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Meconium Exposure and Autism Risk

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Abstract

Objective—This study aims to determine whether fetal meconium passage is associated with autism.

Study Design—This retrospective birth cohort analysis of 9 945 896 children born in California 1991 to 2008 linked discharge diagnosis and procedure codes for prenatal stressors, meconium-stained amniotic fluid (MSAF) and meconium aspiration syndrome (MAS) with autism diagnoses for 47 277 children through 2012. We assessed the relative risk of autism by meconium status using logistic regression, adjusting for demographic and clinical features.

Result—Children exposed to meconium (MSAF and MAS) were more likely to be diagnosed with autism in comparison to unexposed children (0.60% and 0.52%, vs 0.47%, respectively). In adjusted analyses, there was a small increase in autism risk associated with MSAF exposure (adjusted relative risk (aRR) 1.18, confidence interval (CI) 1.12 to 1.25), and a marginal association that failed to achieve significance between MAS and autism (aRR 1.08, 95% CI 0.98 to 1.20).

Conclusion—Resuscitation of neonates with respiratory compromise from *in utero* meconium exposure may mitigate long-term neurodevelopmental damage.

Keywords

Meconium; Meconium Aspiration Syndrome; Autism Spectrum Disorder; Neurodevelopment

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CONFLICTS OF INTEREST

Dr. Walker serves on the Speaker's Bureau for Merck & Co. This work pertains neither to pregnancy complications nor to neurodevelopment.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a set of chronic neurological conditions characterized by persistent deficits in social communication and restricted, repetitive patterns of behavior, interests, or activities that manifest in early childhood and impair function. Autism is the most severe form of ASD, an overarching term used to describe a continuum of disorders codified in the DSM-V in 2013, which broadened diagnostic inclusion criteria based on the recognized interrelationships and overlap between component characteristics. Of concern, over the last three decades the incidence of autism has increased more than ten-fold(1) and newer studies show a 30% increase in the last two years alone with a current incidence of 1 in 68.(2) Progress has been made in identification of gestational environmental risk factors for ASD; including extremes of gestational age(3) and birthweight appropriateness,(4) micronutrient insufficiency,(5) medication usage(6, 7), infections,(8–10) and maternal conditions associated with metabolic dysfunction. (11, 12) Fetal hypoxia and stress have been proposed as unifying mechanisms for several of these ASD risk factors. (13, 14)

Meconium, the tar-like primary feces composed of non-digested waste products, typically is eliminated shortly after birth. *In utero* release of meconium is associated with conditions indicative of placental insufficiency, leading to the hypothesis that fetal stressors, such as transient hypoxia, may trigger premature meconium release. (15, 16) In 5 to 25% of term births, meconium passes prior to delivery resulting in meconium stained amniotic fluid (MSAF). Whereas neonates born with MSAF typically do well, ~5% develop meconium aspiration syndrome (MAS). (17, 18) It is important to understand how MSAF and MAS affect long-term developmental outcomes.

A number of studies have tied MAS to neurodevelopmental disorders, including ASD and developmental delay. A Chicago study of 29 infants with MAS reported that 21% of children treated conventionally developed cerebral palsy or global neurodevelopmental delay.(19) In addition, a comprehensive meta-analysis of perinatal ASD risks found that children with MAS had on average a sevenfold higher risk of developing ASD.(20) These studies did not explore whether the association was due to MAS itself, its antecedent risk factors or immediate sequelae.

The goal of this study was to utilize a large birth cohort to determine the association between fetal meconium exposure and autism. Unique to our study, we attempted to determine the residual risk of MSAF and MAS on autism unaccounted for by antecedent stressors. We hypothesized that *in utero* meconium passage, as a marker for perinatal hypoxia, would be associated with autism, and that MAS, as a more severe clinical presentation with increased morbidity and likelihood for continued hypoxia, would be a more potent risk for autism.

METHODS

This study was a population-based cohort, approved by the California Committee for the Protection of Human Subjects (Protocol # 13-06-1255). We utilized a database merging three California administrative data sources to evaluate perinatal risk factors for developmental disabilities. The patient-discharge-diagnosis-birth cohort was generated by

linking Vital Statistics Birth and Infant Death Files published by the California Department of Health Services with maternal and infant hospital discharge records from the Office of Statewide Health Planning and Development for the period 1 January 1991 through 31 December 2008. This database provided perinatal data collected prospectively at the time of hospital discharge and birth certificate filing. We linked these data through Vital Statistics information to the California Department of Disabilities database in order to identify children with autism. We restricted our study population to infants born between 23 and 43 weeks gestation who survived to one year of age, as the birth data only included data through age one year old, and excluded children with comorbid congenital fetal anomalies.

In this analysis, the predictive variable was meconium exposure with two levels of severity, MAS and MSAF. We used presence of Internal Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) diagnosis codes to identify children with MAS (ICD-9-CM 770.11 & 770.12) and MSAF (ICD-9-CM 779.84), and used absence of these codes to delineate unexposed children as our referent group.

The outcome was a diagnosis of autism. Within California, 75 to 80% of children diagnosed with autism are followed up by the California Department of Developmental Services (DDS), which provides services for individuals with autism and other disabilities.(16) The DDS Client Development Evaluation Report database was utilized to identify children with autism by: (1) an autistic level of “one” (full syndrome autism) on any Client Development Evaluation Report; or (2) an ICD-9 code of 299.0 (autistic disorder), 299.8 or 299.9. While autism is typically diagnosed by age 3 years, the analysis included children identified by DDS through 31 December 2012, at which time the youngest members of our cohort were 4 years old, leaving time for children born towards the end of the cohort with some delay in diagnosis or entry to care to be included in the analysis. Children without any DDS diagnosis served as controls.

Possible confounders were identified based on previous research tying them to both meconium exposure and autism. They included maternal obesity,(21) preeclampsia/placental insufficiency,(14, 22) post-term delivery (>42 weeks gestation),(13, 23–26) large-for-gestational-age,(19, 24) fetal hypoxia,(5, 27) abnormal presentation,(15, 19) intra-amniotic infection(26, 28) and delivery mode.(27, 29) We calculated relative risks and 95% confidence intervals (CI) to estimate the strength of association between meconium exposures and autism. Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Our study population consisted of 9 945 896 children born in California from 1991 to 2008, 47 277 of whom were diagnosed with autism. Concerns regarding meconium-associated survivor bias introduced by only including children who survived the first year of life were allayed with findings that only 1.4% of children with MAS died before their first birthday. Demographic and clinical covariate rates were compared across strata of both predictors (Supplemental Tables S1 and S2) and outcomes (Tables 1 and 2).

Children with MSAF were on average 25% more likely to be diagnosed with autism than their unexposed counterparts, whereas those with MAS were 11% more likely to have autism in unadjusted analyses (Table 3). Fetal exposure to MSAF was associated with an 18% increased risk of being diagnosed with autism in logistic regression analyses controlling for cofounders (adjusted relative risk 1.18, 95% CI 1.12 to 1.25). There was only a slight increase in risk for autism that failed to reach significance among children diagnosed with MAS (adjusted relative risk 1. 08, 95% CI 0.98 to 1.20). Taken together, there was a 16% increased risk of being diagnosed with autism in children with either MSAF or MAS (adjusted relative risk 1.16, 95% CI 1.10 to 1.22).

DISCUSSION

Within our large California birth cohort, children with MSAF were slightly more likely to be diagnosed with autism even after comprehensive adjustment for known antepartum stressors. Counter to our expectation of a dose-response relationship, the rare but highly morbid possible complication of MSAF, MAS, conferred an only minimal and non-statistically significant increase in risk for autism, with an effect size half that of MSAF.

Our findings contribute to a body of evidence regarding autism risk following MSAF exposure and MAS that is conflicted at best. Two separate meta-analyses found no association between MSAF and ASD. The first(26) identified six studies, three of which showed no effect, two of which showed a positive association, and one of which showed a negative one; the summary effect measurement showed no association (odds ratio 0.82, 95% CI 0.25 to 2.69). The second study(16) included 10 studies, 2 of which had positive findings, none of which provided adjusted effect estimates that could be included in a pooled in analysis. Similarly, the first study(26) found evidence counter to ours with MAS, reporting a strong association between MAS and autism (odds ratio 7.34, 95% CI 2.30–23.47); however the focus of the study was broad and authors did not identify specific studies or their methods. Failure to adjust for relevant confounding in individual studies limited data available for summary effect measure calculation. In both meta-analyses, pre- and perinatal complications were grouped without particular regard to the individual events and their temporal relationships; as such, they may have controlled for elements within causal pathways limiting statistical precision. Past studies on MAS may have differing results partially because management of MAS has improved greatly over time, leading to less morbidity. In addition, these investigations are likely to have been underpowered given the rarity of the exposure and outcome, as well as the small effect size. Our extremely large birth cohort was needed to identify a difference. The current analysis is unique in its focus on meconium exposure and autism and its care to control for confounders unique to this specific relationship.

The residual association between MSAF and autism after controlling for known gestational complications may reflect our inability to control for perinatal stressors, both undetected and un-coded, associated with fetal meconium passage. Whatever the etiology, our results were counter to the dose-response relationship expected between MSAF, MAS and autism. One possible explanation is that it is not meconium exposure itself that instigates neuronal damage, but rather an unknown perinatal stressor, itself influencing neurodevelopment and

meconium elimination. Aggressive postnatal resuscitation in neonates with meconium-induced respiratory compromise may mitigate not only respiratory damage, but also later neurodevelopmental consequences. We speculate that subtle insults to the fetus, as might occur with low-grade intermittent hypoxia, may cause cellular trauma and trigger meconium release, but in the absence of respiratory distress, may evade neonatal detection and treatment, eventually resulting in some level of neurodevelopmental compromise as is seen in autism.

A few studies have looked at either MSAF or MAS as markers of hypoxic stress within the gestational environment and ASD. The Froehlich-Santino *et al.*(16)California twin study of 194 twin pairs, in which at least one was diagnosed with ASD, evaluated gestational and perinatal risks for ASD. Respiratory distress, which includes MAS, demonstrated the strongest individual association with increased risk for ASDs in the group as a whole (odds ratio 2.11, 95% CI 1.27 to 3.51). Burstyn *et al.*(31)performed a large retrospective cohort in Canada and identified a small correlation between hypoxia determined through blood pH and autism in full-term male children (odds ratio 1.28, 95% CI 1.03 to 1.60). Similarly, MSAF has been associated with both periods of fetal hypoxia and a risk for continuation of hypoxia into neonatal life. Severe hypoxemic insults can lead to global dysfunction, including cerebral palsy.(15) Milder insults may lead to more subtle abnormalities with a delayed onset like ASD.(32)

Specific impacts of fetal hypoxia on the central nervous system have been investigated in animal models. Chronic fetal hypoxia in rodents reduces cortical gray and white matter and augments ventricle volume.(15) Although cortical volume may be reestablished through increased neurogenesis and prolongation of the neurogenesis window,(33) maturation of interneurons and myelin structure is less likely to recover, resulting in defects in learning and memory.(33, 34) Similarly, hypoxia delays maturation of GABAergic neurons in the cerebral cortex, leading to neuron deregulation.(35) The dose and duration of fetal hypoxia, from mild to severe and acute to chronic, determines the form and extent of neurodevelopmental impairment.(33, 36) Numerous studies have reported that children with ASD have disorganized neuronal overgrowth, as well as over- and under-connectivity in various regions of the brain.(37) It seems plausible that processes of repair and regeneration in neurons and glial cells damaged perinatally would have a range of success. Perhaps children exposed to perinatal hypoxia manifesting as MSAF who go without resuscitation are able to broadly compensate for neuronal loss, but either form inappropriate synaptic connections or fail to prune this quickly regenerated neural network resulting in clinical phenotypes that comprise ASD.

Perinatal care providers already go to great lengths to prevent, recognize and treat suspected perinatal hypoxia to limit adverse neurodevelopmental outcomes. Clinical management of neonates exposed to MSAF has evolved in response to evidence from clinical outcomes research, resulting in abandonment of the practices of amnioinfusion and nasal-oropharyngeal suctioning in favor of expectant management.(38) Meconium-exposed neonates showing signs of compromise commonly undergo aggressive oxygenation, hydration, and supportive care, which have been shown to reduce the incidence of MAS as well as other morbidities and mortality.(27) Once MAS is diagnosed, therapy depends on the

clinical severity and ranges from respiratory optimization with suction and antibiotics to more intensive treatment with ventilation, inhaled nitric oxide, surfactant therapy and extracorporeal membrane oxygenation.(39). One attractive explanation for our findings is that these efforts also may mitigate long-term damage from hypoxia and reduce autism risk in neonates with MSAF without respiratory compromise.

A primary strength of this study is that we focused on a single exposure and explored its mechanisms along with specific confounders separately to understand the relative contribution of each within a complex web of influence. Another important asset of this analysis is the large and comprehensive 18-year birth cohort we utilize. The study population, including both cases and controls, is extremely diverse and representative of California's unique population with respect race, ethnicity, socioeconomic and cultural factors. Clinical data were collected prospectively and universally by all acute care hospitals in the state, avoiding recall and selection biases. Given the seriousness of MAS, its coding is likely to have been valid. Children who presented for DDS services underwent diagnostic confirmation using standardized clinical assessments, creating high-quality clinically validated outcome data.

Several weaknesses are inherent in our study design. Reported rates of MSAF were low, likely reflecting under-coding in births without clinically-relevant complications.(20, 27) This sort of bias, however, would be most likely to attenuate the association of interest. Although the enormity of our cohort allowed for the exploration of rare exposures and outcomes, it's sheer size may have highlighted associations that were simply due to chance. We excluded the 1.4% of children with extreme cases of MAS who died within the first year of life and those with cerebral palsy, given that they did not have the ability to be diagnosed with autism. Finally, although children with a DDS diagnosis of autism are likely to have the disorder, DDS files do not capture children who do not utilize state services, and these children would have been misclassified.

CONCLUSION

Children with MSAF had an 18% elevation in autism risk compared with those who were unexposed, though neonates with MAS had a lower and non-significant increase in autism risk. *In utero* adversity, often involving fetal hypoxemia, increases the risk of meconium passage; and when the exposure results in respiratory distress, resuscitation efforts may not only treat damaged pulmonary tissue but may also afford some neuroprotection. While the strength of the effect of MSAF on autism risk was small and of unclear clinical significance, our findings support a small role for meconium as a sentinel both for *in utero* adversity and increase for autism risk. This small risk, when magnified across the population, may have substantial impact and warrant revision of existing prevention efforts originally designed to limit adverse outcomes evident in the short term. Clinical signs of this sort – alone or in combination – provide valuable information to focus perinatal prevention efforts, allowing for identification of newborns at risk of neurodevelopmental compromise who may benefit from early interventions. Secondary prevention efforts developed to prevent immediate adverse clinical outcomes could be reassessed to accommodate findings that raise concern regarding long-term neural impairment associated with MSAF. Elucidation of the molecular

mechanisms underlying specific clinical stressors that prompt *in utero* meconium passage will serve to focus primary prevention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic Features by Autism Status

		Autism		Typical	
		#	%	#	%
Sex of Child	Male	39262	83	5040978	50.9
	female	8015	17	4857588	49.1
	missing	0	0	53	0
Age of Mother	<=20	3868	8.2	1461021	14.8
	21–25	9275	19.6	2395298	24.2
	26–30	12993	27.5	2694787	27.2
	30–35	12722	26.9	2178470	22
	35–40	7005	14.8	989378	10
	41+	1414	3	179665	1.8
Maternal Race / Ethnicity	Non-Hispanic White	16338	34.6	3146357	31.8
	African American	3592	7.6	630985	6.4
	Hispanic	19407	41	4848114	49
	Asian	4430	9.4	672919	6.8
	Pacific islander	2914	6.2	480223	4.9
	Other	596	1.3	120021	1.2
Parity	Nulliparous	20954	44.3	3888247	0.1
	1	15831	33.5	3088250	39.3
	2	6486	13.7	1679092	31.2
	3	2484	5.3	726289	17
	4	889	1.9	286237	7.3
	5 or higher	607	1.3	225509	2.9
	missing	26	0.1	4995	2.3
Payer	MediCal	17239	36.5	4619776	46.7
	Private insurance	16567	35	2851239	28.8
	Managed care	12193	25.8	2099325	21.2

	Autism		Typical	
	#	%	#	%
Self pay/uninsured	765	1.6	244081	2.5
Other insurance	423	0.9	61644	0.6
missing	90	0.2	22554	0.2

Table 2

Clinical Features by Autism Status

	Autism		Typical	
	#	%	#	%
Preeclampsia/Eclampsia	1823	3.9%	289404	2.9%
Maternal obesity	942	2.0%	140955	1.4%
Post-term	3403	7.2%	804904	8.1%
Placental insufficiency	6117	12.9%	1144916	11.6%
Fetal hypoxia	827	1.8%	168173	1.7%
Abnormal presentation	2396	5.1%	414519	4.2%
Intraamniotic infection	1252	2.7%	216844	2.2%
Large for gestational age	5992	12.7%	1226017	12.4%

Table 3

Results of Logistic Regression Analysis: Autism Odds in Relation to Meconium Exposure

	Autism v Typical			
	Crude / Unadjusted		Fully Adjusted*	
	cRR	95% CI	aRR	95% CI
	N=6,088,159		N=5,945,655	
MSAF vs None	1.25	1.19 – 1.33	1.18	1.12 – 1.25
MAS vs None	1.108	1.00 – 1.23	1.083	0.98 – 1.20
Either Exposure v None	1.22	1.16 – 1.28	1.16	1.10 – 1.22

*Adjusted for maternal age, race, parity, payer, obesity, and preeclampsia; as well as placental insuffiecnecy, breech presentation, and child sex.

cRR: Crude relative risk
aRR: Adjusted relative risk
CI: 95% confidence intervals