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The Risk of Autism Spectrum Disorder (ASD) in Preterm and Low Birth Weight Infants

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Abstract

**THE RISK OF AUTISM SPECTRUM DISORDER (ASD) IN PRETERM AND LOW BIRTH WEIGHT
INFANTS**

By

SONIA SANCHEZ-ALVAREZ

December 2020

INTRODUCTION: Autism Spectrum Disorder (ASD) is characterized by challenges in the areas of repetitive behaviors, social skills, and speech and nonverbal communications. According to the Centers for Disease Control and Prevention (CDC), 1 in 54 children (8 years old) in the United States have ASD.

AIM: This study aimed to investigate and examine the association between both gestational age & low birth weight (LBW) and autism spectrum disorder (ASD).

METHODS: This study used secondary data from the National Survey of Children’s Health (NSCH), a cross-sectional survey that examines the emotional and physical health of children in the United States from birth to 17 years of age, for the years 2016-2018. Logistic regression models were used to examine any effects that may be due to prematurity and low birth weight on ASD outcomes. The two ASD outcomes considered were whether caretakers had a health care provider who “Ever Told” them their child has an ASD or whether their child “Currently” has an ASD diagnosis.

RESULTS: Univariate models showed that both LBW and gestational ages are associated with increased odds of ASD, ever or current diagnosis. When birth weight and gestational age were conjointly considered, there was only a moderate association between preterm birth and ASD. In multivariate models with relevant covariates (e.g., controlling for presence of developmental delays; health insurance) prematurity continued to be associated with ever or current ASD status, but birth weight was not.

DISCUSSION: The study fits in with previous literature that have reported consistent associations between preterm birth and ASD, but mixed findings between birth weight and ASD. Most studies do not include both gestational age and birth weight in their analyses. These results may be used to inform future prenatal care research aimed at understanding ASD’s etiology.

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Author's Statement Page

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Sonia Sanchez-Alvarez

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Chapter I: Introduction

1.1 Background

According to the Centers for Disease Control and Prevention (CDC, 2020), 1 in 54 children (aged 8 years old) in the United States, have an autism spectrum disorder (ASD). The prevalence of children with autism has been increasing over the years; in 2004, 1 in 125 children in the United States were diagnosed with autism, while in 2014, 1 in 59 were diagnosed with autism (CDC, 2020a). ASD is characterized by challenges in the areas of repetitive behaviors, social skills, and speech and nonverbal communications (Autism Speaks, 2019). Individuals with ASD present with a wide spectrum of behaviors and abilities, but impaired social interactions and communication abilities are core attributes shared by those ultimately diagnosed with this condition (Autism Speaks, 2019).

1.2 Etiological Risk Factors

With ASD on the rise, it is important to examine and analyze the possible causes and risk factors of this condition (Agrawal et al., 2018; Goldin & Matson, 2016). Although the specific causes for developing ASD are not well understood (Harel-Gadassi et al., 2018), researchers suggest that 60-65% of ASD could be due to maternal factors, including prenatal, perinatal, and postnatal factors (Gardener et al., 2011; Limperopoulos, 2009; Tchaconas & Adesman, 2013), and 35-40% could be due to genetic factors (Froehlich-Santino et al., 2014; Hallmayer et al., 2011). Furthermore, a number of sociodemographic characteristics have also been proposed as possible risk factors for ASD (Kuzniewicz et al., 2014; Matheis et al., 2018; Pinborough-Zimmerman, et al., 2011; Russell et al., 2011; Wang et al., 2017; Xie et al., 2016). The primary focus of this study will be on sociodemographic and maternal factors.

1.2.1 Sociodemographic factors

Sociodemographic factors associated with ASD include sex/gender, race/ethnicity, maternal age at birth, birth order, primary language spoken in the household, and socioeconomic and insurance status (Kuzniewicz et al., 2014; Matheis et al., 2018; Pinborough-Zimmerman, et al., 2011; Russell et al., 2011; Wang et al., 2017; Xie et al., 2016). ASD is four times more common among boys compared to girls (CDC, 2020a; Frazier et al., 2014; Leavey et al., 2013; Morgan et al., 2012; Msall, 2010). For example, analyses from the 2005-2006 National Survey of Children with Special Health Care Needs (NS-CSHCN) found that 78.4% of children with autism were male and 21.6% were female from a sample of 192,083 (Cheak-Zamora et al., 2012). Another study found more ASD cases among males, as well as among mothers who were over the age of 34 and mothers who were non-Hispanic White (Pinborough-Zimmerman, et al., 2011). Additionally, infants born to older parents (e.g., maternal age ≥ 35 and paternal age ≥ 40) demonstrate a greater risk for ASD (Durkin et al., 2008; Limperopoulos, 2009; Sharma et al., 2018). Thus, a growing body of evidence suggests a link between ASD, parental age, and gender.

Historically, the reported prevalence of ASD was higher in White children than other races and ethnicities (Jarquin et al., 2011; Mandell et al., 2002; Mandell et al., 2007; Mandell et

al., 2009), but in more recent years, official rates show Black-White differences equalizing and White-Hispanic differences staying unequal (CDC, 2020d). Recent research using other data sets indicates prevalence in some non-White groups is even greater than White prevalence (Downey, 2020; Kogan et al., 2018; Nevison & Parker, 2020; Nevison & Zahorodny, 2019). Since reports of ASD diagnoses among non-White children have been increasing recently, the literature varies when comparing ASD among different races and ethnicities. For example, a meta-analysis found that the parental race of White and Asian both increased the risk for ASD (Wang et al., 2017). Yet, the 2007 National Survey of Children's Health (NSCH) and the 2009-2010 NS-CSHCN showed increased odds of ASD in Hispanic non-English speaking households versus non-Hispanic Whites (Simon et al., 2013). Thus, it is not clear if one race or ethnicity is more associated with ASD compared to other race or ethnicities.

A number of other sociodemographic factors are also associated with ASD. For example, in the 2007 NSCH and the Interactive Autism Network (IAN) Registry, researchers found increased odds of ASD in children who were older and those born early in the birth order (Frazier et al., 2014; Simon et al., 2013). Furthermore, family poverty level (FPL) and health insurance status may also be associated with ASD. For example, in the 2005-2006 NS-CSHCN, there was a greater percentage among ASD cases within the 200-399% FPL compared to the 0-99% FPL, and greater ASD cases among those with private health insurance coverage compared to those uninsured and those having public insurance coverage only (Cheak-Zamora et al., 2012). Finally, parental education is another factor discussed in the literature, but with inconsistent findings. Some researchers have found an increased risk for ASD among parents who have a college education or greater (Wang et al., 2017), while other researchers have found greater ASD diagnoses among those with a lower parental education (Amr et al., 2012). Therefore, including other covariates in the analysis is an important step as many could be associated with autism, as seen with these studies. Collectively, there is evidence among the relationship between ASD and a variety of sociodemographic factors.

1.2.2 Prenatal factors

Evidence is emerging suggesting the association between factors during the prenatal period, which lasts from conception to 38 weeks of gestation (Encyclopedia of Children's Health, 2020) and ASD, but the available research is informative. For instance, Baron-Cohen (2002) developed the 'extreme male brain theory' which suggests that biological sex differences can explain higher ASD rates among males, who tend to systemize more than empathize. Specifically, this theory maintains that in-utero exposure to testosterone and androgens "masculinizes" the brain in a way that leads to increased interest in mechanical/physical interests and decreased social interests (Furfaro, 2019). Further, there is a decrease in cognitive empathy that makes it more difficult to recognize the emotions of others from the excess testosterone (Furfaro, 2019; Van Honk et al., 2013) (for counter evidence: McCarthy, 2019; Nadler, 2019; Paddock, 2019). Furthermore, other prenatal factors, such as gestational diabetes, gestational hypertension, parental age, parental race, and threatened abortion have also been found to be risk

factors of ASD (Hadjkacem et al., 2016; Limperopoulos, 2009; Şahin et al., 2019; Wang et al., 2017). Overall, a growing body of evidence suggests that a number of prenatal factors are associated with an increased risk of autism (Limperopoulos, 2009).

1.2.3 Perinatal factors

The perinatal period, which is linked to maternal health, is the period that starts at 22 completed weeks of gestation and ends seven days after birth (WHO, 2013). A number of studies suggest that delivery methods and outcomes could be risk factors linked to ASD; in particular, cesarean delivery, fetal distress, parity (the number of times a woman has completed a pregnancy reaching 20 weeks' gestation; Opara, & Zaidi, 2007), and gestational age (<37 weeks)/prematurity have been associated with increased risk of ASD (Hadjkacem et al., 2016; Kuzniewicz et al., 2014; Şahin et al., 2019; Wang et al., 2017). For example, studies have shown that the prevalence of ASD was greater in infants born <37 weeks compared to infants born >37 weeks gestational age (Kuzniewicz et al., 2014; Sugie et al., 2005). Researchers also found that infants born 27 to 36 weeks gestational age were at increased risk for ASD after adjusting for sex, cesarean delivery method, and maternal age and education (Kuzniewicz et al., 2014). Further, other researchers compared ASD with attention deficit hyperactivity disorder (ADHD) and specific learning disability (SLD), and they found that prematurity was more associated with ASD (Şahin et al., 2019). Additionally, obstetric complications, such as fetal distress, cesarean delivery, and maternal hypertension can increase risk of autism (Limperopoulos, 2009). Collectively, research indicates a relationship between a number of perinatal factors and ASD.

1.2.4 Postnatal factors

The postnatal period occurs immediately after childbirth and extends up to six weeks after birth (WHO, 2013). Evidence demonstrates that postnatal factors are associated with ASD, such as low birth weight, postpartum & intracranial hemorrhage, respiratory infections, and brain anomalies (Hadjkacem et al., 2016; Kuzniewicz et al., 2014; Wang et al., 2017). For example, babies who are born with a low birth weight and survive are generally at risk for a number of disabilities across the lifespan, including ASD (WHO, 2018b). Further, a meta-analysis (total of 17 studies) found that postpartum hemorrhage, low birth weight, and brain anomalies increased the risk for autism (Wang et al., 2017). A retrospective cohort study found higher frequencies of intracranial hemorrhage and ventilation associated with ASD in infants born <34 weeks (Kuzniewicz et al., 2014). Additionally, a cross-sectional study found that 24% of children diagnosed with ASD had a respiratory infection in early life (Hadjkacem et al., 2016), and a comparative study found that children with ASD showed greater neonatal (newborn) complications (e.g., respiratory distress) compared to typically developing children (Sugie et al., 2005). Overall, research indicates a relationship between a number of postnatal factors and ASD.

1.3 Preterm Birth and ASD

Infants who are born preterm tend to have difficulties with social and emotional communication and attention, which are suggestive signs of ASD (Lederman et al., 2018). The World Health Organization (WHO, 2018b) defines preterm birth as being born alive before 37 weeks of the pregnancy are completed. Preterm birth is a perinatal factor with subcategories including extremely preterm (<28 weeks), very preterm (28-32 weeks), moderate to late preterm (32-37 weeks), and full term (>37; WHO, 2018b). Globally, the prevalence of infants born preterm is 15 million or 1 in 10 (WHO, 2018a). In 2017, 17% of infant deaths were due to prematurity and low birth weight in the United States, but those who survive can have developmental delays and other problems (e.g., cerebral palsy, hearing problems; CDC, 2019). Further, infants born <33 weeks of gestation are at a 2-fold increase for ASD (Schendel & Bhasin, 2008), and infants who are born extremely preterm have greater risks for behavioral disorders and developmental problems, including learning disabilities, language disorders and cognitive delays, which continue into school age (Lowe et al., 2019).

The research on gestational age and ASD is suggestive, but non-uniform as there is a mix of supportive and non-supportive findings, and this variance across study findings likely stems from a number of methodological factors (e.g., epidemiological vs. clinical studies, sample size). For example, a large Canadian population-based cohort (N = 218,110) used delivery records to identify the gestational age at birth among singleton live births and reported that ASD risk increases as gestational age decreases, in which a total of 17,830 (8.2%) preterm births (23-36 weeks' gestation) were reported with 1,135 (0.52%) being diagnosed with ASD (Leavey et al., 2013). However, a clinical study that recruited 916 children diagnosed with ASD and 739 children with atypical development from the Louisiana Part C Early Intervention program found that premature birth (<37 weeks' gestation) was twice as common among the children with atypical development compared to the children diagnosed with ASD (Goldin & Matson, 2016). There is a mix of findings, with some researchers showing no association between preterm birth and ASD (Goldin & Matson, 2016), while other researchers have shown that prematurity is associated with a gradual increase of ASD with 'each decreasing week of gestation' (Joseph et al., 2016, p. 3; Kerstjens et al., 2012, p. 1098; Kuzniewicz et al., 2014, p. 24; Leavey, et al., 2013, p. 363). Collectively, the literature is mainly supportive of the association between preterm birth and ASD.

One important source of variance is that studies differ in how ASD is measured. For example, some studies only rely on ASD screening tools, which are less refined than diagnostic tests because screening does not provide a diagnosis, but may identify areas requiring further assessment; that is, if the child is presenting behaviors associated with ASD, they should be referred to a primary or health care provider who will provide a formal assessment (CDC, 2020b). Examples of screening tools used in the preterm birth literature include the Modified Checklist for Autism in Toddlers (M-CHAT), the Child Behavior Checklist (CBC), and the Social Communication Questionnaire (SCQ), with some studies following up with a diagnostic assessment to determine if those who screened positive actually have ASD (Sugie et al., 2005),

while others do not (Stephens et al., 2012; Limperopoulos et al., 2008b). Further, a true diagnosis includes high quality assessments and measures including both parent interviews and behavioral observations from a professional or primary care provider (Barger et al., 2018; CDC, 2020c; Joseph et al., 2016; Klin et al., 2005). The Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), and the Childhood Autism Ratings Scale (CARS) are diagnostic tests that have been used to determine whether or not a child has autism (Agrawal et al., 2018; Joesph et al., 2017). A recent meta-analysis included 18 different studies (N = 3,366 preterm infants) that used diagnostic tests and excluded studies that used screening tools; overall, they found that the pooled ASD prevalence for preterm infants was 7% (Agrawal et al., 2018). Further, a clinical study that recruited 554 18-22-month-old children from the Neonatal Research Network found that 20% of infants screened positive for ASD on at least one of the following: The Pervasive Developmental Disorders Screening Test, 2nd Edition (PDDST-II), the response to joint attention on the ADOS, or the response-to-name item on ADOS (Stephens et al., 2012). Although this clinical study used several screening tools, the authors concluded that “further diagnostic assessment is needed to evaluate the sensitivity and specificity of these screens and determine true rates of ASD in extremely preterm infants” (p. 6). That being said, the differences in ASD prevalence seen across the studies (7% vs. 20%) are due to the variability in ASD measurement. Though the clinical study showed a “greater” prevalence of autism in extremely preterm infants (20%), the meta-analysis captures a more accurate rate of ASD cases (7%) because they only included studies that used diagnostic assessments. Thus, the updated Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) diagnostic criteria should be followed in order to receive more accurate diagnoses of autism, which can include the use of both ADOS and ADI-R (Autism Speaks, 2020a; Esler, 2015).

Another important source of variance across studies involves how conditions are defined. For example, studies vary in their definitions of gestational age, using very preterm or extremely preterm interchangeably; some studies define prematurity as <33 weeks’ gestation (Agrawal et al., 2018; Lampi et al., 2010; Schendel & Bhasin, 2008); other studies define prematurity as 23 to 27 weeks’ gestation (Joseph et al., 2016; Joseph et al., 2017; Leavey et al., 2013). Additionally, studies vary in how ASD is defined. For example, some studies define ASD as having a range of neurodevelopmental conditions that impair communication and social interaction (Johnson et al., 2010; Leavey et al., 2013; Lederman et al., 2018; Stephens et al., 2012), while other studies define ASD as debilitating, repetition in behavior patterns, and motor deficits (Agrawal et al., 2018; Goldin & Matson, 2016). Further, studies vary in the diagnostic criteria used; under the new DSM-V criteria, the autism definitions/categories changed from including Autistic disorder, Asperger syndrome, Childhood disintegrative disorder, and Pervasive developmental disorder-not otherwise specified (PDD-NOS) to the broader categories of persistent deficits in social communication/interaction, and restricted, repetitive patterns of behavior (Autism Speaks, 2020b). Because of the several diagnostic categories under the DSM-IV, researchers developed DSM-V to better and more broadly define mental and psychiatric disorders (Stein et al., 2010). For example, DSM-IV defined mental disorders as an “association

with present distress or disability or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom,” while DSM-V defines mental/psychiatric disorders as “the consequences of which are clinically significant distress or disability” (Stein et al., 2010, p. 1761). Thus, children previously diagnosed with DSM-IV under Asperger’s syndrome, autistic disorder, or PDD-NOS, should be given the diagnosis of “autism spectrum disorder” (Autism Speaks, 2020b).

While the clinical literature is mixed, the population-based literature uniformly suggests a relationship between gestational age and ASD. For example, an early study found an increase in atypical social-behavioral functioning among extremely premature infants, which is strongly suggestive of ASD (Limperopoulos, 2009). Other studies have found that up to a quarter of extremely preterm infants screen positive for ASD (Limperopoulos et al., 2008b). Furthermore, in a large population-based case-control study (N = 4,713), there was evidence of an increased risk for childhood autism and pervasive developmental disorder (PPD) in very low gestational age infants (less than 32 weeks) compared to infants with a gestational age of >37 weeks (Lampi et al., 2010). Another study found that of 219 extremely preterm (<26 weeks’ gestation) children, 8% were ultimately given an ASD diagnosis; no one from the 153-full-term group was given an ASD diagnosis (Johnson et al., 2010). Further, researchers from a prospective multi-center birth cohort (14 institutions and 889 participants) found that children who are born in the lowest gestational age category (23-24 weeks) are at greater risk for ASD without intellectual disabilities (Joseph et al., 2017). Other studies have clinically assessed the prevalence of potential ASD in preterm to full term infants showing that 13% of preterm infants and 3.9% of full-term infants screened positive for ASD (Gray et al., 2015). Ultimately, a recent meta-analytic study concluded that about 900,000 additional pre-term children will develop ASD each year suggesting a strong link (Agrawal et al., 2018).

A notable source of variance across studies is the inclusion of important covariates. For example, in a large population-based case-control study (Lampi et al., 2010), there was a statistical relationship between preterm birth and ASD after adjusting for smoking during pregnancy, maternal age, and congenital anomalies. In addition, another study that screened for autism in extremely preterm infants controlled for the child’s sex and acute intrapartum hemorrhage, in which both were significantly associated with abnormal ASD screening scores (Limperopoulos et al., 2008b). Further, a 2010 population-based cohort found that pre-term birth was associated with ASD even when controlling for child sex, presence of abnormal cerebral ultrasounds, and vaginal breech delivery (Johnson et al.). In a 2015 clinical assessment, researchers found that those who scored positive on the M-CHAT were born to young, non-White mothers, and had a higher incidence of being small for their gestational age (Gray et al., 2015). Others have found that sicker pre-term children with greater degrees of impairment and smaller infants were more likely to screen positive for ASD (Stephens et al., 2012). Collectively, research indicates that there is a relationship between preterm birth and ASD even when controlling for a number of important covariates.

1.4 Low Birth Weight and ASD

Infants who are born with a low birth weight (LBW) have been identified as having disturbances in communication, behavior, social interactions in adulthood, and greater externalizing and internalizing behavior problems compared to their counterparts, which are suggestive signs of ASD (Limperopoulos et al., 2008a). LBW, which is a postnatal factor, is defined as newborns weighing less than 2,500g (5lbs & 5oz.) at birth (WHO, 2014). The birth weight categories include extremely low birth weight (ELBW) weighing less than 1,000g (2lbs & 3oz.), very low birth weight (VLBW) weighing less than 1,500g (3lbs & 9oz.), and LBW weighing less than 2,500g (WHO, 2014). The main cause of LBW is being born premature (before the 37 weeks of pregnancy are completed; Boston Children's Hospital, 2020). Although some babies are born full term (>37 weeks), some might still weigh less than 2,500g (WHO, 2018a). Surviving LBW infants have higher rates of positive screening from the M-CHAT and evidence indicates greater risk for developing ASD (Kuzniewicz et al., 2014).

The research on birth weight and ASD is largely non-uniform as there is a mix of supportive and non-supportive findings. For example, a large cohort of 4,800 children that were classified as normal weight ($\geq 2500\text{g}$), moderately LBW ($< 2500\text{g}$), and VLBW ($\leq 1500\text{g}$) found that being born VLBW increased the odds of ASD (Moss & Chugani, 2014). Another large cohort (N = 1,850), however, conducted a secondary data analysis on the 2011-2012 NSCH and found that there was no correlation between LBW and ASD (Ghadge et al., 2016). Further, a smaller Japanese study of 204 VLBW infants wherein 35 had ASD participants and 169 no-ASD or intellectual disability found that the ASD group had lower birth weight (Kihara & Nakamura, 2015). However, another smaller retrospective cohort study collected clinical data on 59 participants, and researchers found that the birth weight among infants did not differ between the ASD group and the non-ASD group (Ikejiri et al., 2016). Lastly, Schendel & Bhasin (2008) found that the prevalence of ASD in LBW infants was much lower than in those with other developmental disabilities. Thus, there seems to be a mix of findings in the association between birth weight status and ASD.

Notably, studies vary in terms of participant recruitment and ASD measurement. For example, a study that recruited 75 children born ELBW and VLBW from three different hospitals assessed ASD using multiple screening tools and found that 32 of them (42.7%) tested positive on at least one of three screening tools; after only 19 participated in the follow-up, eight were ultimately diagnosed using ADOS plus a clinical evaluation (Dudova et al., 2014). Further, a statewide prevalence study compared 78 cases who had autism and five controls per case using data from birth certificates, resulting in 2.40 greater odds of ASD among cases being born with a LBW ($< 2,500\text{g}$) compared to the matching controls (Burd et al., 1999). Thus, the importance and validity of these studies are their use of diagnostic tests or confirmed ASD diagnoses from an autism registry.

Although there is some variability in the literature, most data support the association between LBW and ASD. For example, an early cohort study found an increase in ASD positive screening among LBW infants compared to their peers (Limperopoulos et al., 2008b). Further, another

study recruited 110 adults who were born with a VLBW and 104 term-born adults; they found that the VLBW adults scored worse on social interactions compared to the full-term adults, and lower on their attention to details (Pyhälä et al., 2014). Moreover, a large population-based case-control study (N = 4,713) showed evidence of an increased risk for childhood autism and pervasive developmental disorder (PPD) in VLBW (<1,500g) and in LBW (<2,500g) infants compared to infants born with a normal birth weight (Lampi et al., 2010). It has also been estimated that every 100g increase in birth weight leads to a 13% reduction in risk of ASD (Losh et al., 2012). Thus, the literature generally supports the hypothesis that children born with a lower birth weight are at a greater risk for ASD.

Another notable source of variance across studies is the inclusion of important covariates. For example, one study found that the children who tested positive for ASD were more likely to be male, had a lower gestational age, were born to women with pre-eclampsia (maternal high blood pressure) and with increasing maternal age, and were also more likely to be diagnosed with Down Syndrome, Patau Syndrome, or with a congenital brain anomaly (Mann et al., 2009). Moreover, researchers included parental education, Caucasian maternal race, gestational age (<36 weeks), Apgar score 5, and other terminations of pregnancy as covariates in their study, and the results showed that ASD cases had 2.25 greater odds of maternal education of less than grade 12 compared to the controls; however, they found no significance in the associations between maternal race White, Apgar score 5, gestational age (<36 weeks), and other terminations of pregnancy and ASD (Burd et al., 1999). Further, in a large population-based case-control study there was still a statistical relationship between LBW and ASD after adjusting for confounders, including smoking during pregnancy, maternal age, and congenital anomalies (Lampi et al., 2010). Lastly, Schendel & Bhasin (2008) found a 4-fold increased risk in LBW girls for ASD only when accompanied by mental retardation, and a 2-fold increased risk in a birth weight of <2,500g among girls; this study is non-supportive of the several studies that found a greater association of ASD among boys because when the researchers examined autism alone, they found no significance in LBW boys. Collectively, research indicates that there is a relationship between LBW and ASD even when controlling for a number of important covariates.

Chapter II: Current Analysis

2.1 Overview

The need for this analysis comes from the gradual increase of ASD prevalence (CDC, 2020a). Several studies have found preterm birth and LBW to be ASD risk factors, while others have reported mixed findings. Although prematurity is the main cause of having a LBW (Boston Children's Hospital, 2020), preterm infants aren't always born with a LBW. Since these risk factors covary, it is reasonable to consider them conjointly as risk factors for autism (Mann et al., 2009). That being said, several studies have conjointly investigated LBW and prematurity on their relationship with ASD (Joseph et al., 2017; Lampi et al., 2010; Mann et al., 2009; Matheis et al., 2018; Schendel & Bhasin, 2008; Schieve et al., 2016; Wang et al., 2017). Critically, Schendel & Bhasin (2008) is the only study finding lower odds of ASD when including other developmental delays and intellectual disabilities. While, a prospective cohort found that children who are born 23 to 24 weeks' gestation are at greater risk for ASD without intellectual disabilities (Joseph et al., 2017). Thus, the present analysis includes prematurity and LBW as well to determine whether the odds of ASD will be similar or different to Schendel's and Joseph's study findings. One other study looked at the effect on LWB and prematurity on ASD incidence using the National Survey of Children's Health (NSCH, 2011-2012), but did not indicate whether they used the "ever" or "current" ASD outcome variable (Ghadge et al., 2016). Therefore, the present analysis will fill the gap in determining whether or not the measured variables have an association with one or both ASD outcomes. Finally, some studies have smaller sample sizes (Ikejiri et al., 2016; Kihara, & Nakamura, 2015; Limperopoulos et al., 2008b) or may only analyze data from one state (Burd et al., 1999; Mann et al., 2009), but these data (NSCH) are from a large and complex nationally-represented survey.

2.1.1 Objective

The purpose of this analysis is to determine the odds of autism for children who were born premature and underweight.

2.1.2 Research Question

Do preterm and low birth weight infants have greater odds of being diagnosed with autism spectrum disorder (ASD)?

Chapter III: Methods

3.1 Secondary Data Collection

Data were collected from the National Survey of Children's Health. The NSCH is a cross-sectional survey that examines the emotional and physical health of children in the United States, which includes all 50 states and the District of Columbia. This survey was sponsored by the Maternal and Child Health Bureau of the Health Resources and Services Administration. The datasets used for this analysis include NSCH 2016, 2017, & 2018.

3.2 Participants

Since 2016, household addresses have been randomly selected from the Census Master Address File (MAF) and are identified by which households are likely to have children. The information collected from the participants are based on the health and well-being of children, such as neighborhood characteristics, parental physical and mental health, access and utilization of health care, family interactions, and receipt of care in a medical home. The age range for this analysis include all children from the survey, from birth to 17 years old. Overall, 50,212 completed the topical questionnaire in 2016, 21,599 completed the topical questionnaire in 2017, and 30,530 completed the topical questionnaire in 2018. In total, 102,341 observations were seen from the topical questionnaires of 2016 to 2018.

3.3 Measures

3.3.1 Outcome Variables

ASD Identification. From the cross-sectional survey, two primary ASD outcomes were used: "Has a doctor or other health care provider EVER told you that this child has Autism or Autism Spectrum Disorder (ASD)?" and "Does this child CURRENTLY have the condition?" Both questions include the diagnosis of Pervasive Developmental Disorder (PDD) or Asperger's Disorder. It was appropriate to include both outcomes as other researchers using the NSCH have also included both outcomes in their research when analyzing ASD (Kogan et al., 2018; Schieve et al., 2012a; Schieve et al., 2012b; Thomas et al., 2016).

3.3.2 Primary Predictor Variables

Gestational Age and Birth Weight Status. The following predictor variables of gestational age and birth weight were used: "Was this child born more than 3 weeks before his or her due date?" and "Birth weight status", respectively. The gestational age predictor variable is a binary variable since the parents/caregivers only had two options to choose from, yes or no [Reference]. The birth weight status is an ordinal variable because of the categories available to choose from: not low birth weight [Reference], low birth weight (1,500-2,500g), and very low birth weight (<1,500g).

3.3.3 Secondary Predictor Variables

Other variables used for this analysis included: child-level and family/parental-level variables. The child-level variables are as follows: sex (female [Reference], and male), age (<4 [Reference], 4-8, 9-12, and ≥ 13 years old), developmental delays (no [Reference], and yes), intellectual disabilities (no [Reference], and yes), birth order (third or greater older child [Reference], only child, oldest child, and second oldest child), and race/ethnicity. Race and ethnicity were combined into the following categories: non-Hispanic Other [Reference], non-Hispanic White, non-Hispanic Black, and Hispanic. The family/parental-level variables are as follows: age of mother at birth (18-24 [Reference], 25-29, 30-34, and ≥ 35 years old), family structure (2 parents married [Reference], 2 parents not married, single mother, and other), usual source of care (no usual source [Reference], usual source), highest level of education among reported adults (more than high school [Reference], and high school or less), primary language in household (non-English [Reference], and English), insurance type (private only [Reference], public only, public and private, and uninsured), personal doctor or nurse (yes, one person [Reference], yes, more than one person, and no), and family poverty ratio [FPL] (400+ poverty [Reference], <100% poverty, 100-199% poverty, and 200-399% poverty).

3.4 Statistical Analysis

All analyses were done using R, a programming language used for statistical computing. The R package called “survey” was used for conducting weighted and stratified analyses of the combined datasets from all three years. Survey weighted and stratified analyses were developed to ensure percentages for each variable on ASD cases and non-ASD cases are representative of the U.S. population. Univariate analysis was used to help determine if there was a proportional difference between the two main predictors, preterm birth and birth weight status, and socio-demographic characteristics on both ASD outcomes. In the univariate and multivariate analyses, the odds ratio and confidence intervals were obtained for each variable. Odds ratio (OR) and 95% confidence intervals (CI) examine the strength of the correlation between two events, in this case being ASD outcome and premature birth and/or low birth weight. Three logistic regression models were employed to examine any effects that may be due to prematurity alone, prematurity & birth weight status, and prematurity, birth weight status, & socio-demographic characteristics on the two ASD outcomes.

Since logistic regression models were created in the analyses, OR and 95% CIs were calculated in the univariate and multivariate analyses. Further, given the low ASD rate of <10%, Chen, Cohen, & Chen’s (2010) framework for interpreting OR was used to interpret the analyses in this paper. They propose that ORs of 1.68, 3.47, and 6.71 are interpreted as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$), respectively, where d is the popular standardized mean difference for parametric outcome data (Chen, Cohen, & Chen, 2010).

Chapter IV: Results

4.1 Table 1 Results

The weighted percentages of the predictor variables from the 2016-2018 NSCH are shown in Table 1. The table includes data on the total sample (N = 102,341) of children from birth to 17 years old with and without ASD, separating children who had ever been told they have ASD and children who currently have ASD (from the time their caregivers filled out the surveys). For every variable, “ever told” and “currently” had almost the same percentage, so there was no difference when comparing both ASD outcomes. About 4% of preterm infants had ASD, while about 2% of preterm infants did not have ASD. There was a greater prevalence of autism among VLBW (~5%) when compared to children with no LBW (2.3-2.4%) and children with a LBW (3.1-3.3%). There was a small difference in the percentages for ASD across all age ranges for mother’s age at birth, but mothers 30-34 years old had the lowest percentage of children with ASD (2%) compared to mothers 18-24 years old (~2.5%). Further, the percentages for ASD among Hispanic children was 3%, which was greater than the other races and ethnicities who also had ASD. Almost 4% of males and 1.1% of females had ASD, which is consistent with the literature stating that males are almost 4 times greater than females to have autism (CDC, 2020a; Frazier et al., 2014; Leavey et al., 2013; Morgan et al., 2012; Msall, 2010). Additionally, age was a good ASD indicator when separated into age categories; older children (9-12 & ≥13 years of age) were more likely to be diagnosed with ASD (~3%), while younger children were least likely to be diagnosed (0.7% to 2.7%). Developmental delays and intellectual disabilities are also predictors associated with ASD; 25.5 to 26.7% of children with developmental delays also had ASD, and 40.8 to 41% of children with intellectual disabilities also had ASD. Children who were an only child (2.9-3.1%) or the oldest (2.7-2.9%) among their siblings were more likely to be diagnosed with ASD compared to children who were the third or greater oldest child (1.3%). Parents who were not married, parents who had an education of high school or less, and those with usual source of care were greater associated with an ASD diagnosis. There was no association between primary household language and ASD. In addition, having more than one personal doctor or nurse, being in the <100% FPL, and having both public and private health insurance were greater associated with an ASD diagnosis.

Table 1*Percentages of predictor variables from the National Survey of Children's Health, 2016-2018*

Variable	Sample Size (N)	ASD (Ever Told)	Non-ASD (Ever Told)	ASD (Currently)	Non-ASD (Currently)
Total	102,341	2.6%	97.4%	2.4%	97.6%
Preterm					
No	90,042	2.2%	97.8%	2.1%	97.9%
Yes	10,935	4.4%	95.6%	4.1%	95.9%
Birth Weight Status					
Not LBW	89,023	2.4%	97.6%	2.3%	97.7%
LBW (1500-2500g)	6,617	3.3%	96.7%	3.1%	96.9%
VLBW (<1500g)	1,238	5.5%	94.5%	4.7%	95.3%
Mother's Age at Birth					
18-24	17,743	2.6%	97.4%	2.4%	97.6%
25-29	25,753	2.7%	97.3%	2.5%	97.5%
30-34	31,307	2.1%	97.9%	2.0%	98.0%
≥35	23,438	2.8%	97.2%	2.7%	97.3%
Race/Ethnicity					
Non-Hispanic White	71,294	2.3%	97.7%	2.1%	97.9%
Non-Hispanic Black	6,207	2.9%	97.1%	2.6%	97.4%
Hispanic	11,622	3.1%	96.9%	3.0%	97.0%
Other	13,218	2.0%	98.0%	1.9%	98.1%
Child's Sex					
Female	49,564	1.1%	98.9%	1.1%	98.9%
Male	52,777	3.9%	96.1%	3.7%	96.3%
Child's Age					
<4	19,030	0.8%	99.2%	0.7%	99.3%
4-8	24,640	2.7%	97.3%	2.5%	97.5%
9-12	22,312	3.2%	96.8%	3.0%	97.0%
≥13	36,359	3.2%	96.8%	3.0%	97.0%
Developmental Delays					
No	95,502	0.9%	99.1%	0.8%	99.2%
Yes	6,839	26.7%	73.3%	25.5%	74.5%
Intellectual Disability					
No	101,214	2.1%	97.9%	2.0%	98.0%
Yes	1,127	41.0%	59.0%	40.8%	59.2%
Birth Order					
Only Child	42,145	3.1%	96.9%	2.9%	97.1%
Oldest Child	26,765	2.9%	97.1%	2.7%	97.3%

Second Oldest	26,084	2.3%	97.7%	2.2%	97.8%
Third or Greater Oldest	7,347	1.3%	98.7%	1.3%	98.7%
Family Structure					
2 Parents Married	73,287	2.2%	97.8%	2.1%	97.9%
2 Parents Not Married	6,602	3.6%	96.4%	3.3%	96.7%
Single Mother	15,096	3.3%	96.7%	3.1%	96.9%
Other	5,617	3.0%	97.0%	2.4%	97.6%
Primary Language in HH					
English	95,071	2.6%	97.4%	2.4%	97.6%
Non-English	6,601	2.4%	97.6%	2.3%	97.7%
Parental Education					
High School or less	15,157	3.0%	97.0%	2.9%	97.1%
More than High School	85,987	2.4%	97.6%	2.2%	97.8%
Usual Source of Care					
Usual Source	84,205	2.7%	97.3%	2.6%	97.4%
No Usual Source	17,752	2.0%	98.0%	1.8%	98.2%
Personal Doctor or Nurse					
No	22,991	2.3%	97.7%	2.2%	97.8%
Yes, One Person	57,625	2.2%	97.8%	2.0%	98.0%
Yes, More than One Person	21,209	3.7%	96.3%	3.5%	96.5%
Poverty Level					
<100% Poverty	11,254	3.3%	96.7%	3.2%	96.8%
100-199% Poverty	16,340	3.1%	96.9%	2.9%	97.1%
200-399% Poverty	31,381	2.3%	97.7%	2.1%	97.9%
400+ Poverty	43,366	1.8%	98.2%	1.7%	98.3%
Health Insurance					
Uninsured	4,565	1.9%	98.1%	1.9%	98.1%
Public Only	19,610	3.6%	96.4%	3.4%	96.6%
Private Only	73,478	1.7%	98.3%	1.6%	98.4%
Public and Private	3,762	6.2%	93.8%	5.9%	94.1%

Note. Sample size is the raw number of selected children.

4.2 Table 2 Results

The univariate analysis for each predictor variable and “ever told” and “currently” ASD outcomes are shown in Table 2 using the Chen, Cohen, & Chen (2010) OR interpretations. Being born preterm had a moderate association with both ASD outcomes [OR_{ever}: 1.98; 95% CI: 1.54, 2.55; OR_{current}: 1.99; 95% CI: 1.52, 2.59]. Further, the odds of having autism was greater among children born with a VLBW (<1,500g) [OR_{ever}: 2.35; 95% CI: 1.46, 3.78; OR_{current}: 2.13 95% CI: 1.28, 3.54], a moderate association, compared to children with a LBW [OR_{ever}: 1.37; 95% CI: 1.09, 1.74; OR_{current}: 1.39; 95% CI: 1.09, 1.77], a small association. All age ranges for mother’s age at birth had a weak association with both ASD outcomes. Further, being non-Hispanic White and Black also had a small effect on both ASD outcomes, but being Hispanic had a moderate effect on both ASD outcomes [OR_{ever}: 1.55; 95% CI: 1.12, 2.14; OR_{current}: 1.62; 95% CI: 1.16, 2.25]. Being male also had a moderate effect on both ASD outcomes [OR_{ever}: 3.62; 95% CI: 2.85, 4.59; OR_{current}: 3.56; 95% CI: 2.78, 4.58]. All age ranges for the selected child had a moderate effect on ASD outcomes, with ages 9-12 and ≥ 13 years having greater odds among the “currently” ASD diagnosis. Moreover, both developmental delays [OR_{ever}: 40.23; 95% CI: 31.82, 50.87; OR_{current}: 41.87; 95% CI: 32.55, 53.84] and intellectual disabilities [OR_{ever}: 32.17; 95% CI: 23.50, 44.04; OR_{current}: 34.55; 95% CI: 25.17, 47.43] had a very strong association with the ASD outcomes. Children of any birth order had a moderate association with ASD outcomes, but being the only child had the greatest odds [OR_{ever}: 2.34; 95% CI: 1.59, 3.44; OR_{current}: 2.25; 95% CI: 1.52, 3.34]. Among family structure, all had a weak association with ASD outcomes, except for 2 parents not married and its moderate association to only the “ever told” ASD outcome [OR: 1.67; 95% CI: 1.11, 2.51]. Having English as the primary household language, parents having an education of high school or less, and having a usual source of care all had small effects among ASD outcomes. Having more than one personal doctor or nurse [OR_{ever}: 1.72; 95% CI: 1.44, 2.07; OR_{current}: 1.79; 95% CI: 1.48, 2.16] had a moderate association among ASD outcomes, while having no personal doctor or nurse [OR_{ever}: 1.06; 95% CI: 0.80, 1.41; OR_{current}: 1.10; 95% CI: 0.82, 1.48] had a weak association among ASD outcomes. Children living in the <100% FPL [OR_{ever}: 1.84; 95% CI: 1.40, 2.41; OR_{current}: 1.92; 95% CI: 1.45, 2.54] had greater odds, a moderate effect, of being diagnosed with ASD compared to children living in 200-399% FPL [OR_{ever}: 1.23; 95% CI: 1.03, 1.48; OR_{current}: 1.25; 95% CI: 1.03, 1.51], a small effect. Lastly, the odds of having ASD was greater for those who had both private and public health insurance [OR: 3.77; 95% CI: 2.84, 5.01; OR_{current}: 3.82; 95% CI: 2.84, 5.13], a moderate effect, compared to public health insurance alone [OR: 2.15; 95% CI: 1.74, 2.66; OR_{current}: 2.17; 95% CI: 1.74, 2.71], a moderate effect, or those who were uninsured [OR: 1.12; 95% CI: 0.66, 1.89; OR_{current}: 1.16; 95% CI: 0.67, 2.00], a small effect.

Table 2

Univariate analyses displaying the odds of ASD diagnosis by predictor variables from the National Survey of Children's Health, 2016-2018

Variable	OR (95% CI) [Ever Told]	p-value [Ever Told]	OR (95% CI) [Currently]	p-value [Currently]
Preterm				
No	REF	REF	REF	REF
Yes	1.98 (1.54, 2.55)	<0.001	1.99 (1.52, 2.59)	<0.001
Birth Weight Status				
Not LBW	REF	REF	REF	REF
LBW (1500-2500g)	1.37 (1.09, 1.74)	0.01	1.39 (1.09, 1.77)	0.01
VLBW (<1500g)	2.35 (1.46, 3.78)	0.00	2.13 (1.28, 3.54)	0.00
Mother's Age at Birth				
18-24	REF	REF	REF	REF
25-29	1.04 (0.80, 1.37)	0.75	1.07 (0.81, 1.41)	0.63
30-34	0.81 (0.64, 1.02)	0.07	0.84 (0.67, 1.06)	0.15
≥35	1.08 (0.80, 1.45)	0.64	1.12 (0.83, 1.53)	0.46
Race/Ethnicity				
Other	REF	REF	REF	REF
Non-Hispanic White	1.14 (0.94, 1.39)	0.17	1.14 (0.93, 1.39)	0.20
Non-Hispanic Black	1.42 (1.04, 1.94)	0.03	1.40 (1.02, 1.91)	0.04
Hispanic	1.55 (1.12, 2.14)	0.01	1.62 (1.16, 2.25)	0.00
Child's Sex				
Female	REF	REF	REF	REF
Male	3.62 (2.85, 4.59)	<0.001	3.56 (2.78, 4.58)	<0.001
Child's Age				
<4	REF	REF	REF	REF
4-8	3.38 (2.16, 5.29)	<0.001	3.79 (2.45, 5.88)	<0.001
9-12	4.05 (2.61, 6.29)	<0.001	4.55 (2.96, 6.99)	<0.001
≥13	4.07 (2.65, 6.27)	<0.001	4.54 (2.98, 6.91)	<0.001
Developmental Delays				

No	REF	REF	REF	REF
Yes	40.23 (31.82, 50.87)	<0.001	41.87 (32.55, 53.84)	<0.001
Intellectual Disabilities				
No	REF	REF	REF	REF
Yes	32.17 (23.50, 44.04)	<0.001	34.55 (25.17, 47.43)	<0.001
Birth Order				
Third or Greater Oldest	REF	REF	REF	REF
Only Child	2.34 (1.59, 3.44)	<0.001	2.25 (1.52, 3.34)	<0.001
Oldest	2.25 (1.53, 3.32)	<0.001	2.12 (1.43, 3.14)	0.00
Second Oldest	1.78 (1.17, 2.71)	0.01	1.70 (1.10, 2.62)	0.02
Family Structure				
2 Parents Married	REF	REF	REF	REF
2 Parents Not Married	1.67 (1.11, 2.51)	0.01	1.61 (1.04, 2.49)	0.03
Single Mother	1.50 (1.22, 1.85)	0.00	1.50 (1.21, 1.87)	0.00
Other	1.35 (0.95, 1.91)	0.09	1.15 (0.83, 1.61)	0.39
Primary Language in HH				
Non-English	REF	REF	REF	REF
English	1.10 (0.73, 1.66)	0.66	1.06 (0.69, 1.61)	0.80
Parental Education				
More than High School	REF	REF	REF	REF
High School or Less	1.28 (1.00, 1.63)	0.049	1.34 (1.04, 1.72)	0.02
Usual Source of Care				
No Usual Source	REF	REF	REF	REF
Usual Source	1.39 (1.07, 1.82)	0.02	1.47 (1.12, 1.94)	0.01
Personal Doctor or Nurse				
Yes, One Person	REF	REF	REF	REF
Yes, More than One Person	1.72 (1.44, 2.07)	<0.001	1.79 (1.48, 2.16)	<0.001
No	1.06 (0.80, 1.41)	0.69	1.10 (0.82, 1.48)	0.52
Poverty Level				
400+ Poverty	REF	REF	REF	REF
< 100% Poverty	1.84 (1.40, 2.41)	<0.001	1.92 (1.45, 2.54)	<0.001
100 – 199% Poverty	1.73 (1.33, 2.24)	<0.001	1.69 (1.29, 2.23)	0.00
200 – 399% Poverty	1.23 (1.03, 1.48)	0.02	1.25 (1.03, 1.51)	0.02

Health Insurance				
Private Only	REF	REF	REF	REF
Public Only	2.15 (1.74, 2.66)	<0.001	2.17 (1.74, 2.71)	<0.001
Public and Private	3.77 (2.84, 5.01)	<0.001	3.82 (2.84, 5.13)	<0.001
Uninsured	1.12 (0.66, 1.89)	0.68	1.16 (0.67, 2.00)	0.60

Note. Odds ratios (ORs) of 1.68, 3.47, and 6.71 are interpreted as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$), respectively; d is the standardized mean difference (Chen, Cohen, & Chen, 2010).

4.3 Table 3 Results

Logistic regression models for the relationship between “ever told” ASD and gestational age, birth weight, and the socio-demographic variables are shown in Table 3 using the Chen, Cohen, & Chen (2010) OR interpretations. Model 1 displays the univariate analysis between preterm birth and “ever told” ASD diagnosis. Model 2 displays the bivariate analysis between preterm birth & birth weight status and “ever told” ASD diagnosis. Model 3 displays the multivariate analysis between preterm birth, birth weight status, & socio-demographic characteristics and “ever told” ASD diagnosis. In models 1 and 2, preterm birth had a moderate association with ASD. In models 2 and 3, birth weight status had a weak association with ASD. Preterm birth had a weak association with ASD in model 3 when other variables were controlled for. Model 3 shows that the odds for mother’s age at birth was greater among ≥ 35 -year-olds, a small association, compared to the other ages. The odds for race/ethnicity was greater among Hispanic children, a small effect, compared to the other race and ethnicities. Furthermore, being male had a moderate association with having an ASD outcome [OR: 2.54]. All ages for the selected child had a moderate association with ASD, but children ages 9-12 years old had greater odds of being diagnosed with ASD [OR: 4.01]. Children with developmental delays had a very large association with having ASD [OR: 32.49], while children with intellectual disabilities had only a moderate association with having ASD [OR: 2.65]. Among birth order, children who were an only child had greater odds of having ASD [OR: 2.32], a moderate effect, compared to the oldest child [OR: 1.92], a moderate effect, and to the second oldest child [OR: 1.67], a small effect. Children who had 2 parents not married had greater odds of having ASD, a small effect, compared to children with a single mother and to other family structures. Having English as the primary household language, parents having an education of high school or less, and having a usual source of care were all weak associations among the ASD outcome. The odds of having autism was greater among children with no personal doctor or nurse, a small effect, compared to children with more than one personal doctor or nurse, which is the opposite from the univariate analysis in Table 2. Further, children living in the 100-199% FPL had greater odds of having ASD [OR: 1.25], a small effect, as did children with both public and private health insurance [OR: 1.72], a moderate effect.

Table 3

Logistic Regression Models displaying the relationship between Ever Told ASD diagnosis, gestational age, birth weight, and socio-demographics from the National Survey of Children's Health, 2016-2018

Variables	Model 1			Model 2			Model 3		
	β	OR (95% CI)	p-value	β	OR (95% CI)	p-value	β	OR (95% CI)	p-value
(Intercept)	-3.77	0.02 (0.02, 0.03)	<0.001	-3.76	0.02 (0.02, 0.03)	<0.001	-7.48	0.00 (0.00, 0.00)	<0.001
Preterm									
No (Ref)									
Yes	0.68	1.98 (1.54, 2.55)	<0.001	0.67	1.96 (1.38, 2.78)	0.00	0.35	1.43 (0.88, 2.32)	0.15
Birth Weight Status									
Not LBW (Ref)									
LBW (1500-2500g)				-0.09	0.91 (0.66, 1.26)	0.57	-0.47	0.63 (0.40, 0.98)	0.04
VLBW (<1500g)				0.31	1.36 (0.78, 2.38)	0.28	-0.70	0.50 (0.22, 1.11)	0.09
Mother's Age at Birth									
18-24 (Ref)									
25-29							0.16	1.17 (0.88, 1.56)	0.27
30-34							0.11	1.12 (0.84, 1.49)	0.44
≥35							0.33	1.40 (1.00, 1.96)	0.05
Race/Ethnicity									

Non-Hispanic Other (Ref)			
Non-Hispanic White	-0.08	0.92 (0.72, 1.17)	0.50
Non-Hispanic Black	-0.19	0.83 (0.53, 1.28)	0.39
Hispanic	0.15	1.16 (0.84, 1.59)	0.37
Child's Sex			
Female (Ref)			
Male	0.93	2.54 (1.93, 3.34)	<0.001
Child's Age			
<4 (Ref)			
4-8	1.02	2.76 (1.68, 4.53)	<0.001
9-12	1.39	4.01 (2.42, 6.67)	<0.001
≥13	1.31	3.71 (2.24, 6.15)	<0.001
Developmental Delays			
No (Ref)			
Yes	3.48	32.49 (26.10, 40.43)	<0.001
Intellectual Disabilities			
No (Ref)			
Yes	0.97	2.65 (1.88, 3.74)	<0.001

Birth Order				
Third or Greater Oldest (Ref)				
Only Child		0.84	2.32 (1.49, 3.63)	0.00
Oldest Child		0.65	1.92 (1.26, 2.93)	0.00
Second Oldest Child		0.51	1.67 (1.08, 2.56)	0.02
Family Structure				
2 Parents Married (Ref)				
2 Parents Not Married		0.14	1.15 (0.76, 1.73)	0.51
Single Mother		-0.05	0.95 (0.72, 1.25)	0.71
Other		-0.43	0.65 (0.38, 1.12)	0.12
Primary Language in HH				
Non-English (Ref)				
English		-0.09	0.91 (0.57, 1.44)	0.69
Parental Education				
More than High School (Ref)				
High School or Less		-0.06	0.94 (0.72, 1.23)	0.67
Usual Source of Care				
No Usual Source (Ref)				

Usual Source	0.24	1.27 (0.90, 1.77)	0.17
Personal Doctor or Nurse			
Yes, One Person (Ref)			
Yes, More than One Person	0.01	1.01 (0.82, 1.24)	0.95
No	0.09	1.09 (0.79, 1.51)	0.61
Poverty Level			
400+ Poverty (Ref)			
< 100% Poverty	0.12	1.13 (0.80, 1.58)	0.49
100 – 199% Poverty	0.22	1.25 (0.94, 1.67)	0.13
200 – 399% Poverty	0.06	1.06 (0.84, 1.34)	0.61
Health Insurance			
Private Only (Ref)			
Public Only	0.36	1.43 (1.08, 1.90)	0.01
Public and Private	0.54	1.72 (1.23, 2.40)	0.00
Uninsured	0.35	1.42 (0.76, 2.65)	0.27

Note. Odds ratios (ORs) of 1.68, 3.47, and 6.71 are interpreted as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$), respectively; d is the standardized mean

difference (Chen, Cohen, & Chen, 2010).

4.4 Table 4 Results

Logistic regression models for the relationship between “currently” ASD and gestational age, birth weight, and the socio-demographic variables are shown in Table 4 using the Chen, Cohen, & Chen (2010) OR interpretations. Model 1 displays the univariate analysis between preterm birth and “currently” ASD diagnosis. Model 2 displays the bivariate analysis between preterm birth & birth weight status and “currently” ASD diagnosis. Model 3 displays the multivariate analysis between preterm birth, birth weight status, & socio-demographic characteristics and “currently” ASD diagnosis. In models 1 and 2, preterm birth had a moderate association with ASD. In models 2 and 3, birth weight status had a weak association with ASD. Preterm birth had a weak association with ASD in model 3 when other variables were controlled for. Model 3 shows that the odds for mother’s age at birth was greater among ≥ 35 -year-olds, a small effect, when compared to the other ages. The odds for race/ethnicity was greater among Hispanic children, a small effect, when compared to the other race and ethnicities. Furthermore, being male had a moderate association with having autism [OR: 2.44]. All ages for the selected child had a moderate association with ASD, but children ages 9-12 years old had greater odds of being diagnosed with autism [OR: 4.76]. Children with developmental delays had a very large association with having ASD [OR: 33.75], while children with intellectual disabilities had only a moderate association with having ASD [OR: 2.85]. Among birth order, children who were an only child had greater odds of having ASD [OR: 2.21], a moderate effect, compared to the oldest child [OR: 1.71], a moderate effect, and to the second oldest child [OR: 1.54], a small effect. Children who had 2 parents not married had greater odds of having ASD, a small effect, compared to children with a single mother and to other family structures. Having English as the primary household language, parents having an education of high school or less, and having a usual source of care were all weak associations among ASD. The odds of having ASD was greater among children with no personal doctor or nurse, a small effect, compared to children with more than one personal doctor or nurse, which is the opposite from the univariate analysis in Table 2. Further, children living in the 100-199% FPL had greater odds of having ASD [OR: 1.21], a small effect, as did children with both public and private health insurance [OR: 1.66], a moderate effect.

Table 4

Logistic Regression Models displaying the relationship between Currently ASD diagnosis, gestational age, birth weight, and socio-demographics from the National Survey of Children's Health, 2016-2018

Variables	Model 1			Model 2			Model 3		
	β	OR (95% CI)	p-value	β	OR (95% CI)	p-value	β	OR (95% CI)	p-value
(Intercept)	-3.84	0.02 (0.02, 0.02)	<0.001	-3.83	0.02 (0.02, 0.02)	<0.001	-7.73	0.00 (0.00, 0.00)	<0.001
Preterm									
No (Ref)									
Yes	0.69	1.99 (1.52, 2.59)	<0.001	0.70	2.01 (1.39, 2.90)	0.00	0.38	1.47 (0.89, 2.44)	0.14
Birth Weight Status									
Not LBW (Ref)									
LBW (1500-2500g)				-0.10	0.90 (0.64, 1.27)	0.57	-0.47	0.62 (0.39, 0.99)	0.05
VLBW (<1500g)				0.19	1.21 (0.67, 2.19)	0.54	-0.88	0.41 (0.18, 0.96)	0.04
Mother's Age at Birth									
18-24 (Ref)									
25-29							0.15	1.16 (0.86, 1.56)	0.33
30-34							0.13	1.14 (0.35, 1.54)	0.38
≥35							0.34	1.40 (0.99, 1.99)	0.06
Race/Ethnicity									

Non-Hispanic Other (Ref)			
Non-Hispanic White	-0.12	0.88 (0.69, 1.13)	0.33
Non-Hispanic Black	-0.24	0.79 (0.51, 1.20)	0.27
Hispanic	0.16	1.17 (0.85, 1.62)	0.33
Child's Sex			
Female (Ref)			
Male	0.89	2.44 (1.83, 3.25)	<0.001
Child's Age			
<4 (Ref)			
4-8	1.17	3.22 (2.05, 5.05)	<0.001
9-12	1.56	4.76 (3.01, 7.51)	<0.001
≥13	1.47	4.35 (2.81, 6.72)	<0.001
Developmental Delays			
No (Ref)			
Yes	3.52	33.75 (26.90, 42.34)	<0.001
Intellectual Disabilities			
No (Ref)			
Yes	1.05	2.85 (2.03, 4.00)	<0.001

Birth Order				
Third or Greater Oldest (Ref)				
Only Child		0.79	2.21 (1.39, 3.50)	0.00
Oldest Child		0.54	1.71 (1.13, 2.59)	0.01
Second Oldest Child		0.43	1.54 (0.99, 2.40)	0.05
Family Structure				
2 Parents Married (Ref)				
2 Parents Not Married		0.03	1.03 (0.67, 1.58)	0.90
Single Mother		-0.09	0.91 (0.68, 1.21)	0.52
Other		-0.77	0.47 (0.29, 0.75)	0.00
Primary Language in HH				
Non-English (Ref)				
English		-0.09	0.91 (0.57, 1.47)	0.71
Parental Education				
More than High School (Ref)				
High School or Less		0.01	1.01 (0.78, 1.32)	0.93
Usual Source of Care				

No Usual Source (Ref)			
Usual Source	0.33	1.39 (0.99, 1.94)	0.05
Personal Doctor or Nurse			
Yes, One Person (Ref)			
Yes, More than One Person	0.06	1.07 (0.87, 1.31)	0.55
No	0.15	1.16 (0.83, 1.61)	0.39
Poverty Level			
400+ Poverty (Ref)			
< 100% Poverty	0.18	1.20 (0.84, 1.70)	0.31
100 – 199% Poverty	0.19	1.21 (0.90, 1.63)	0.21
200 – 399% Poverty	0.08	1.08 (0.85, 1.38)	0.51
Health Insurance			
Private Only (Ref)			
Public Only	0.35	1.42 (1.05, 1.91)	0.02
Public and Private	0.51	1.66 (1.18, 2.34)	0.00
Uninsured	0.39	1.47 (0.77, 2.80)	0.24

Note. Odds ratios (ORs) of 1.68, 3.47, and 6.71 are interpreted as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$), respectively; d is the standardized mean difference (Chen, Cohen, & Chen, 2010).

Chapter V: Conclusion

5.1 Discussion of Research Question

In the present study, there was a greater ASD prevalence among preterm children compared to non-preterm children. There was also a moderate association between preterm birth and ASD, but when controlling for secondary variables, prematurity on ASD outcomes was no longer significant. Further, children born with a very low birth weight (<1,500g) had a greater ASD prevalence compared to children with a low birth weight (1,500-2,500g) and to children who were born with a normal weight. Having a VLBW had a moderate association to ASD, but was no longer significant when controlling for secondary variables.

This analysis fits in with previous literature that has reported an association between preterm birth and ASD (Agrawal et al., 2018; Gray et al., 2015; Hadjkacem et al., 2016; Joseph et al., 2016; Kuzniewicz et al., 2014; Lampi et al., 2010; Leavey et al., 2013; Lederman et al., 2018; Limperopoulos et al., 2008b; Limperopoulos, 2009; Şahin et al., 2019; Schendel & Bhasin, 2008; Sharma et al., 2018; Stephens et al., 2012; Wang et al., 2017). The present analysis showed a weak association between VLBW and LBW on ASD outcomes in the logistic regression models, but the odds of VLBW status was greater than no LBW weight in the univariate analysis. The literature has shown a mix of findings among LBW infants and an ASD diagnosis (Pyhälä et al., 2014), which was seen with the present analysis as well; in particular, the 2011-2012 NSCH study that found no association among LBW and ASD (Ghadge et al., 2016). Previous literature has shown that the lower the birth weight, the greater the risk for having ASD, which was seen in the present analysis when other variables were not controlled for (table 1; Dudova et al., 2014; Limperopoulos et al., 2008a; Losh et al., 2012; Pyhälä et al., 2014). When considered in light of the previous literature, it is clear that greater care must be taken to include relevant covariates to determine the precise relationship between premature birth, birthweight and ASD status.

5.2 Discussion of Secondary Variables

Many of the covariates used in the present analysis have also been used in previous studies, which helped guide this paper. For example, the age of the mother at birth has often been included in research with similar hypotheses, which is examining the relationship between preterm birth and/or LBW and ASD outcomes. The present analysis, however, included ages 18 to 45 for mother's age at birth, while most studies include only ages 35 and older; nevertheless, our analysis showed greater odds among older mothers (≥ 35 years), though a small effect, being more likely to give birth to a child with ASD compared to younger mothers (Durkin et al., 2008; Pinborough-Zimmerman, et al., 2011; Sharma et al., 2018). Furthermore, while the present analysis found greater odds of ASD among being an only child (a moderate association), other researchers have found increased odds of ASD in children who were older in the birth order (Frazier et al., 2014; Simon et al., 2013). Additionally, this analysis, along with previous findings, showed the statistical significance of males being more likely to have autism compared to females (CDC, 2020a; Frazier et al., 2014; Leavey et al., 2013; Morgan et al., 2012; Wang et

al., 2017). Moreover, the present analysis showed a greater ASD prevalence among Hispanic children, but there have been a variety of findings in ASD outcomes among all race and ethnicities; some researchers have shown greater ASD prevalence among Hispanic children (Nevison, & Parker, 2020; Nevison, & Zahorodny, 2019; Simon et al., 2013), while others have found greater ASD prevalence among non-Hispanic White children (Pinborough-Zimmerman, et al., 2011; Wang et al., 2017). Thus, these data resonate with the previous literature indicating that maternal age, presence of siblings, gender, and race/ethnicity are important sources of variance related to ASD status.

There are some differences, however, in the present analysis compared to previous literature. A study that used the NS-CSHCN included ASD severity in their analysis and found that to be associated with the age at which children get diagnosed with autism; this could be an important predictor in the present analysis that determines how soon or late preterm children are being diagnosed with autism and to determine how severe their autism is based on their actual gestation age and their birth weight (Jo et al., 2015). The present analysis, however, only aimed at determining whether or not there was an association between preterm birth & low birth weight status in ASD cases. It's also important to note that most of the literature excluded participants with other disabilities, disorders, or impairments from their studies (Agrawal et al., 2018; Brayette et al., 2019; Dudova et al., 2014; Hadjkacem et al., 2016; Harel-Gadassi et al., 2018; Ikejiri et al., 2016; Joseph et al., 2016; Joseph et al., 2017; Kerstjens et al., 2012; Kuban et al., 2009; Lampi et al., 2010; Lederman et al., 2018; Limperopoulos, 2008b; Pyhälä et al., 2014; Stephens et al., 2012), which is why this analysis also excluded them. Future research should aim to determine if prematurity and birth weight are unique to ASD status, or part of a general relationship to disability.

5.3 Outcomes of the Current Analysis

The current analysis included two outcomes: “Has a doctor or other health care provider EVER told you that this child has Autism or Autism Spectrum Disorder (ASD)?” and “Does this child CURRENTLY have the condition?” Other studies usually only include one ASD outcome, whether the child screened positive through the M-CHAT or through another ASD screening or diagnostic tool. Although the percentages in Table 1 were almost identical between “ever told” and “currently” ASD outcomes, some variables had greater odds among “ever told” vs. “currently”, and vice-versa. For example, VLBW was more significant among the “ever told” outcome (Table 3), while child’s age was more significant among the “currently” outcome (Table 4). Some predictors had a small association with ASD among “ever told” but had a moderate association with ASD among “currently”, and vice-versa. Since these differences were observed, it was important to include both ASD outcomes in the analysis. Further, this stands out from previous literature because even if a child had ever been told they have ASD, it does not mean that they currently have the condition, which is why “currently” is a sub question of “ever told.” Indeed, some children who receive an early ASD diagnosis may ‘outgrow’ their symptoms, thus resulting in a different diagnosis later on in life (National Institutes of Health, 2015). As such, consideration of both EVER and CURRENT ASD status helped to control for effects of children whose ASD diagnosis may have changed over time.

5.4 Discussion of Strengths

The current analysis included many variables that have been included in other studies, such as mother's age at birth, preterm birth, birth weight status, birth order, health insurance status, sex, race/ethnicity, family poverty level, and parental education. It was also important and beneficial to include both outcomes, "ever told" and "currently", because there were some differences and it gave a better understanding as to how one can be more significant than the other. Moreover, the current analysis also included a large sample size because the NSCH is a national survey whose weights and stratifications result in an adequate representation of the U.S. population of children birth to 17. Considering that there is a fair amount of variance across studies in terms of the representativeness of their sample sizes and proportion of their sample with ASD (Agrawal et al., 2018; Johnson et al., 2010; Lampi et al., 2010; Limperopoulos et al., 2008b; Stephens et al., 2012), use of the NSCH helps provide estimates and results that are more likely representative of the population at large. Furthermore, the large sample allowed us to control for a more relevant co-variates than smaller sample more typical of clinical population.

5.5 Discussion of Limitations

In this analysis, there were some limitations. For example, studies have shown that maternal factors, such as pre-, peri-, and post-natal characteristics are risk factors for autism spectrum disorder, but NSCH did not include these factors. For example, previous literature has asked questions about delivery methods, fetal distress, and parity (Hadjkacem et al., 2016; Kuzniewicz et al., 2014; Şahin et al., 2019; Wang et al., 2017), but the NSCH survey did not include questions about the mother's pregnancy or delivery. Finally, previous literature has included maternal hypertension and maternal diabetes as risk factors for autism (Hadjkacem et al., 2016; Wang et al., 2017), but the NSCH also did not have these available.

Although the NSCH survey had its advantages given the large sample size, there was no follow-up given that it was a cross-sectional survey; a cross-sectional survey only measures a certain point in time so it cannot analyze behavior or health and well-being over a period of time (Setia, 2016). Moreover, since the NSCH is a self-completed questionnaire, the parents/caregivers may have trouble recalling some information and/or events, misinterpret the questions, or leave some questions blank (Debois, 2019). Also, the NSCH only asks whether or not the selected child had ever been told or if they currently had ASD, but it would be helpful to ask which diagnostic tool was used to assess and diagnose the disorder. Finally, the NSCH did not provide different categories for preterm birth (e.g., extremely [<28 weeks] or very preterm [28-32 weeks]) like they did for birth weight status (VLBW, LBW, & not LBW), so it is unknown during which week of pregnancy the selected child was actually born in, whether between 24-26 weeks or 27-32 weeks, which can make a difference.

5.6 Future Directions

It is important to continue the research on whether prematurity and birth weight status are risk factors for ASD given the mix of supportive and non-supportive findings. Additionally, more research is also needed because there is "insufficient evidence to implicate any one

perinatal or neonatal factor in autism etiology” (Gardener et al., 2011, p. 349). Previously, it was not quite believed or known that prenatal and perinatal factors could be risk factors for ASD, but growing evidence indicates otherwise (Burd et al., 1999). If this is the case, the data and literature can help in prevention strategies, as well as decreasing the severity of the disorder (Burd et al., 1999).

Furthermore, it could be that being born extremely preterm is actually a risk factor for ASD, but it can also be that other developmental disabilities, aside from autism, can increase positive screening results, such as being marked as ‘fail’ on the M-CHAT even though the infant/child might not actually have any social or language impairments or disabilities (Kuban et al., 2009). It is also unclear if preterm infants with neurodevelopmental disabilities have been characterized as ASD more often because these disabilities and difficulties, such as attention, cognitive and language impairments often overlap with ASD symptoms, which makes it much more difficult to diagnose children with a specific disorder or disability (Harel-Gadassi et al., 2018; Kuzniewicz et al., 2014). That the presence of developmental delay was the strongest predictor of ASD, indicates that future research should be conducted to determine if prematurity and or low birth weight strongly predicts delays (CDC, 2019). It may be that the relationship between these variables and ASD is mediated by developmental delays, which are common to children with ASD.

Ultimately, there is limited research on ASD prevalence among infants who are born preterm and with a LBW, and “adequate resources are needed to improve the outcomes of these children” (Agrawal et al., 2018, p. 11). To conclude, the results from the present analysis can be used in research and in future interventions to show the importance of prenatal and perinatal care in order to reduce the prevalence in preterm births, while possibly decreasing the prevalence of autism or other developmental delays (Nitin et al., 2016).

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