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Research Paper

Assessing the Role of Asthma on the Relationship between Neurodevelopmental Disabilities and Adverse Birth Outcomes

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ABSTRACT

Background: Investigating asthma as an effect modifier between adverse birth outcomes and neurodevelopmental disabilities (NDDs) across different races is crucial for tailored interventions and understanding variable susceptibility among diverse populations.
Methods: Data were collected through the National Survey of Children's Health. This cross-sectional study included 131,774 children aged 0 to 17 years. Study exposures comprised adverse birth outcomes including preterm birth and low birth weight. Weighted prevalence estimates and odds ratios with 95% confidence intervals (CIs) among children with and without adverse birth outcomes were calculated for NDDs including attention-deficit/hyperactivity disorder, autism spectrum disorder, cerebral palsy, seizure, and several others including behavior problems. Adjusted odds ratios were stratified by asthma status and separate interactions were assessed for each outcome.
Results: Of 131,774 participants, 10,227 were born low birth weight (9.12%; 95% CI: 8.77% to 9.49%), 14,058 were born preterm (11.35%; 95% CI: 10.94% to 11.76%), and 16,166 participants had asthma (11.97%; 95% CI: 11.58% to 12.37%). There were 68,100 males (51.11%), 63,674 females (48.89%), 102,061 non-Hispanic Whites (NHW) (66.92%), 8,672 non-Hispanic Blacks (NHB) (13.97%), and 21,041 participants (19.11%) categorized as other. NHB children with adverse birth outcomes had higher prevalence of several NDDs compared to NHW children.
Conclusions: Asthma was not shown to be an effect modifier of the association between adverse birth outcomes and NDDs. Nevertheless, these results suggest that NDDs are more prevalent within US children with adverse birth outcomes, with higher rates among NHB compared to NHW children. These findings support screening for NDDs in pediatric health care settings among patients with adverse birth outcomes, particularly among those from ethnic minority backgrounds.

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Introduction

Neurodevelopmental disabilities (NDDs) are a group of disorders that affect nervous system development and impair brain function.[1] NDDs include behavioral conditions, including autism spectrum disorder, intellectual disabilities, and motor function disabilities.[1,2] With approximately 53 million children diagnosed with NDDs globally, these conditions are a significant burden and cause of morbidity in children.[3-6]

Two major causes of NDDs are preterm birth (birth that occurs before 37 weeks of pregnancy) and low birth weight (weighing 2500 g or less at birth).[7-9] A major risk factor for preterm birth and low birth weight is maternal race/ethnicity. Non-Hispanic black (NHB) race/ethnicity (compared with non-Hispanic white [NHW] race/ethnicity) continues to be a significant risk factor for preterm birth and low birth weight.[10-14] Previous studies have found that NHB women have a significantly higher risk of preterm birth and low birth weight compared with NHW women.[10-14]

Although advances in prenatal care have significantly decreased the morbidity of preterm infants and infants born with low birth weight, disparities remain, and many of these infants still suffer from a range of NDDs and comorbidities such as asthma as they grow older.[9,15] Asthma is one of the most common chronic illnesses worldwide, posing significant societal burden and health care costs.[4] Furthermore, several studies have found that asthma is associated with various NDDs.[16-18]

Although neurodevelopment disabilities are associated with asthma, preterm birth, and low birth weight, very few studies have investigated the role of asthma as a potential modifier of NDDs and adverse birth outcomes relationship. The studies that have investigated this relationship were smaller-scale studies or had very limited external validity (e.g., study samples restricted to one gender or demographic group).[17,18] We recognize the need to conduct a large-scale study to generate findings in developmental biology that are more generalizable to the population at large.

We therefore examined the role of asthma and its relationship with (1) preterm birth and NDDs and (2) low birth weight and NDDs in a large, representative population-based sample. We hypothesized that the strength and direction of associations would be conditional on asthma status, such that birth indicators would be more strongly and positively related to NDDs among individuals with asthma.

Materials and Methods

Data source and sample design

A total of 131,774 children aged zero to 17 years who participated in the National Survey of Children's Health (NSCH) from 2016 to 2019 were included in this cross-sectional study.[19] The NSCH is a national population-based survey that provides data on intersecting aspects of children's health, including physical and mental health, access to health care, and social support. The survey is directed by the Health Resources and Services Administration Maternal and Child Health Bureau. From 2003 to 2012, the NSCH was conducted using telephone surveys every four years. In 2016, the NSCH was significantly modified and merged with the National Survey of Children with Special Health Care Needs to better encompass current pediatric health needs. Since 2016, the NSCH has been conducted annually using web and mail surveys.

US households were randomly contacted by mail to determine whether there was at least one eligible child under age 18 years at home. In each eligible household, one child was randomly selected by the parent to be the subject of the main survey. For the 2016 survey data were collected from June 2016 to January 2017, 2017 survey data were collected from August 2017 to February 2018, 2018 survey data were collected from June 2018 to January 2019, and 2019 survey data were collected from June 2019 to January 2020. To obtain weighted survey estimates representing the population of noninstitutionalized children, each child was assigned a weight that began with a base sampling weight for each household and was then adjusted for screener and topical nonresponse, household with more than one child, and various characteristics of children in different states in the respective study years. The overall weighted response rate was 40.7% (n = 50,212) for 2016, 37.4% (n = 21,599) for 2017, 43.1% (n = 30,530) for 2018, and 42.4% (n = 29,433) in 2019.

Measurements and assessments

Adverse birth outcomes

The study exposures of interest were preterm birth and low birth weight. Preterm birth was defined as a birth that occurs before 37 weeks of pregnancy, and low birth weight was defined as weighing 2500 g or less at birth. To ascertain these exposures the parent was asked “What was the child's birth weight?” and “Was the child born prematurely, that is, more than 3 weeks before [his/her] due date?”

Neurodevelopmental and related disorders

The outcomes of interest were neurodevelopmental and related disorders including, but not limited to, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, cerebral palsy, seizure, blindness, hearing loss, speech problem, intellectual disability, learning disability, developmental delay, Tourette syndrome, brain injury, and behavior problems. Blindness was assessed by the question “Does this child have blindness or problems with seeing, even when wearing glasses?” and hearing loss was assessed by the question “Does this child have deafness or problems with hearing?” All other neurodevelopmental and related disorders were assessed using two questions: “Has a doctor or other health care provider ever told you that this child has the condition?” and “If yes, does this child currently have the condition?”

Covariables

Asthma was evaluated as an effect modifier in our study. The NSCH ascertained asthma by asking the parent the following questions: “Has a doctor or other health care provider ever told you that this child has asthma?” and, if yes, “Does the child currently have the condition?” The survey classified asthma severity as mild, moderate, or severe.[19] Additional covariables included in our analysis included age, sex, race/ethnicity, education, income based on federal poverty level, the number of children in the family, and whether the child lived with a family member with a drug or alcohol problem. These covariables were selected based on observed associations with preterm birth, low birth weight, and/or neurodevelopmental disorders in prior studies.[10-14,20-22]

Statistical methods

Weighted prevalence estimates were generated for demographic characteristics among children born preterm and at term and among children born with low birth weight and normal birth weight. Weighted prevalence estimates and 95% confidence intervals (CIs) were generated for each NDD among children born preterm and at term as well as among children born with low birth

weight and normal birth weight. The prevalence estimates for each NDD were further stratified by race/ethnicity.

Logistic regression was used to estimate the crude odds of NDD among preterm children and low-birth-weight children, separately. Multivariable logistic regression generated the adjusted odds ratio of NDDs and preterm birth and low birth weight, separately, after controlling for the covariables stated above.

To assess whether the presence of asthma influenced the association between NDDs and adverse birth outcomes, multivariable logistic regression was conducted to determine the association between NDDs and preterm birth and low birth weight separately, stratified by the presence or absence of asthma. Furthermore, the interaction between asthma status and preterm birth with respect to NDDs was assessed by including an interaction term for asthma status by preterm birth in the multivariable logistic regression. This interaction term allowed us to determine whether the association between preterm birth and NDDs changed based on the presence or absence of asthma. Similarly, the interaction between asthma status and low birth weight with respect to NDDs was assessed. A two-sided *P* value of 0.05 was considered significant, and all analyses were conducted using STATA 17.[23]

Ethical considerations

This study is exempt from approval from the University of Texas Health Science Center Institutional Review Board because the data used for analysis are deidentified, publicly available data.

Results

Sample characteristics

A total of 131,774 participants were analyzed of whom 37,405 participants (32.21%) were aged zero to five years, 39,935 participants (33.77%) were aged six to 11 years, and 54,434 participants (34.02%) were aged 12 to 17 years (Table 1). There were 68,100 males (51.11%), 63,674 females (48.89%), 102,061 NHWs (66.92%), 8672 NHBs (13.97%), and 21,041 participants (19.11%) categorized as Other. A total of 10,227 were born with low birth weight (9.12%), 14,058 were born preterm (11.35%), and 16,166 participants had asthma (11.97%).

TABLE 1.
Descriptive Characteristics of the Pediatric Study Sample, 2016-2019 National Survey of Children's Health Study (n = 131,774)

Characteristics	Frequency (n)	Weighted Percentage
Age (years)		
0-5	37,405	32.21 (31.62-32.79)
6-11	39,935	33.77 (33.18-34.37)
12-17	54,434	34.02 (33.46-34.59)
Sex		
Male	68,100	51.11 (50.49-51.73)
Female	63,674	48.89 (48.27-49.51)
Race		
Non-Hispanic white	102,061	66.92 (66.30-67.53)
Non-Hispanic black or African American	8672	13.97 (13.52-14.43)
Other*	21,041	19.11 (18.58-19.66)
Low birth weight (g)†		
Yes (<2500)	10,227	9.12 (8.77-9.49)
No (≥2500)	114,818	90.88 (90.51-91.23)
Birth weight status (g)‡		
Very low (≤1500)	1585	1.44 (1.29-1.60)
Low (1500 to 2500)	8642	7.69 (7.36-8.03)
Not low (≥2500)	114,818	90.88 (90.51-91.23)
Preterm birth§		
Yes	14,058	11.35 (10.94-11.76)
No	115,758	88.65 (88.24-89.06)
Ever had asthma‖		
Yes	16,166	11.97 (11.58-12.37)
No	114,417	88.03 (87.63-88.42)
Asthma currently¶		
Yes	10,394	65.69 (64.01-67.34)
No	5668	34.31 (32.66-35.99)
Asthma severity#		
Mild	7300	64.64 (62.39-66.82)
Moderate	2748	30.86 (28.75-33.06
Severe	293	4.50 (3.54-5.70)

* American Indian or Alaska Native, Asian, Native Hawaiian and other Pacific Islander, other.
† Data missing for 6729 children.
‡ Data missing for 180 children.
§ Data missing for 1958 children; preterm birth is defined as born three weeks before due date.
‖ Data missing for 1191 children.
¶ Data missing for 104 children.
# Data missing for 53 children.

Prevalence of NDDs by pregnancy term and birth weight

Overall, the prevalence estimates of NDDs were higher among children born preterm compared with at term and ranged from 1.18% to 13.52% (95% confidence interval [CI]: 0.90% to 14.65%). The two most prevalent NDDs among preterm births compared with term births were speech problem (13.19%; 95% CI: 12.02% to 14.46% vs 6.94%; 95% CI: 6.62% to 7.29%) and developmental delay (13.52%; 95% CI: 12.47% to 14.65% vs 5.46%; 95% CI: 5.18% to 5.75%) (Table 2). Similar trends were found when subgroup analysis compared children born preterm with children born at term by race/ethnicity, except for blindness and behavioral problems.

Similar to preterm birth versus term births, children born with low birth weight had higher prevalence estimates of NDDs compared with children born with normal birth weight for all disabilities except hearing loss, Tourette syndrome, and brain injury (Table S1). The widest disparities in this prevalence were seen among children with speech problems, learning disability, and developmental delay (prevalence ranging from 10.88% to 14.08%; 95% CI: 9.81% to 15.33% for low birth weight vs 5.55% to 7.18%; 95% CI: 5.26 to 7.54% for normal birth weight). Using subgroup analysis comparing children born with low birth weight with children born with normal birth weight by race/ethnicity, comparable results were found among children with speech problems, learning disability, and developmental delay (Table S1).

Association between NDDs and pregnancy term and birth weight

Crude logistic regression showed a significant association between preterm birth and all disability categories in children except for Tourette syndrome (Table 3). Notably, the odds of cerebral palsy were sevenfold greater among children born preterm compared with children born at term (odds ratio [OR]: 7.38; 95% CI: 5.21 to 10.47; $P < 0.001$). Furthermore, the odds of intellectual disability were three times greater among children born preterm compared with children born at term (OR: 3.43; 95% CI: 2.62 to 4.49, $P < 0.001$). All associations remained significant after adjusting for age, sex, race/ethnicity, education, income based on federal poverty, number of children, and child lived with person with alcohol/drug problem.

Crude logistic regression showed a significant association between low birth weight and all disabilities except for hearing loss (Table 3). Similar to children born preterm, the odds of cerebral palsy were seven times greater among children born with low birth weight compared with children born with full birth weight (OR: 7.16; 95% CI: 5.08 to 10.07, $P < 0.001$). There were threefold increased odds of disability in children born with low birth weight

TABLE 2.
Prevalence of Neurodevelopmental Disabilities by Race/Ethnicity Groups by Pregnancy Term Status Through the Period 2016 to 2019 in the National Survey of Children's Health (n = 131,774)

Disabilities	Weighted Prevalence for Neurodevelopmental Disabilities (All Participants)		Weighted Prevalence for Neurodevelopmental Disabilities (White Participants)		Weighted Prevalence for Neurodevelopmental Disabilities (Black or African American Participants)		Weighted Prevalence for Neurodevelopmental Disabilities (Other Participants)	
	Term Birth	Preterm Birth	Term Birth	Preterm Birth	Term Birth	Preterm Birth	Term Birth	Preterm Birth
Behavioral disorders								
ADHD	7.71 (7.42-8.03)	11.71 (10.69-12.83)	7.97 (7.64-8.32)	12.14 (10.99-13.40)	9.77 (8.67-10.99)	14.61 (11.95-17.75)	5.36 (4.74-6.04)	7.96 (5.45-11.49)
Autism spectrum disorder	2.34 (2.14-2.56)	4.63 (3.85-5.57)	2.26 (2.04-2.50)	4.21 (3.58-4.94)	2.60 (2.06-3.28)	4.34 (2.94-6.38)	2.42 (1.88-3.12)	6.31 (3.58-10.89)
Motor disabilities								
Cerebral palsy	0.16 (0.13-0.20)	1.18 (0.90-1.54)	0.16 (0.13-0.21)	1.07 (0.80-1.44)	0.21 (0.12-0.38)	1.43 (0.76-2.70)	0.12 (0.0006-0.22)	1.35 (0.64-2.82)
Seizure	0.83 (0.75-0.93)	1.65 (1.31-2.07)	0.78 (0.69-0.88)	1.65 (1.29-2.11)	1.08 (0.81-1.43)	1.09 (0.53-2.21)	0.85 (0.60-1.19)	2.10 (1.16-3.78)
Vision, hearing, and speech disabilities								
Blindness	1.53 (1.34-1.74)	2.70 (2.27-3.22)	1.55 (1.32-1.82)	2.16 (1.75-2.65)	1.69 (1.17-2.43)	5.24 (3.67-7.45)	1.34 (1.06-1.69)	2.55 (1.59-4.07)
Hearing loss	1.25 (0.80-1.45)	1.84 (1.50-2.27)	1.12 (0.97-1.30)	1.81 (1.40-2.33)	1.59 (0.99-2.57)	2.55 (1.56-4.13)	1.46 (1.00-2.13)	1.41 (0.83-2.37)
Speech problem	6.94 (6.62-7.29)	13.19 (12.02-14.46)	7.25 (6.87-7.64)	13.59 (12.27-15.03)	7.12 (6.17-8.20)	13.28 (10.49-16.68)	5.76 (4.98-6.65)	11.77 (8.70-15.73)
Cognitive disabilities								
Intellectual disability	0.79 (0.68-0.92)	2.66 (2.14-3.29)	0.74 (0.60-0.91)	2.44 (1.87-3.17)	1.18 (0.90-1.54)	3.73 (2.38-5.79)	0.70 (0.49-0.99)	2.55 (1.40-4.62)
Learning disability	5.70 (5.40-6.01)	11.75 (10.6113.00)	5.41 (5.10-5.74)	11.11 (9.95-12.39)	7.99 (6.97-9.14)	15.2 (12.34-18.57)	5.06 (4.29-5.95)	11.19 (7.84-15.72)
Developmental delay	5.46 (5.18-5.75)	13.52 (12.47-14.65)	5.28 (4.97-5.59)	13.54 (12.36-14.82)	7.42 (6.40-8.59)	15.42 (12.71-18.58)	4.71 (4.09-5.43)	11.96 (9.27-15.32)
Other								
Tourette syndrome	0.21 (0.18-0.26)	0.47 (0.21-1.05)	0.25 (0.20-0.30)	0.30 (0.18-0.50)	0.00098 (0.00048-0.20)	0.28 (0.00068-1.17)	0.18 (0.10-0.32)	1.19 (0.25-5.56)
Brain injury	2.94 (2.78-3.10)	4.26 (3.73-4.86)	be3.53 (3.34-3.74)	4.91 (4.23-5.69)	1.57 (1.22-2.00)	2.35 (1.53-3.59)	1.81 (1.48-2.22)	3.59 (2.48-5.18)
Behavior problems	7.21 (6.90-7.53)	10.39 (9.43-11.44)	6.82 (6.49-7.17)	9.90 (8.86-11.05)	10.92 (9.71-12.25)	15.11 (12.26-18.50)	5.94 (5.27-6.69)	8.33 (6.00-11.46)

Abbreviation:
ADHD = Attention-deficit/hyperactivity disorder

compared with children born with normal birth weight for the following disabilities: intellectual disability, Tourette syndrome, and developmental delay (OR range: 2.79 to 3.59; 95% CI range: 1.12 to 7.03). After adjusting for age, sex, race/ethnicity, education, income based on federal poverty, number of children, and child lived with person with alcohol/drug problem, all significant associations remained significant except for Tourette syndrome.

Interaction between asthma and adverse birth outcomes with respect to NDDs

We generated a directed acyclic graph to visualize the role of asthma in the relationship between adverse birth outcomes and NDDs (Fig). We observed that asthma did not have a confounding effect (through a backdoor path) in the primary association, leading us to investigate asthma as an effect modifier (Fig). The interaction between asthma status and preterm birth with respect to NDDs was not significant for any disability (Table 4). When stratified by the presence of asthma, the association between preterm birth and all NDDs was significant except for hearing loss and Tourette syndrome. In the absence of asthma, all associations remained significant, as well as the addition of hearing loss (adjusted OR [aOR]: 1.38; 95% CI: 1.01 to 1.88, $P = 0.041$). Notably, among children with asthma, the adjusted odds of cerebral palsy were 5.07 (95% CI: 2.66 to 9.65, $P < 0.001$) for children born preterm compared with children born at term. Among children without asthma, the adjusted odds increased to 6.96 (95% CI: 4.70 to 10.29, $P < 0.001$).

The interaction between asthma status and low birth weight with respect to NDDs was not significant for any disability (Table 5). When stratified by asthma status, with the exception of hearing loss and Tourette syndrome, the association between low birth weight and NDDs was significant in the presence of asthma. The greatest odds were seen among low-birth-weight children with cerebral palsy compared with normal-birth-weight children (aOR: 6.27; 95% CI: 3.06 to 12.87, $P < 0.001$). Children born with low birth weight also had three times the odds of a disability compared with normal-birth-weight children for the following disabilities: seizure (aOR: 3.03; 95% CI: 1.65 to 5.54, $P < 0.001$) and developmental delay (aOR: 2.93; 95% CI: 2.28 to 3.77, $P < 0.001$). In the absence of asthma, all associations were significant. The adjusted odds of cerebral palsy increased to 7.46 (95% CI: 4.99 to 11.16, $P < 0.001$) for children born with low birth weight compared with children born with normal birth weight. The adjusted odds of intellectual disability also increased to 3.84 (95% CI: 2.73 to 5.40, $P < 0.001$). However, since the interaction terms were not significant for any disability, the comparison of the ORs between the stratified asthma statutes should be interpreted with caution.

Discussion

Using nationally representative data for children aged zero to 17 years, this analysis showed interesting findings concerning associations between adverse birth outcomes and NDDs with respect to the presence and absence of childhood asthma. First, we found that the prevalence estimates of NDDs were higher among children born preterm compared with at term for disabilities including ADHD, cerebral palsy, speech problems, blindness and hearing difficulties, learning disabilities, and intellectual disabilities. Second, we also found that children born with low birth weight had higher prevalence estimates of NDDs compared with children born with normal birth weight for all disabilities except hearing loss, Tourette syndrome, and brain injury. Third, when stratified by race/ethnicity, a greater occurrence of blindness and behavior problems was observed among NHB children with low birth weight and preterm birth compared with NHW children. Fourth, we found no

TABLE 3.
The Odds of Neurodevelopmental Disabilities Among the Pediatric Population With Preterm Birth and Low Birth Weight in the National Study of Children's Health From 2016 to 2019 (n = 131,774)

Neurodevelopment Disability	Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratio* (95% CI)	*P* Value
Preterm birth				
ADHD	1.59 (1.42-1.78)	<0.001†	1.58 (1.41-1.78)	<0.001†
ASD	2.03 (1.64-2.52)	<0.001†	1.90 (1.54-2.35)	<0.001†
Cerebral palsy	7.38 (5.21-10.47)	<0.001†	6.74 (4.82-9.42)	<0.001†
Seizure	2.00 (1.54-2.58)	<0.001†	1.90 (1.48-2.45)	<0.001†
Blindness	1.79 (1.44-2.24)	<0.001†	1.79 (1.42-2.25)	<0.001†
Hearing loss	1.49 (1.15-1.93)	0.003†	1.39 (1.06-1.81)	0.02†
Speech problem	2.04 (1.81-2.29)	<0.001†	2.03 (1.79-2.30)	<0.001†
Intellectual disability	3.43 (2.62-4.49)	<0.001†	3.40 (2.58-4.48)	<0.001†
Learning disability	2.20 (1.94-2.51)	<0.001†	2.23 (1.95-2.55)	<0.001†
Developmental delay	2.71 (2.43-3.02)	<0.001†	2.70 (2.43-3.02)	<0.001†
Tourette syndrome	2.20 (0.95-5.10)	0.065	1.20 (0.72-2.01)	0.49
Brain injury	1.47 (1.27-1.71)	<0.001†	1.46 (1.26-1.69)	<0.001†
Behavior problems	1.49 (1.33-1.68)	<0.001†	1.45 (1.28-1.64)	<0.001†
Low birth weight				
ADHD	1.42 (1.26-1.61)	<0.001†	1.44 (1.27-1.63)	<0.001†
ASD	1.73 (1.42-2.10)	<0.001†	1.74 (1.42-2.12)	<0.001†
Cerebral palsy	7.16 (5.08-10.07)	<0.001†	7.58 (5.33-10.80)	<0.001†
Seizure	2.28 (1.74-2.98)	<0.001†	2.33 (1.77-3.06)	<0.001†
Blindness	2.13 (1.68-2.69)	<0.001†	2.10 (1.65-2.68)	<0.001†
Hearing loss	1.23 (0.94-1.64)	0.131	1.23 (0.92-1.65)	0.16
Speech problem	1.86 (1.65-2.10)	<0.001†	1.96 (1.73-2.23)	<0.001†
Intellectual disability	3.59 (2.72-4.74)	<0.001†	3.59 (2.69-4.78)	<0.001†
Learning disability	1.99 (1.75-2.26)	<0.001†	2.03 (1.77-2.33)	<0.001†
Developmental delay	2.79 (2.49-3.13)	<0.001†	2.94 (2.61-3.31)	<0.001†
Tourette syndrome	2.80 (1.12-7.03)	0.028†	1.59 (0.90-2.78)	0.11
Brain injury	1.21 (1.02-1.44)	0.025†	1.32 (1.11-1.57)	0.002†
Behavior problems	1.56 (1.38-1.77)	<0.001†	1.58 (1.38-1.81)	<0.001†

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Autism spectrum disorder
CI = Confidence interval
* Variables adjusted for age, sex, race, education, income based on federal poverty, number of children, and child lived with person with alcohol/drug problem.
† *P* value <0.05 is considered significant.

modifying effect of asthma on the relationship between adverse birth outcomes and NDDs.

This study examined the possible modifying role of childhood asthma in the relationship between adverse birth outcomes and NDDs in the US pediatric population. Literature in the past has indicated several common immune-mediated pathways linking higher childhood asthma occurrence among children who are either born with low birth weight or preterm.[24-27] In addition to NDDs, preterm and low-birth-weight infants may have delayed developmental changes that may affect the respiratory system, which in turn may increase sensitivity to environmental stimuli and thereby increase the likelihood of asthma.[27] Moreover, studies have also shown using population-based representative datasets that children with adverse birth outcomes such as low birth weight

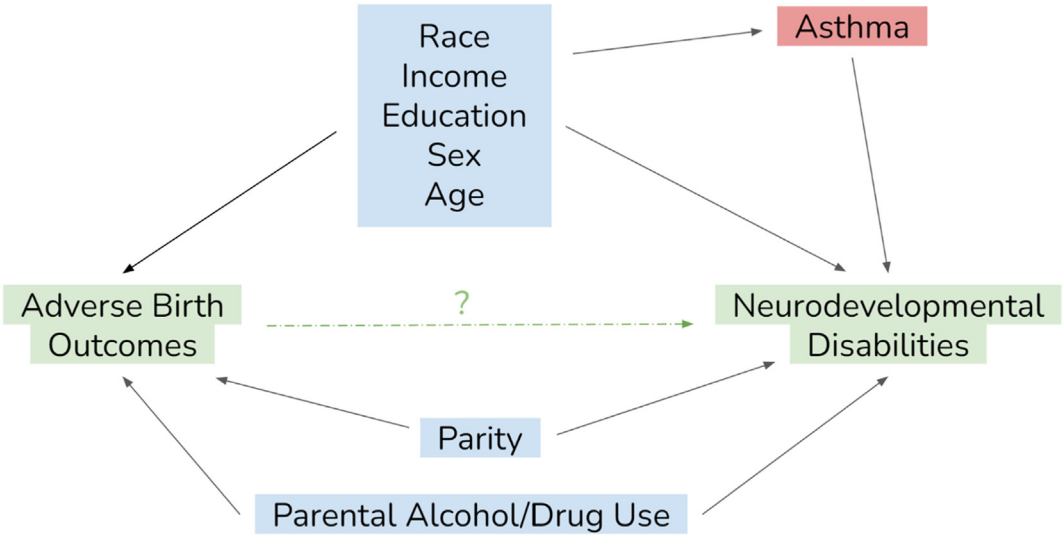

FIGURE. Directed acyclic graph representing the relationship between adverse birth outcomes and neurodevelopmental disabilities adjusting for race/ethnicity, sex, age, education, income, parity, and parental drug or alcohol use. Asthma is presented as an effect modifier. The color version of this figure is available in the online edition.

TABLE 4.
Interaction Between Asthma Status and Preterm Birth With Respect to Neurodevelopmental Disabilities Among the Pediatric Population in the National Study of Children's Health From 2016 to 2019 (n = 131,774)

Neurodevelopment Disability	Preterm Birth					
	Presence of Asthma			Absence of Asthma	Interaction Between Asthma and Preterm Birth	
	Adjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)	*P* Value (Interaction)
ADHD	1.42 (1.15-1.75)	0.001†	1.53 (1.32-1.77)	<0.001†	0.94 (0.73-1.22)	0.67
ASD	1.92 (1.31-2.80)	0.001†	1.85 (1.43-2.39)	<0.001†	1.01 (0.63-1.63)	0.95
Cerebral palsy	5.07 (2.66-9.65)	<0.001†	6.96 (4.70-10.29)	<0.001†	0.73 (0.34-1.54)	0.40
Seizure	2.39 (1.42-4.01)	0.001†	1.66 (1.25-2.19)	<0.001†	1.45 (0.80-2.62)	0.22
Blindness	2.38 (1.60-3.53)	<0.001†	1.52 (1.15-2.01)	0.003†	1.56 (0.95-2.55)	0.08
Hearing loss	1.24 (0.73-2.13)	0.43	1.38 (1.01-1.88)	0.04†	0.89 (0.43-1.62)	0.70
Speech problem	2.13 (1.70-2.66)	<0.001†	1.93 (1.67-2.24)	<0.001†	1.10 (0.83-1.44)	0.52
Intellectual disability	2.98 (1.82-4.91)	<0.001†	3.39 (2.43-4.71)	<0.001†	0.92 (0.51-1.68)	0.79
Learning disability	2.22 (1.75-2.80)	<0.001†	2.12 (1.80-2.50)	<0.001†	1.07 (0.80-1.44)	0.63
Developmental delay	2.83 (2.26-3.55)	<0.001†	2.57 (2.27-2.91)	<0.001†	1.10 (0.85-1.43)	0.45
Tourette syndrome	0.55 (0.18-1.66)	0.29	1.52 (0.85-2.71)	0.16	0.37 (0.11-1.26)	0.11
Brain injury	1.36 (1.02-1.83)	0.03†	1.42 (1.19-1.69)	<0.001†	1.00 (0.71-1.39)	0.98
Behavior problems	1.59 (1.27-2.00)	<0.001†	1.31 (1.14-1.52)	<0.001†	1.23 (0.93-1.62)	0.14

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Autism spectrum disorder
CI = Confidence interval
OR = Odds ratio
* Variables adjusted for age, sex, race, education, income based on federal poverty, number of children, and child lived with person with alcohol/drug problem.
† *P* value <0.05 is considered significant.

and preterm births have a greater likelihood of developing adverse NDDs in adolescence.[28-30] In particular, preterm infants are more likely to have lower intelligence quotients, while also being at a greater risk of rehospitalizations for conditions related to their compromised health status (e.g., respiratory conditions or heart conditions) during the first few years of life.[30,31]

One condition leading to poor health outcomes in children born preterm is asthma or reactive airway disease.[30] Epidemiologic studies have found that preterm infants develop asthma more frequently than term infants.[32,33] However, previous studies have not explored the role of childhood asthma as a modifier of the relationship between adverse birth outcomes and NDDs.

A previous study that analyzed data from a prospective cohort study of 344 infants assessed three models of association (independent risk, mediation, and effect modification) among birth weight, asthma, and select NDDs.[34] Although the study found that extremely-low-birth-weight infants were more likely to have asthma compared with normal-birth-weight infants (35.7% vs 14.4%, $P < 0.05$), the authors did not find asthma to mediate or modify the relationship between extremely low birth weight and behavioral and emotional problems.[34] These results were similar to the results we obtained when assessing whether asthma was a modifier of the association between NDDs and adverse birth outcomes (preterm birth and low birth weight), separately. Our study

TABLE 5.
Interaction Between Asthma Status and Low Birth Weight With Respect to Neurodevelopmental Disabilities Among the Pediatric Population in the National Study of Children's Health From 2016 to 2019 (n = 131,774)

Neurodevelopment Disability	Low Birth Weight					
	Presence of Asthma	Absence of Asthma				Interaction Between Asthma and Low Birth Weight
	Adjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)*	*P* Value	Adjusted OR* (95% CI)	*P* Value (Interaction)
ADHD	1.42 (1.10-1.83)	0.006†	2.02 (1.17-1.56)	<0.001†	1.13 (0.85-1.50)	0.42
ASD	1.70 (1.10-2.62)	0.02†	1.75 (1.40-2.18)	<0.001†	0.94 (0.58-1.53)	0.82
Cerebral palsy	6.27 (3.06-12.87)	<0.001†	7.46 (4.99-11.16)	<0.001†	0.89 (0.42-1.91)	0.77
Seizure	3.03 (1.65-5.54)	<0.001†	2.03 (1.48-2.75)	<0.001†	1.48 (0.78- 2.80)	0.23
Blindness	2.25 (1.50-3.36)	<0.001†	1.97 (1.46-2.65)	<0.001†	1.13 (0.68-1.87)	0.64
Hearing loss	1.21 (0.68-2.14)	0.52	1.26 (0.90-1.75)	0.17	1.01 (0.53-1.92)	0.98
Speech problem	2.21 (1.72-2.84)	<0.001†	1.86 (1.60-2.15)	<0.001†	1.20 (0.90-1.61)	0.21
Intellectual disability	2.56 (1.54-4.25)	<0.001†	3.84 (2.73-5.40)	<0.001†	0.69 (0.37-1.27)	0.23
Learning disability	1.91 (1.49-2.45)	<0.001†	2.00 (1.70-2.36)	<0.001†	0.98 (0.72-1.32)	0.87
Developmental delay	2.93 (2.28-3.77)	<0.001†	2.85 (2.48 - 3.27)	<0.001†	1.05 (0.79-1.39)	0.74
Tourette syndrome	1.23 (0.36-4.25)	0.74	1.75 (0.93-3.30)	0.08	0.71 (0.17-2.90)	0.64
Brain injury	1.45 (1.02-2.07)	0.04†	1.24 (1.03-1.51)	0.03†	1.19 (0.79-1.79)	0.41
Behavior problems	1.52 (1.17-1.97)	0.002†	1.48 (1.25-1.74)	<0.001†	1.06 (0.77-1.44)	0.74

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
ASD = Autism spectrum disorder
CI = Confidence interval
OR = Odds ratio
* Variables adjusted for age, sex, race, education, income based on federal poverty, number of children, and child lived with person with alcohol/drug problem.
† *P* value <0.05 is considered significant.

utilized a larger, nationwide database to build upon this smaller-scale study, providing a higher degree of representativeness and external validity.

While exploring the associations by race/ethnicity in a subgroup analysis, we observed that for both adverse birth outcomes (preterm birth and low birth weight), NHBs were disproportionately impacted in terms of certain neurodevelopmental outcomes, especially blindness and behavioral disorders. These results are in line with a previous study that used data from the 2009 to 2017 National Health Interview Survey to assess the national prevalence of select developmental disabilities in US children aged three to 17 years.[35] The authors found the prevalence of learning disability among NHBs compared with NHWs to be 9.10 vs 8.03, $P < 0.05$. Compared with non-Hispanic white Other, NHBs also had a significantly higher prevalence of ADHD, learning disability, seizures, and speech problems.[35] However, this study did not assess this prevalence among infants born preterm or with low birth weight; this points to a need for further exploration of social determinants of health as well as indicators related to structural racism that might help to account for these associations.

Future implications

Our results indicate the need for full medical and clinical evaluation of children born preterm or low birth weight as they are more likely to have NDDs and physical comorbidities such as asthma when compared with their counterparts born at term or with normal birth weight.[7,9,15-18] Furthermore, these findings suggest race/ethnicity disparities in the prevalence of NDDs that require further attention to improve the quality of life of children affected by these conditions. We recommend screening for NDDs in pediatric health care settings among patients with adverse birth outcomes, particularly among those from ethnic minority backgrounds. Additional research may help better understand the risk factors and comorbidities associated with NDDs, which may ultimately contribute to interventions that can improve health outcomes for those with adverse birth outcomes and NDDs.

Study limitations

Our study should be considered in light of certain limitations. First, we only relied on the epidemiologic assessment of effect modification by asthma status stratification. However, our findings were similar to one previous assessment[34] and point to the need for further studies that involve a deeper understanding of immune-mediated mechanisms through benchwork or laboratory-based studies. Second, associations found in this study are based on statistical analysis and do not provide any biological or causal associations. Furthermore, parent reports of NDD and/or asthma may be prone to recall bias, which may lead to misclassification bias. However, our findings on effect modification were similar to the only previous study we identified, indicating the likely consistency of our data source. Furthermore, recall bias is difficult to assess due to our study's cross-sectional nature.

Conclusion

Comorbid conditions like asthma can affect developmental progress. Although our study found that asthma did not play a significant role as an effect modifier of the relationship between adverse birth outcomes and NDDs, future studies are needed to assess the role of asthma in this complex relationship among infants born preterm and low birth weight, especially with an emphasis on investigating mechanisms including immune response.

CRediT authorship contribution statement

Omobola Oluwafemi: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft. **Sneha Manoharan:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Methodology. **Luyu Xie:** Investigation, Writing – review & editing. **George Pro:** Investigation, Methodology, Writing – review & editing. **Rikinkumar S. Patel:** Investigation, Writing – review & editing. **George L. Delclos:** Investigation, Writing – review & editing. **Andrew Gelfand:** Investigation, Writing – review & editing. **Sarah E. Messiah:** Writing – review & editing, Investigation. **David S. Lopez:** Writing – review & editing. **Jenil Patel:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing, Writing – original draft.

Declaration of competing interest

None.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.04.023.

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