Child development department, Soroka University Medical Center, and The National Autism Research Center of Israel, Ben-Gurion University of the Negev, Beer Sheva, Israel, Asher Bashiri, Obstetrics and Gynecology department, Soroka University Medical Center, Beer Sheva, Israel, Gal Meiri, Pre-School Psychiatry Unit, Soroka University Medical Center, and The National Autism Research Center of Israel, Ben-Gurion University of the Negev, Beer Sheva, Israel.

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