Original Investigation

Association of Autism With Induced or Augmented Childbirth in North Carolina Birth Record (1990-1998) and Education Research (1997-2007) Databases

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IMPORTANCE One in 88 children in the United States is diagnosed as having autism spectrum disorder. Significant interest centers on understanding the environmental factors that may contribute to autism risk.

OBJECTIVE To examine whether induced (stimulating uterine contractions prior to the onset of spontaneous labor) and/or augmented (increasing the strength, duration, or frequency of uterine contractions with spontaneous onset of labor) births are associated with increased odds of autism.

DESIGN, SETTING, AND PARTICIPANTS We performed an epidemiological analysis using multivariable logistic regression modeling involving the North Carolina Detailed Birth Record and Education Research databases. The study featured 625 042 live births linked with school records, including more than 5500 children with a documented exceptionality designation for autism.

EXPOSURES Induced or augmented births.

MAIN OUTCOMES AND MEASURES Autism as assessed by exceptionality designations in child educational records.

RESULTS Compared with children born to mothers who received neither labor induction nor augmentation, children born to mothers who were induced and augmented, induced only, or augmented only experienced increased odds of autism after controlling for potential confounders related to socioeconomic status, maternal health, pregnancy-related events and conditions, and birth year. The observed associations between labor induction/augmentation were particularly pronounced in male children.

CONCLUSIONS AND RELEVANCE Our work suggests that induction/augmentation during childbirth is associated with increased odds of autism diagnosis in childhood. While these results are interesting, further investigation is needed to differentiate among potential explanations of the association including underlying pregnancy conditions requiring the eventual need to induce/augment, the events of labor and delivery associated with induction/augmentation, and the specific treatments and dosing used to induce/augment labor (eg, exogenous oxytocin and prostaglandins).

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Autism comprises a spectrum of behavioral and cognitive disturbances of childhood development including core deficits in social interaction, language development, and patterns of repetitive behaviors and/or restricted interests. Autism spectrum disorders (ASDs) are highly heritable, with the relative risk for siblings to be greater than 18%.[1] It is estimated that 1 in 88 children in the United States is diagnosed as having ASD.[2] A common theme of previous ASD studies is the contribution of genetic predisposition to the development of the disorder; however, discordancy in these same studies demonstrates that environmental factors may influence normal development or alter regulatory processes. A recent study of dizygotic and, more highly concordant, monozygotic twins concluded that environmental factors influencing susceptibility to autism may exert their effect during the prenatal and early postnatal environments.[3]

Currently, significant interest centers on understanding the environmental factors that may contribute to autism risk, especially those that influence early brain development. In this study, we focused on the association between autism and labor induction (defined as stimulating uterine contractions prior to the onset of spontaneous labor)[4] and/or augmentation (defined as increasing the strength, duration, or frequency of uterine contractions in a woman with spontaneous onset of labor).[5] In investigating this association, we recognize the significant maternal and fetal benefits of labor induction and augmentation including reduced fetal/neonatal death and meconium aspiration syndrome[6]; lower cesarean delivery rates[7]; lower risk for neonatal ventilation, sepsis, and intensive care nursery admission[8]; and reduced maternal mortality.[9] Our work must be viewed within this larger framework for optimizing maternal and fetal health outcomes more broadly.

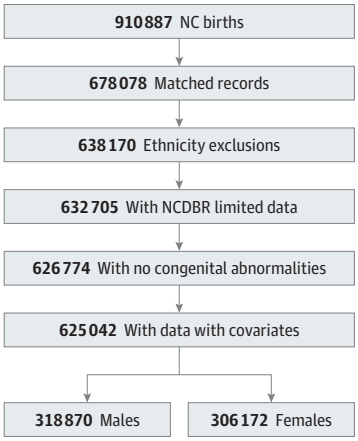
To our knowledge, previous research linking autism risk and labor induction/augmentation has been limited by small sample sizes and characterized by contradictory findings.[3,10-13] We used a population-based data set of more than 625 000 linked child educational and birth records from North Carolina to investigate whether birth induction or augmentation is associated with increased odds of being diagnosed as having autism, controlling for successive sets of potential confounders at the maternal level. Given sex-based differences in the etiology and neuroanatomy of autism development[12] and divergent patterns of autism occurrence in males and females, we also explored the potential for a differential role of induction/augmentation by sex.

Methods

Data Sources

We obtained data on all recorded live births occurring within North Carolina, including information on infant health, maternal and paternal demographics, maternal medical history, gestational age, parity, and events of labor and delivery, from the North Carolina Detailed Birth Record (NCDBR). Trained hospital staff extract these data from prenatal and hospital delivery records, in addition to integrating information on medical history obtained directly from the patient. The accuracy of maternal demographic and birth outcome variables in the NCDBR has been validated in previous work.[14] Potential events and complications occurring during labor and delivery are available in the NCDBR—including fever, meconium-stained fluid, fetal distress, placental abruption, and cord prolapse—and were incorporated into our regression models.

Figure. Filtering Process of Data Included in This Study From the North Carolina (NC) Detailed Birth Record (DBR) and Education Research Data Center Databases



We limited the data set to mothers between the ages of 15 and 49 years, infants weighing at least 400 g at delivery, and infants born at between 24 and 42 weeks' gestation. Births with congenital anomalies were also excluded. We removed records with missing information on key covariates including infant sex, multiple births, maternal education, maternal marital status, maternal smoking status, parity, and mode of delivery. The 1732 records excluded owing to missing covariate information were more likely to have a positive autism diagnosis and less likely to have been induced or augmented than those in the final data set (1.5% vs 0.9% and 19% vs 29%, respectively).

Information on autism diagnosis was extracted from statewide educational records maintained by the North Carolina Education Research Data Center (NCERDC). These records cover all children in North Carolina public schools and contain an indicator for exceptionality including a designation for autism (defined in detail here). This study was performed in compliance with parallel protocols approved by the institutional review boards at the University of Michigan and Duke University.

Study Population

We linked 1990-1998 birth records with educational data from the 1997-1998 to 2007-2008 academic years for the entire state of North Carolina. Records were iteratively matched using a child's first and last name, date of birth, and county of residence according to varying levels of match stringency. Of 910 887 births, 678 078 (74.4%) were successfully matched. Differences between the matched and unmatched data sets are presented in the eTable in Supplement.

The data set was restricted according to the **Figure** and in keeping with standard analytical practice when using the NCDBR.[15-17] Births were restricted to mothers whose self-reported race/ethnicity was non-Hispanic white or non-Hispanic black, given the differential prevalence in Hispanic individuals in the United States, likely the result of cultural and ascertainment factors.[2,18]

Outcome Definition

A federally mandated exceptionality designation of special needs, an autism diagnosis in the NCERDC database is based on a prior clinical diagnosis of autism and further evaluation by a school psychologist that includes standard individualized testing. An individual satisfies the special needs eligibility criteria by displaying deficits in 3 of 4 fields: communication, social reciprocity, behavior, or sensory. During the school years in this study, exceptionality designations were recorded in various formats, with some years allowing for multiple designations while other years restricting to a primary designation. Without guidelines as to how to classify a primary vs alternative designation, the specific designation documented for a child exhibiting multiple exceptionalities was at the discretion of school personnel. We searched all available educational records and exceptionality designations for a given child and constructed a dichotomous variable for whether a child had ever received an autism designation.

Primary Exposure Definition

Using NCDBR variables for labor induction and augmentation, we constructed a 4-category variable to indicate that during delivery a mother was either not induced or augmented (reference), induced and augmented, induced only, or augmented only. Currently, we do not have further granularity of dose rates during induction or additional protocols used during augmentation within the NCDBR.

Statistical Analysis

We estimated the odds of autism associated with induction/augmentation with multivariable logistic regression. We fit 5 model specifications to distinguish between the roles of induction/augmentation and underlying pregnancy and labor conditions in the likelihood of being diagnosed as having autism. Model 1 included only induction/augmentation and infant sex. Model 2 added standard maternal-level characteristics including non-Hispanic black race/ethnicity; maternal age in years measured continuously; whether a child was first born; singleton birth; maternal educational attainment categorized as middle school or less (<8th grade), some high school (<12th grade), completed high school (12th grade; reference), some college (13-15 years of education), and completed college (≥16 years of education); and marital status. Model 3 added maternal medical conditions and health behaviors including hypertension status, diabetes mellitus status, and whether a mother reported smoking during pregnancy. Model 4 expanded model 3 to control for events of labor and delivery including breech presentation, meconium, fetal distress, and febrile status; gestational age in weeks entered as ≤34, 35-36, and ≥37 (reference); and mode of delivery, entered as vaginal (reference), operational vaginal, or cesarean delivery. Model 5 added to model 4 an ordinal variable for child birth year. We additionally investigated the potential for a nonlinear relationship (on the odds scale) between maternal age and autism by fitting corresponding models with maternal age operationalized in 5-year age categories. Because the odds of autism increased approximately linearly with each successive category, we selected to present the simpler specification with maternal age entered continuously. **Table 1** includes an explanation of inclusion for selected covariates.

Table 1. Covariates From the NCDBR and Reasons for Inclusion in the Analysis

NCDBR Variable	Reason for Including Variable
Events of labor and delivery	
Febrile	Marker for chorioamnionitis[19]
Meconium	Meconium aspiration syndrome, which can occur in the setting of meconium-stained fluid, has been shown to be associated with ASDs[3]
Breech presentation	Has been shown to be an independent predictor of ASDs[3,20]
Fetal distress	Catch-all phrase on birth certificates that includes nonreassuring fetal heart rate patterns, among other risk factors associated with acute hypoxic events[3]
Placental abruption	Has been shown to increase the risk for neonatal hypoxic injury and autism[3,21]
Cord prolapse	An acute intrapartum event that is associated with neonatal hypoxic injury[21]
Mode of delivery	Cesarean deliveries increased over the same period as induction/augmentation and autism[22]
Vaginal	
Operational vaginal	
Cesarean	
Unknown	
Maternal medical conditions	Maternal hypertensive disorders and diabetes mellitus have both been associated with neonatal neurologic disorders[21,23]
Hypertension: chronic, gestational, or preeclampsia	
Diabetes mellitus: gestational or pregestational	
Birth outcome status	Prematurity has been shown to be associated with ASDs[24]
Gestational age, wk	
≤34	
35-36	
≥37	
Smoked during pregnancy	Has been shown to be associated with ASDs[22]

Abbreviations: ASDs, autism spectrum disorders; NCDBR, North Carolina Detailed Birth Record.

To examine sex-based differences in the association between induction/augmentation and autism, we reran model 5 adding an interaction between infant sex and induction/augmentation (model 6). We computed the marginal effect of each induction/augmentation category on autism diagnosis by sex. Associated 95% confidence intervals were calculated with the delta method.[25] Based on models 5 and 6, we estimated the covariate-adjusted population attributable risk (PAR) using Stata's REGPAR[26] command. The covariate-adjusted PAR[27] is the proportion of the disease in the population that could be eliminated if all exposed individuals became unexposed, after adjusting out covariate effects. We used model 5 to compute the PAR irrespective of sex group and model 6 to compute the sex-specific PARs, both in the exposed populations.

We conducted sensitivity analyses of our results. First, we examined whether our estimated coefficients from simple lo-

Table 2. Characteristics of Study Population by Sex and Autism Status for North Carolina Births 1990-1998

Variable	No. (%)			
	Males		Females	
	Noncases (n = 314 585)	Autistic Cases (n = 4285)	Noncases (n = 304 809)	Autistic Cases (n = 1363)
Induction/augmentation category				
Induced or augmented	90 233 (28.68)	1361 (31.76)	86 326 (28.32)	400 (29.35)
Induced and augmented	5755 (1.83)	98 (2.29)	5342 (1.75)	23 (1.69)
Induced only	39 668 (12.61)	597 (13.93)	37 887 (12.43)	154 (11.3)
Augmented only	44 810 (14.24)	666 (15.54)	43 097 (14.14)	223 (16.36)
Not induced or augmented	224 352 (71.32)	2924 (68.24)	218 483 (71.68)	963 (70.65)
Events of labor and delivery				
Breech	11 660 (3.71)	186 (4.34)	13 088 (4.29)	48 (3.52)
Fetal distress	30 021 (9.54)	524 (12.23)	25 167 (8.26)	163 (11.96)
Meconium	22 778 (7.24)	384 (8.96)	24 626 (8.08)	149 (10.93)
Febrile	6247 (1.99)	91 (2.12)	5796 (1.9)	33 (2.42)
Cord prolapse	1368 (0.43)	10 (0.23)	1180 (0.39)	3 (0.22)
Placental abruption	2297 (0.73)	28 (0.65)	2042 (0.67)	9 (0.66)
Mode of delivery				
Cesarean delivery	74 918 (23.81)	1122 (26.18)	67 085 (22.01)	298 (21.86)
Operational vaginal	41 989 (13.35)	592 (13.82)	35 557 (11.67)	147 (10.79)
Vaginal	197 678 (62.84)	2571 (60)	202 167 (66.33)	918 (67.35)
Maternal medical conditions				
Hypertension	20 473 (6.51)	308 (7.19)	19 536 (6.41)	78 (5.72)
Diabetes mellitus	8786 (2.79)	171 (3.99)	8712 (2.86)	49 (3.6)
Gestational age, wk				
≤34	12 824 (4.08)	230 (5.37)	11 991 (3.93)	75 (5.5)
35-36	18 184 (5.78)	270 (6.3)	17 173 (5.63)	91 (6.68)
≥37	283 577 (90.14)	3785 (88.33)	275 645 (90.43)	1197 (87.82)
Singleton birth	306 677 (97.49)	4140 (96.62)	296 847 (97.39)	1304 (95.67)
Maternal race/ethnicity				
Non-Hispanic white	212 604 (67.58)	2611 (60.93)	203 868 (66.88)	725 (53.19)
Non-Hispanic black	101 981 (32.42)	1674 (39.07)	100 941 (33.12)	638 (46.81)
Maternal age, mean (SD), y	26 (5.87)	27 (6.06)	26 (5.89)	27 (5.99)
First born	138 695 (44.09)	1969 (45.95)	133 768 (43.89)	544 (39.91)
Maternal educational attainment level				
≤Middle school	7336 (2.33)	65 (1.52)	7342 (2.41)	29 (2.13)
Some high school	60 112 (19.11)	619 (14.45)	58 834 (19.3)	215 (15.77)
High school diploma	122 443 (38.92)	1509 (35.22)	118 897 (39.01)	507 (37.2)
Some college	68 734 (21.85)	1025 (23.92)	66 642 (21.86)	299 (21.94)
≥College	55 960 (17.79)	1067 (24.9)	53 094 (17.42)	313 (22.96)
Not married	107 499 (34.17)	1416 (33.05)	105 127 (34.49)	502 (36.83)
Smoked during pregnancy	58 853 (18.71)	621 (14.49)	57 022 (18.71)	208 (15.26)

gistic regression were substantively affected by bias from having a rare outcome such as autism.[28] We fit models 5 and 6 using a correction adjustment for rare events data operationalized with the ReLogit function in Stata version 11.0.[29] Second, to examine the possibility of confounding by multifetal gestations, we refit models 5 and 6 while restricting the data set to singleton births.

All analyses were conducted in Stata version 11.0 (StataCorp) and R version 2.15.1 (The R Foundation for Statistical Computing, 2012).

Results

Approximately 1.3% and 0.4% of male and female children were diagnosed as having autism, respectively (**Table 2**). Among both sexes, the percentage of induced or augmented mothers was higher among children with autism compared with noncases. Moreover, children with autism were more likely to have a birth characterized by fetal distress or meconium. Although we had initially intended to examine placental abruption and

cord prolapse, small cell sizes, particularly among female children, precluded including these risk factors.

Table 3 presents the 5 regression model specifications. In model 1, which controlled only for male infant sex, a child whose mother was induced and augmented during delivery had 23% higher odds of being diagnosed as having autism than a child whose mother was neither induced nor augmented (odds ratio [OR], 1.23; 95% CI, 1.02-1.47). The odds ratios for the induced-only and augmented-only categories were 1.10 (95% CI, 1.01-1.19) and 1.15 (95% CI, 1.07-1.24), respectively. Compared with female children, males exhibited increased odds of autism diagnosis (OR, 3.04; 95% CI, 2.86-3.24).

In models 2 through 4, the inclusion of successive sets of potential confounders related to socioeconomic status, maternal health, and pregnancy-related events and conditions did not substantively alter the estimated ORs for induction/augmentation from those observed in model 1. However, in model 5, the inclusion of a child's birth year shifted the magnitude of the ORs. Compared with the reference group, a child whose mother was both induced and augmented at delivery had 27% higher odds of being diagnosed as having autism (OR, 1.27; 95% CI, 1.05-1.52). The ORs for the induced-only and augmented-only categories indicated an approximate 13% to 16% increase in the odds of autism, respectively, relative to the reference group.

Because the ORs for maternal-level risk factors were largely unchanged across models 2 through 5, we described observed associations in model 5. Among events of labor and delivery, fetal distress and meconium presented a detrimental association with autism diagnosis (OR for fetal distress, 1.25; 95% CI, 1.15-1.36; OR for meconium, 1.22; 95% CI, 1.11-1.34). A child born very preterm (≤34 weeks) experienced an average 25% increased odds of autism compared with a child born at full term (OR, 1.25; 95% CI, 1.11-1.41). Mothers with diabetes mellitus had 23% higher odds of having a child with autism than mothers without diabetes mellitus (OR, 1.23; 95% CI, 1.07-1.41). The estimated ORs for the mode of delivery categories were each near null. Non-Hispanic black race/ethnicity, first birth, older maternal age, and higher maternal education were associated with elevated odds of autism.

Model 6 added to model 5 an interaction term between infant sex and induction/augmentation (**Table 4**). Because ORs for the maternal-level factors were essentially unchanged from those shown in model 5, the left side of Table 4 presents only the log-odds coefficients for induction/augmentation, infant sex, and their interaction necessary to compute the marginal effects of induction/augmentation on autism diagnosis by sex group. Marginal effects and associated 95% CIs are displayed to the right. Among females, the OR associated with the augmented-only category was 1.18 (95% CI, 1.02-1.36). In contrast, among males, each induction/augmentation category exhibited increased odds of an autism diagnosis relative to children born to mothers who were neither induced nor augmented. Male children born to mothers who received both induction and augmentation had 35% higher odds of autism diagnosis than the reference group (95% CI, 1.10-1.66).

Based on model 6, among male children born to a mother who received induction and/or augmentation, the covariate-adjusted PAR was 0.002 (95% CI, 0.001-0.003), indicating that if male exposed children (ie, those whose mothers received induction and/or augmentation) theoretically became unexposed, 2 of 1000 children would no longer have a positive autism diagnosis. Among female exposed children, the corresponding PAR was 0.0003, with the associated 95% CI rightward leaning but containing the null (95% CI, −0.0002 to 0.0008). These sex-specific PARs compared with the overall PAR in the exposed population of 0.001 (95% CI, 0.0007-0.002), as computed from model 5, which did not include a treatment by sex interaction.

In sensitivity analysis, the estimated coefficients in models 5 and 6 did not substantively change using a correction adjustment for rare-events data (results not shown), most likely because of our large sample size. Moreover, restricting the data set to singleton births also left associations unchanged (results not shown).

Discussion

Compared with children whose mothers were neither induced nor augmented during labor, children born to mothers who were either induced and augmented, induced only, or augmented only experienced increased odds of autism. Autism diagnosis differentially associated with induction/augmentation by sex, whereby a stronger association was observed among male children. To our knowledge, this is the first large-scale study to address the relationships among birth induction/augmentation and autism. This study also confirmed previously documented risk factors for autism such as advanced maternal age and maternal education, parity, and singleton birth (as reviewed by Gardener et al[3] and Guinchat et al[13]).

Genetic and epidemiological data consistently report an average 4:1 bias of male individuals with autism to females in overall cohort analyses.[30] We found male children to have increased odds of autism compared with female children. In interaction models, male children were more sensitive to birth induction/augmentation, while only augmentation was significantly associated with autism diagnosis among female children. Other studies have demonstrated the association of fetal distress,[31] meconium-stained fluid,[31] preterm delivery,[24] and maternal diabetes mellitus status[23] with ASD. We controlled for each of these variables and found that labor induction and augmentation continued to be independently associated with ASD in offspring.

One possible explanation for the induction/augmentation-ASD association is through exposure to exogenous oxytocin. An estimated 50% to 70% of women who undergo labor induction receive exogenous oxytocin,[32-35] a suggested contributor to the development of autism.[36] Furthermore, 2 large European studies demonstrated that 30% to 50% of women in spontaneous labor required oxytocin augmentation during the course of labor.[32,34] Biologically, oxytocin signaling plays important prosocial roles influencing social behavior and cognitive function[37,38] and displays sexually dimorphic roles in brain function and behavior.[39] Exposure to exogenous oxytocin during induction/augmentation may have a functional effect through, as yet, unidentified genetic or epigenetic factors. For

Table 3. Multivariable Logistic Regression Models of Autism Diagnosis on Induction/Augmentation Treatment Status for 3rd- to 8th-Grade Children[a,b]

	Odds Ratio (95% CI)				
	Model 1	Model 2: Model 1+Maternal-Level Characteristics	Model 3: Model 2+Maternal Conditions Harmful to Pregnancy	Model 4: Model 3+Events of Labor and Delivery, Mode of Delivery, and Gestational Age	Model 5: Model 4+Year Birth of Child
Induction/augmentation treatment category					
Not induced and not augmented	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Induced and augmented	1.23 (1.02-1.47)	1.21 (1.01-1.46)	1.21 (1.01-1.46)	1.2 (1-1.44)	1.27 (1.05-1.52)
Induced only	1.1 (1.01-1.19)	1.11 (1.02-1.2)	1.11 (1.02-1.2)	1.1 (1.02-1.19)	1.13 (1.04-1.22)
Augmented only	1.15 (1.07-1.24)	1.14 (1.06-1.23)	1.14 (1.06-1.23)	1.14 (1.05-1.22)	1.16 (1.07-1.25)
Male	3.04 (2.86-3.24)	3.06 (2.87-3.25)	3.06 (2.87-3.25)	3.05 (2.87-3.25)	3.05 (2.87-3.25)
Non-Hispanic black		1.67 (1.57-1.78)	1.64 (1.54-1.75)	1.6 (1.51-1.71)	1.59 (1.49-1.7)
Maternal age[c]		1.3 (1.26-1.35)	1.31 (1.27-1.35)	1.3 (1.26-1.34)	1.31 (1.26-1.35)
First born		1.21 (1.15-1.29)	1.21 (1.14-1.28)	1.19 (1.12-1.26)	1.19 (1.12-1.26)
Singleton		0.72 (0.63-0.83)	0.72 (0.63-0.83)	0.76 (0.66-0.89)	0.76 (0.65-0.88)
Maternal educational attainment level					
Middle school		0.99 (0.8-1.22)	1.01 (0.82-1.25)	1.01 (0.82-1.25)	1.01 (0.82-1.24)
Some high school		0.96 (0.88-1.05)	0.98 (0.9-1.07)	0.98 (0.9-1.06)	0.98 (0.9-1.06)
High school		1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Some college		1.1 (1.03-1.19)	1.09 (1.02-1.17)	1.09 (1.02-1.17)	1.11 (1.03-1.19)
College		1.33 (1.24-1.44)	1.3 (1.21-1.41)	1.31 (1.21-1.41)	1.33 (1.23-1.44)
Not married		1.05 (0.97-1.12)	1.06 (0.99-1.14)	1.05 (0.98-1.13)	1.07 (0.99-1.15)
Maternal conditions harmful to pregnancy					
Hypertension			0.95 (0.85-1.05)	0.93 (0.84-1.04)	0.94 (0.84-1.05)
Diabetes mellitus			1.24 (1.08-1.42)	1.24 (1.08-1.42)	1.23 (1.07-1.41)
Smoking			0.87 (0.81-0.94)	0.86 (0.79-0.93)	0.85 (0.79-0.92)
Events of labor and delivery					
Breech				1.03 (0.9-1.19)	1.04 (0.9-1.2)
Fetal distress				1.27 (1.17-1.38)	1.25 (1.15-1.36)
Meconium				1.21 (1.11-1.33)	1.22 (1.11-1.34)
Febrile				0.99 (0.83-1.19)	1 (0.83-1.2)
Gestational age, wk					
≤34				1.24 (1.1-1.4)	1.25 (1.11-1.41)
35-36				1.09 (0.98-1.22)	1.09 (0.98-1.22)
≥37				1 [Reference]	1 [Reference]
Mode of delivery					
Vaginal				1 [Reference]	1 [Reference]
Cesarean				0.97 (0.91-1.04)	0.97 (0.9-1.03)
Operational vaginal				0.98 (0.9-1.07)	0.97 (0.89-1.05)
Birth year of child					
1990					1 [Reference]
1991					1.44 (1.28-1.61)
1992					1.47 (1.31-1.65)
1993					1.5 (1.33-1.68)
1994					1.51 (1.34-1.69)
1995					1.4 (1.24-1.57)
1996					1.05 (0.92-1.18)
1997					0.9 (0.79-1.02)
1998					0.89 (0.78-1.01)

[a] For each model, the total number of records is 625 042, including 619 394 noncases and 5648 cases. For cell counts corresponding to each covariate, Table 1 presents the numbers by sex and autism status.

[b] For academic years 1999-2000 through 2007-2008 in North Carolina.

[c] Maternal age was centered at the overall sample mean (26) and scaled to represent a 1 standard deviation increase (5.88).

Table 4. Associations of Induction/Augmentation Treatment Status with Autism Diagnosis by Sex for 3rd- to 8th-Grade Children[a]

Model 6[b,c]				
Logit Regression Model		Effects of Induction/Augmentation Status by Sex		
			Odds Ratio (95% CI)	
Selected Coefficients	Beta (95% CI)	Induction/ Augmentation Status	Females	Males
Not induced and not augmented	1 [Reference]	Not induced and not augmented	1 [Reference]	1 [Reference]
Induced and augmented	0.01 (−0.4 to 0.43)	Induced and augmented	1.01 (0.67 to 1.53)	1.35 (1.1 to 1.66)
Induced only	−0.05 (−0.22 to 0.12)	Induced only	0.95 (0.8 to 1.13)	1.18 (1.08 to 1.3)
Augmented only	0.16 (0.02 to 0.31)	Augmented only	1.18 (1.02 to 1.36)	1.15 (1.05 to 1.25)
Male sex	1.09 (1.01 to 1.16)			
Induced and augmented × male[d]	0.29 (−0.17 to 0.75)			
Induced only × male	0.22 (0.03 to 0.41)			
Augmented only × male	−0.02 (−0.19 to 0.14)			

[a] For academic years 1999-2000 through 2007-2008 in North Carolina.

[b] As in Table 3, the total number of records is 625 042. Of 318 870 males, 314 585 records were noncases and 4285 were cases. Of 306 172 females, 304 809 were noncases and 1363 were cases. (Table 1 provides further details.)

[c] Model 6 additionally controlled for the same variables as model 5 in Table 3.

[d] The χ^2 test for interaction between the sex and induction/augmentation status with 3 degrees of freedom equaled 6.68 (P = .08).

example, we recently found differential methylation of the promoter region of the oxytocin receptor (OMIM: 167055, OXTR) in autism case and control populations.[40]

Our study was not without limitations. First, although we observed an association between induction/augmentation and diagnosis of ASD following adjustment for underlying conditions related to neonatal neurologic injury and fetal hypoxia that are recorded in the NCDBR, we did not have data for every potential confounder or potential source for neonatal neurologic injury. For example, the NCDBR does not contain information on maternal prenatal or intrapartum medication exposures, nor does it contain information on labor abnormalities such as uterine tachysystole, which may be associated with neonatal neurologic injury when accompanied by abnormalities in the fetal heart rate tracing.[41] Second, the NCDBR has substantial missing data on paternal age, and we were unable to link siblings. Third, the education data did not provide any indication of where a child lay on the autism spectrum; thus, the estimated associations represent an average effect over varying degrees of autism presentation. Fourth, for certain years of the education data, children with a secondary diagnosis of autism would not necessarily have been identified in our data set given that we specified an exceptionality of only autism and not autism as part of a syndromic presentation. Despite this measurement challenge, autism prevalence in our study sample was consistent with that reported nationally and in the state of North Carolina.[2]

While we found a significant association between labor induction/augmentation and autism, there are significant benefits to labor induction/augmentation. Labor induction and augmentation are used to expedite delivery in women with conditions that pose an increased risk for fetal death if the fetus remains in utero. Furthermore, postdate pregnancy is associated with fetal/neonatal death and meconium aspiration syndrome, a severe complication with significant morbidity. An Australian study of 877 037 births from 1997-2008 demonstrated a reduction in meconium aspiration syndrome, while at the same time, the induction rate increased from 22% to 27% and the percentage of women delivering at greater than 40 weeks' gestation fell from 57% to 47%.[6] A Cochrane Database Systematic Review summarized 22 trials consisting of more than 9300 women and found that a policy of labor induction for term women resulted in fewer fetal deaths and fewer cases of meconium aspiration syndrome and resulted in a lower cesarean delivery rate compared with a policy of expectant management of women at term.[7] Finally, the Consortium for Safe Labor analyzed data from 115 528 births from 2002-2008 and found that elective induction was associated with lower risk for neonatal ventilation, sepsis, and intensive care nursery admission.[8]

In conclusion, although increasing labor induction rates have been associated with decreases in neonatal mortality rates,[42] our results suggest the need for further research focusing on the association of labor induction/augmentation with autism. It remains unclear whether (1) the act of labor induction/augmentation itself or the medications used underlie the association; (2) the medical and obstetric conditions that are associated with labor induction/augmentation drive the association; or (3) acute intrapartum events that are more common among women with labor induction/augmentation drive its association with autism. In future work entailing careful review and analysis of medical records, we plan to investigate these 3 potential pathways. Our results are not sufficient to suggest altering the standard of care regarding induction or augmentation; our results do suggest that additional research is warranted.

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