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Regional differences in autism and intellectual disability risk associated with cesarean section delivery

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Abstract

Prior epidemiological studies investigating the association between delivery mode (i.e., vaginal birth and cesarean section [C-section]) and autism spectrum disorder (ASD) and intellectual disability (ID) risk have reported mixed findings. This study examined ASD and ID risks associated with primary and repeat C-section within diverse US regions. During even years 2000–2016, 8-years-olds were identified with ASD and/or ID and matched to birth records [ASD only (N = 8566, 83.6% male), ASD + ID (N = 3445, 79.5% male), ID only (N = 6158, 60.8% male)] using the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network methodology. The comparison birth cohort (N = 1,456,914, 51.1% male) comprised all births recorded in the National Center for Health Statistics corresponding to birth years and counties in which surveillance occurred. C-section rates in the birth cohort demonstrated significant regional variation with lowest rates in the West. Overall models demonstrate increased odds of disability associated with primary and repeat C-section. Adjusted models, stratified by region, identified significant variability in disability likelihood associated with repeat C-section: increased odds occurred for all case groups in the Southeast, for ASD only and ID only in the Mid-Atlantic, and no case groups in the West. Regional variability in disability risk associated

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CONFLICT OF INTEREST STATEMENT

Deborah Bilder is a consultant for Encoded Therapeutics, BioMarin Pharmaceuticals, Synlogic Therapeutics, and Taysha Gene Therapies; she has attended an advisory board meeting for Sanofi. The remaining authors report no conflicts of interest.

ETHICS STATEMENT

Each ADDM site functioned as a public health authority under the HIPAA Privacy Rule and met applicable local Institutional Review Board and privacy/confidentiality requirements under 45 CFR 46.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

with repeat C-section coincides with differences in birth cohorts' C-section rates. This suggests increased likelihood of disability is not incurred by the procedure itself, but rather C-section serves as a proxy for exposures with regional variability that influence fetal development and C-section rates.

Lay Summary

Prior studies of the risk of developmental disabilities associated with repeat cesarean sections—typically a planned procedure—report mixed results. The current study examined a diverse US population to investigate autism spectrum disorder and intellectual disability risks associated with the cesarean section procedure. Significant differences were found in both cesarean section rates and the link between planned cesarean sections and the risk of developmental disability across geographic regions.

Keywords

autism; cesarean section; epidemiology; intellectual disability; prenatal risk factors

INTRODUCTION

Autism spectrum disorder (ASD) and intellectual disability (ID) are common co-occurring developmental disabilities (DD). In combination, ASD and ID (ASD + ID) lead to substantially greater disability than either disability in isolation (Maenner et al., 2021; Matson et al., 2009; Patrick et al., 2021). Risk factors for ASD and ID are multifactorial—encompassing genetic, epigenetic, and environmental factors (Parenti et al., 2020). Understanding how pre- and perinatal risk factors are associated with ASD and ID provides insight into obstetrical phenomena that may contribute to the development of these conditions.

Prior epidemiological studies including two meta-analyses (Curran, O'Neill, et al., 2015; Zhang et al., 2019) investigating the association between delivery mode (i.e., vaginal birth and cesarean section) and ASD and ID risk have reported mixed findings. Curran, Dalman, et al., 2015 found increased risk for ASD linked to Cesarean section (C-section) overall and primary C-section, but not repeat C-section. Zhang et al., 2019 identified an association between C-section births and ASD irrespective of C-section type; however, the high degree of heterogeneity observed among studies measuring the association between repeat C-section and ASD risk limited interpretability (Zhang et al., 2019). Additionally, this meta-analysis (Zhang et al., 2019) included analyses from two studies using general population control while excluding their respective sibling control analyses to avoid the inclusion of overlapping case groups (Curran, Dalman, et al., 2015; Glasson et al., 2004; Zhang et al., 2019). While the analyses using population-based comparison groups found a significant association between repeat C-section and ASD risk, both of the respective sibling control analyses in Curran et al. and Glasson et al. reported null associations between repeat C-section and ASD risk (Curran, Dalman, et al., 2015; Glasson et al., 2004). Understanding the potential for residual confounding that may account for these differences remains a gap in the current literature (Curran, O'Neill, et al., 2015; Zhang et al., 2019).

Residual confounding may arise from the role of C-section as a proxy for preexisting maternal conditions and medical indications for the procedure itself. Medical decision-making surrounding delivery method selection is complex and influenced by factors that overlap with DD (Bilder et al., 2009; Bilder et al., 2013; Branch & Silver, 2012; Chien et al., 2014; Langridge et al., 2013). This includes consideration of antenatal maternal and fetal health and tolerance during labor (e.g., fetal hypoxia/acidosis and chorioamnionitis) in nulliparous women with additional factors for multiparous women related to prior pregnancy complications (Bobrow & Soothill, 1999; Bommarito et al., 2016; Branch & Silver, 2012; Hure et al., 2017; Vassilaki et al., 2014). Several risk factors for C-section overlap with those for DD including higher maternal prepregnancy body mass index, advanced maternal age, preterm labor, diabetes, hypertension, and racial/ethnic minority background (Bilder et al., 2009; Bilder et al., 2013; Branch & Silver, 2012; DeBolt et al., 2022; Edmonds et al., 2016; Haberman et al., 2014; Hisle-Gorman et al., 2018; Hure et al., 2017; Janevic et al., 2014; Kawakita et al., 2016; Krakowiak et al., 2012; Lyall et al., 2022; Maenner et al., 2023; Nahum Sacks et al., 2016; Vanderlaan et al., 2020).

C-section rates vary significantly across geographic regions, sociodemographic groups, and birth years (Edmonds et al., 2016; Hure et al., 2017; Janevic et al., 2014; Vassilaki et al., 2014). Implementing a study design that captures a diverse population and extends over a significant duration of time optimizes the evaluation of ASD and ID risk associated with delivery mode. ASD prevalence and C-section rates in the US are often reported by state. Like C-section rates, however, states with higher co-occurrence of ASD and ID tend to cluster regionally rather than segregate individually (Etyemez et al., 2022; Hughes et al., 2023). Thus, regional investigation of DD risk associated with C-section is merited to evaluate how this may vary across US regions that differ in C-section rates and in the prevalence of maternal health factors that influence these rates (e.g., obesity, diabetes, and hypertension).

The Centers for Disease Control and Prevention’s Autism and Developmental Disabilities Monitoring Network (ADDM) provides an opportunity to examine ASD and ID risk associated with delivery mode over 16 years within diverse communities across the United States (Maenner et al., 2020).

ADDM implemented methodologies for case ascertainment and definition that were consistent across participating sites within study years. ADDM provides a unique opportunity to evaluate how DD may be associated with delivery mode in a large, population-based US cohort while providing a regional context in which to interpret results. The aims of the current study were to (1) evaluate the relationships between ASD and/or ID (ASD/ID) risk and delivery mode and (2) explore differences in ASD/ID risk associated with delivery method across geographic regions in the US.

METHODS

Study sites

ADDM surveillance activities targeted the total population of eight-year-olds born during even years between 1992 and 2008 residing in specific continuous areas, often defined by

county, within select states. Study site and year inclusion required concurrent ASD and ID surveillance. While all ADDM sites linked 8-year-old children identified with DD to birth certificate records, pre-/perinatal risk factor availability varied by site and study year. For inclusion, only sites providing the following variables were included: maternal age, maternal race/ethnicity, gestational age, birthweight, and delivery method. These sites and corresponding even study years were Arkansas (AR, 2002, 2008, 2010), Arizona (AZ, 2002–2016), Georgia (GA, 2000–2012), Maryland (MD, 2008, 2010, 2014, 2016), Minnesota (MN, 2014, 2016), New Jersey (NJ, 2008–2016), North Carolina (NC, 2002–2012, 2016), South Carolina (SC, 2012), and Utah (UT, 2002, 2008–2012). With the exception of MN, ADDM sites were grouped within the following US regions: Mid-Atlantic (NJ, MD), Southeast (NC, SC, GA, AR), and West (UT, AZ). While West Virginia, Tennessee, and Colorado sites also conducted concurrent ASD and ID surveillance, birth record variable availability was insufficient for study inclusion. Figure 1 depicts sites meeting initial inclusion criteria for the respective study year (i.e., ascertaining both ASD and ID) and the subsequent exclusion of sites with insufficient availability of birth record variables for the respective study year. No mid-Atlantic site met study eligibility requirements during the first four birth cohorts, nor did a Southeast site contribute to the 2006 birth cohort. The West region was represented across all birth cohorts.

Surveillance methods and case definitions

In brief, the ADDM methodology for ID and ASD surveillance involved multiple source screening and records abstraction for 8-year-old children residing in the ADDM ascertainment area during each study year. Each study site accessed both health and education records. In specialty medical settings providing assessment and care for children with developmental and behavioral concerns, records selected for abstractor review were identified through an electronic query of *International Classification of Diseases* (ICD) codes for a broad spectrum of child DD and mental health diagnoses that are associated with ASD and/or ID. In educational settings, the records of all children receiving special education services were reviewed. ID case determination was based on the most recent IQ score (IQ score below or equal to 70) or the presence of a statement by a qualified provider indicating that the child met criteria for ID. The ASD case determination process, which has previously been validated, was based on the number and pattern of ASD characteristics identified in source records through clinician review (Bakian et al., 2015). ASD criteria were based on the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) for birth years 1992–2004 (DSM-IV-TR) and 2006–2008 (DSM-5), respectively (American Psychiatric Association, 1996; American Psychiatric Association, 2013). Children with ID and ASD met criteria for both conditions based on the definitions described above. Children with ASD and/or ID are referred to as “case groups.”

Participant characteristics

The number of 8-year-old children who were in the ASD and/or ID case groups was as follows: ASD without ID (ASD only, $N = 8566$; 83.6% male), ASD and ID (ASD + ID, $N = 3445$, 79.5% male), and ID without ASD (ID only, $N = 6158$, 60.8% male).

A case-cohort design was used to maximize efficiency and flexibility compared to other study designs such as a nested case-control design (O'Brien et al., 2022). The comparison birth cohort (N = 1,456,914; 51.1% male) was identified from the National Center for Health Statistics (NCHS) National Vital Statistics System birth files and collectively referred to as the "NCHS cohort." All births from mothers whose residential birth address corresponded with the county in which ADDM surveillance occurred and birth year of case groups were included. Matching by both surveillance county and birth year for each ADDM cohort minimized residual confounding arising from regional and temporal variability in maternal and fetal health, race/ethnicity, and socioeconomic status between the case and comparison groups.

Children missing birth records, delivery method data, or who were from multifetal births were excluded. Figure 1 describes the identification of the case and cohort groups, and Figure 2 depicts the regional distribution of case groups.

Pre-/perinatal characteristics

Pre-/perinatal characteristics were derived from birth records linked to children in the case groups by each ADDM site and obtained from NCHS for children in the NCHS cohort. These characteristics were delivery method (i.e., vaginal birth, vaginal birth after C-section [VBAC], primary C-section, and repeat C-section), birth year, gestational age, birthweight, parity, multifetal status, maternal age, maternal education, maternal race/ethnicity, maternal smoking, and breech presentation. The child's sex was derived from birth records (NCHS cohort) and records review (case groups).

Analyses

Multinomial logistic regression was used to estimate odds ratios as the measure of association, which closely approximates the risk ratio because of low DD prevalence among all births (Cummings, 2009). As such, "odds," "likelihood," and "risk" are used interchangeably in referring to study results. For each case status within each geographic region, percentage of live births delivered by each delivery mode and the corresponding 95% confidence intervals (CI) were calculated using the one-sample binomial test. Nonoverlapping CIs indicated differences in delivery mode rate between groups. To assess the association between delivery method and odds of DD, an unadjusted multinomial logistic regression model was created using ASD/ID case status as the dependent variable (ASD only, ASD + ID, ID only, NCHS cohort [reference]) and delivery method (primary C-section, repeat C-section, VBAC, vaginal birth [reference]) as the independent variable. The entire sample was included in the initial model, and then models were stratified by geographic region. Stratified analyses included only the subset of case and comparison groups that corresponded to that region. Adjusted multinomial logistic regression models included birth year, maternal education at delivery, maternal race/ethnicity, geographic region, sex, gestational age, birthweight, parity, maternal age at delivery, maternal smoking status, and breech presentation. All variables except gestational age, birthweight, parity, and maternal age were treated as categorical variables. Categories within variables are listed in Table 1. Adjusted models were determined a priori to include variables that are: (1) known to be associated with both obstetrical complications and developmental disability

to reduce potential confounding and (2) consistently available across birth years and sites. The chi-square test was used to test for differences between children identified as a case in the surveillance area who were excluded from the analysis due to a missing/incomplete birth record or multifetal birth. Covariates included in the analyses were limited to those with less than 2.5% missingness, and missing data were addressed through listwise deletion. All statistical analyses were conducted using SPSS software version 28, and statistical significance was assessed at $\alpha = 0.05$.

RESULTS

Participant characteristics and birth risk factors

Table 1 describes characteristics and birth risk factors for the case groups and NCHS cohort. Figure 2 demonstrates regional variation in proportion of ASD only, ASD + ID, and ID only case groups. Table S1 compares the proportion of children ascertained with ASD only, ASD + ID, and ID only who were included versus excluded because of missing/incomplete birth records or multifetal births. Overall, the case groups with the highest and lowest proportions of children included in the analyses were ID only (71.6%) and ASD only (68.5%), respectively ($p < 0.001$). Although statistical differences were found, differences were proportionally small, suggesting minimal differences in the proportion of those included versus excluded from case groups.

Method of delivery in the NCHS cohort

Across all sites, proportions of births by method of delivery in the NCHS cohort were as follows: vaginal birth 75.4% (95% CI: 75.3–75.5), primary C-section 14.0% (95% CI: 13.9–14.0), repeat C-section 8.9% (95% CI 8.9–9.0), and VBAC 1.9% (95% CI: 1.8–1.9).

By region, there were differences in the rate of vaginal delivery in the NCHS cohort with the West having the highest rate (78.8%, 95% CI: 78.7–78.9), Southeast, an intermediary rate (75.2%, 95% CI: 75.1–75.3), and Mid-Atlantic, the lowest rate (66.6%, 95% CI: 66.4–66.8). See Figure 3. Inversely, primary C-section rates varied across regions with the Mid-Atlantic having the highest (18.9%, 95% CI: 18.7–19.1), Southeast, intermediary (14.7%, 95% CI: 14.6–14.8) and West, the lowest rate (11.4%, 95% CI: 11.3–11.5). Similar to primary C-section rates, repeat C-section occurred most frequently in the Mid-Atlantic (12.7%, 95% CI: 12.6%–12.9%) while Southeast and West rates were equivocal (8.3%, 95% CI: 8.3%–8.4%). VBAC was infrequent, at a rate of 2.0% in the Mid-Atlantic and Southeast and 1.7% in the West.

DD risk and delivery method (in comparison to the NCHS cohort and vaginal birth)

Adjusted models demonstrated attenuation of the relationship between C-section and case status relative to crude models. See Table S2 for crude model results.

In overall adjusted models, both primary C-section and repeat C-section were associated with a modest increase in odds ratios for all case groups (i.e., ASD only, ASD + ID, ID only), while VBAC was not associated with increased odds ratios for any case status in any model. See Table 2.

Stratified by region, primary C-section was significantly associated with increased odds ratios of all DDs (range of ORs = 1.21–1.68, $p < 0.004$); however, VBAC was not associated with increased odds ratios for any case group in any region. See Table 2. Repeat C-section was associated with significantly increased odds of DD in the Southeast (ASD only: AOR = 1.16, 95% CI: 1.02–1.32, $p = 0.03$; ASD + ID: AOR = 1.26, 95% CI: 1.07–1.49, $p = 0.005$; ID only: 1.35, 95% CI: 1.20–1.51, $p < 0.001$) and for ASD only and ID only in the Mid-Atlantic (AOR = 1.21, CI: 1.08–1.35, $p = 0.001$; AOR = 1.35, 95% CI: 1.09–1.66, $p = 0.006$, respectively). Results were attenuated for ASD + ID in the Southeast and all case groups in the West.

DISCUSSION

Using population-based ASD and ID surveillance, the current study examined DD likelihood associated with delivery method for 8-year-old children living within ADDM communities spanning 9 states over 17 years. This study improved upon previous research in terms of racial, ethnic, and geographical diversity, as well as sample size for children identified with ASD and/or ID through a records review process (Bilder et al., 2009; Bilder et al., 2013; Liu et al., 2022). Selection of delivery method results from a medical decision-making process that reflects a range of indications (Branch & Silver, 2012; Chien et al., 2014). The evaluation of associations between the C-section procedure and DD necessitates consideration of overlapping factors between C-section indications and DD likelihood as well as regional variation in C-section rates.

Consistent with prior epidemiologic studies, primary C-section was significantly associated with all disability categories regardless of region and after adjustment for covariates (Bilder et al., 2009; Bilder et al., 2013; Curran, Dalman, et al., 2015; Curran, O'Neill, et al., 2015; Eaton et al., 2001; Glasson et al., 2004; Zhang et al., 2019). Common indications for primary C-section include breech presentation, labor arrest (e.g., related to cephalopelvic disproportion and labor dystocia), suspected macrosomia, and non-reassuring fetal status (Branch & Silver, 2012; Chien et al., 2014). Because many of these indications are also risk factors for ASD and/or ID, the current analysis adjusted for available covariates that impact some of these conditions (e.g., breech presentation, maternal age, birthweight, gestational age) (Bilder et al., 2009; Bilder et al., 2013; Langridge et al., 2013). Birth records, however, are limited in the breadth of maternal and fetal conditions captured, which subsequently diminishes the degree to which DD risk can be isolated to the primary C-section procedure itself. While primary C-section is frequently precipitated by a non-reassuring fetal heart rate tracing, repeat C-section is performed for most subsequent births to avert uncommon —though severe—VBAC complications (e.g., uterine rupture, fetal acidosis, and hypoxic injury) (Landon et al., 2004). Unlike primary C-section, the most common indication for repeat C-section is having a previous pregnancy delivered by C-section. Thus, repeat C-section is typically a planned procedure, providing more opportunity to investigate potential risks associated with the C-section procedure itself. Of note, some prior studies have used the term "elective" rather than "repeat" to refer to a planned C-section. While not identical, most repeat C-sections are elective, and these terms are used comparably herein.

In the current study, repeat C-section overall in the crude and adjusted models was significantly associated with all case groups. A potential causal link between the C-section procedure and increased DD risk has been suggested to involve altered newborn microbiome colonization (Codagnone et al., 2019; Heiss & Olofsson, 2019). C-section delivery, perinatal antibiotic use, and infant diet have been linked to differences in infant microbiome (Azad et al., 2013;Ferretti et al., 2018; van Best et al., 2015). While multiple maternal sites, including skin and vagina, seed the newborn's microbiome to varying degrees, the maternal gut appears to have the strongest and most sustained association with the infant's microbiome (Ferretti et al., 2018). Healthy gut microbiome serves several important functions for the infant including modulating the immune system, improving nutrient absorption, and defending against pathologic bacteria (Ferretti et al., 2018; van Best et al., 2015). Clinical consideration of the perinatal vaginal microbial environment focuses primarily on avoiding newborn exposure to specific pathogenic bacteria and viruses that could infect the infant during passage through the birth canal. When maternal colonization or infection is known, antenatal antimicrobial administration significantly reduces serious neonatal infections (Harris & Holmes, 2017; Lim et al., 2021; Siberry, 2014). The vaginal microbiome has also been implicated in obstetrical complications such as preterm birth and low birthweight, both of which are linked to ASD/ID (He et al., 2018; Schieve et al., 2015). Because in utero exposure to inflammation is also a well-recognized risk factor for ASD/ID, further understanding of how vaginal microbiome during pregnancy may vary by geography, ancestry, maternal body habitus, and age—beyond impact from the C-section procedure—merits further understanding in the context of DD risk (He et al., 2018; Kim et al., 2020; Serrano et al., 2019; Tun et al., 2018).

The relationship between repeat C-section and DD likelihood varied substantially when stratified by region following adjustment for covariates. Repeat C-section in the Southeast was associated with all case groups while in the West, associations were attenuated. Findings among the Mid-Atlantic cohorts were mixed with repeat C-section associated with odds of ASD only and ID only, but attenuated for ASD + ID. Significant regional variation in C-section rates occurs in the US and is well represented by the Mid-Atlantic, Southeast, and West ADDM sites contributing to this study (Branch & Silver, 2012; Centers for Disease Control and Prevention (CDC), n. d.). While indications for primary versus repeat C-section are quite different, with the former being the primary indication for the latter (Montoya-Williams et al., 2017), maternal risk factors for primary and repeat C-section overlap considerably. These include higher maternal prepregnancy body mass index, short stature, advanced maternal age, preterm labor, diabetes, hypertension, racial/ethnic minority background, and public insurance (Branch & Silver, 2012; Edmonds et al., 2016; Haberman et al., 2014; Hure et al., 2017; Janevic et al., 2014; Kawakita et al., 2016; Vanderlaan et al., 2020). The presence of these factors varies regionally, likely contributing to differences in C-section rates. Several of these risk factors are also shared with ASD and/or ID (Bilder et al., 2009; Bilder et al., 2013; DeBolt et al., 2022; Hisle-Gorman et al., 2018; Krakowiak et al., 2012; Lyall et al., 2022; Maenner et al., 2023; Nahum Sacks et al., 2016).

The lowest C-section rates in the West coincided with attenuation in DD risk associated with repeat C-section across all three case groups following adjustment for covariates. These results support the possibility that increased DD likelihood associated with repeat C-section

in the overall analysis could result from residual confounding by factors that contribute to both C-section and DD risk that vary across US regions and are insufficiently captured in birth records. A role for this residual confounding is also supported by sub-analyses within the Curran, Dalman, et al., 2015 and Zhang et al., 2019 meta-analyses. Curran et al. demonstrated the loss of significance between C-section and ASD risk when analyses were restricted to repeat C-section; Zhang et al., 2019 reported high heterogeneity across studies in ASD risk associated with elective C-section and greater likelihood of ASD linked to C-section among studies reporting higher C-section rates (Curran, O'Neill, et al., 2015; Zhang et al., 2019). Likewise, two studies that compare results using population (between-mother) versus sibling (within-mother) comparison groups support the presence of residual confounding: DD risk associated with repeat C-section occurred in the between-mother, but not the within-mother analysis. Within-mother analyses reduce residual confounding from maternal characteristics and obstetrical complications that either remain unchanged or often recur in subsequent pregnancies.

Maternal metabolic conditions (i.e., prepregnancy obesity and preexisting/gestational diabetes and hypertension) are associated with both C-section and DD risk, are inconsistently documented in birth records, and tend to recur in subsequent pregnancy (DeBolt et al., 2022; Hisle-Gorman et al., 2018; Hjartardottir et al., 2006; Kim et al., 2007; Krakowiak et al., 2012; Lyall et al., 2022; Maenner et al., 2023; Nahum Sacks et al., 2016; Tano et al., 2021). Regional variation in obesity, diabetes, and hypertension is also well recognized. Rates of gestational hypertension are lowest in the West and generally highest in the Southeast, with the exception of eclampsia, which occurs most frequently in the Northeast (Wallis et al., 2008). In the adult US population, the lowest obesity rates occur in the West, and midrange rates are in the Mid-Atlantic and Southeast (Gurka et al., 2018). For diabetes, the highest rates occur in the Mid-Atlantic with midrange rates occurring in the Southeast and West (Gurka et al., 2018). Maternal metabolic conditions serve as modifiable targets for intervention; further investigation is merited to evaluate whether mechanistic links exist between these conditions and increased DD risk (Bilder et al., 2023; Worsham et al., 2021).

Study limitations include the absence of available data on maternal metabolic conditions, preempting the current study's capacity to investigate potential mediating roles that maternal metabolic conditions could play in the relationship between DD likelihood and repeat C-section. Similarly, the current study lacks information about whether a trial of labor preceded either primary or repeat C-section, negating the ability to evaluate whether a trial of failed labor influenced DD risk associated with either C-section type. This study's sole reliance on birth records for pre-/perinatal risk factors creates the potential for residual confounding and inaccuracy of more complex factors relying on historical recall or related to obstetrical complications (Buescher et al., 1993; Dobie et al., 1998). Additionally, the records review methodology inherently biases case status towards children with better access to developmental assessments and services. ADDM is not nationally representative, and only regions with ADDM sites that participated in concurrent ASD and ID surveillance were represented in this study. While the NCHS cohort attempted to capture the background population of 8-year-old children living in the surveillance area, it did not account for children moving into or out of the surveillance area, and some surveillance areas were

not entirely aligned with county boundaries. Differences in birth years represented within regions and ASD/ID groups may have also influenced study results. County and birth year matching to the comparison cohort, as well as inclusion of birth year as a fixed factor in the adjusted analyses, were implemented to minimize the effect of these differences on study results.

Study strengths include ASD and ID case ascertainment over 17 years through ADDM population-based surveillance, which implemented consistent case definitions within each study year across racially, ethnically, and geographically diverse communities. The NCHS cohort provided a meaningful comparison by approximating this diversity. As such, regional variation in DD odds associated with repeat C-section could be evaluated in the context of background variation in C-section rates.

Increased odds for ASD and/or ID in the US are associated with both primary and repeat C-section overall, yet significant regional variability exists for procedural rates and repeat C-section's link to increased DD risk. Reduction of DD risk and improvement of maternal health could be informed by future research examining the relationships across maternal metabolic conditions, DD risk, and delivery method using different study designs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Due to restrictions related to The National Center for Health Statistics, research data are not shared.

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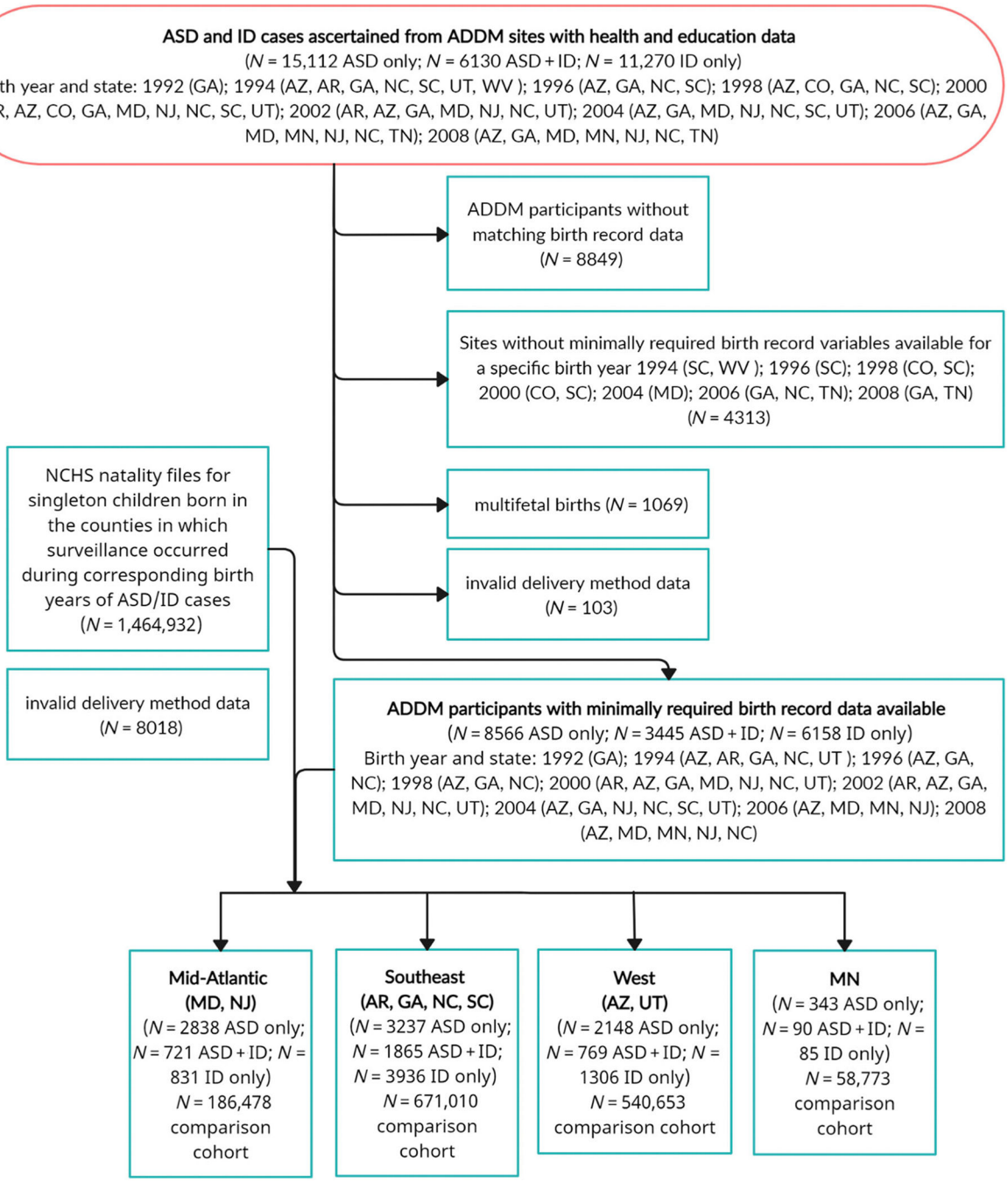

FIGURE 1.

ADDM, Autism and Developmental Disabilities Monitoring Network; AR, Arkansas; ASD, autism spectrum disorder; AZ, Arizona; CO, Colorado; GA, Georgia; ID, intellectual disability; MD, Maryland; MN, Minnesota; NC, North Carolina; NCHS, National Center for Health Statistics; NJ, New Jersey; SC, South Carolina; TN, Tennessee; UT, Utah; WV, West Virginia.

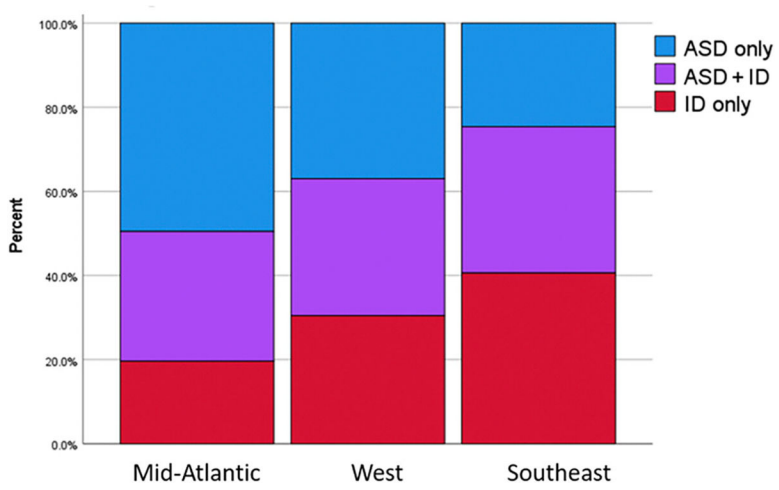

FIGURE 2.

Distribution of cases across ASD only, ASD and ID, and ID only categories within each region. ASD, autism spectrum disorder, ID, intellectual disability. Mid-Atlantic (New Jersey, Maryland; n = 2838 with ASD only, 721 with ASD + ID, 831 with ID only), West (Arizona, Utah; n = 2148 with ASD only, 769 with ASD + ID, 1306 with ID only), Southeast (Georgia, North Carolina, South Carolina; n = 3237 with ASD only, 1865 with ASD + ID, 3936 with ID only).

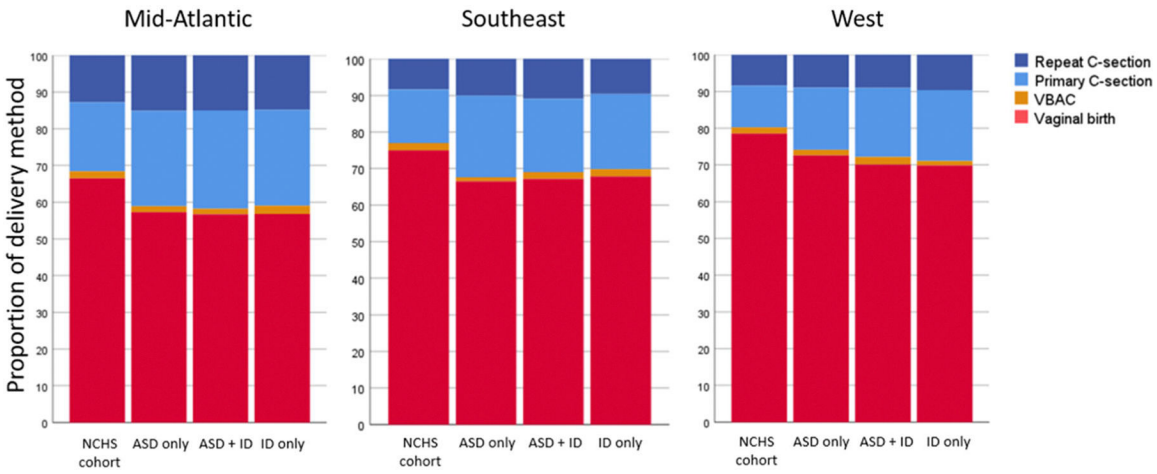

FIGURE 3.

Regional distribution of delivery method within the National Center for Health Statistics cohort and case groups. ASD, autism spectrum disorder; C-section, cesarean section; ID, intellectual disability; NCHS, National Center for Health Statistics; VBAC, vaginal birth after cesarean section. Mid-Atlantic (New Jersey, Maryland), Southeast (Georgia, North Carolina, South Carolina), West (Arizona, Utah).

TABLE 1

Comparison of pre–/perinatal characteristics across the National Center for Health Statistics (NCHS) cohort and children classified with autism spectrum disorder (ASD) without intellectual disability (ID), with both ASD and ID, and with ID without ASD through the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network.

	ASD without ID		ASD and ID		ID without ASD		NCHS cohort	
Pre–/perinatal characteristic	***N* = 8566**	**% (SD)**	***N* = 3445**	**% (SD)**	***N* = 6158**	**% (SD)**	***N* = 1,456,914**	**% (SD)**
Child's sex								
male	7162	83.6	2740	79.5	3741	60.8	744,567	51.1
female	1404	16.4	705	20.5	2416	39.2	712,347	48.9
Birth year								
1992	97	1.1	73	2.1	254	4.1	42,991	3.0
1994	436	5.1	290	8.4	1040	16.9	168,108	11.5
1996	306	3.6	175	5.1	443	7.2	116,356	8.0
1998	489	5.7	316	9.2	657	10.7	126,624	8.7
2000	999	11.7	485	14.1	793	12.9	206,585	14.2
2002	2105	24.6	828	24.0	1179	19.1	265,403	18.2
2004	1777	20.7	628	18.2	1005	16.3	240,555	16.5
2006	1059	12.4	268	7.8	316	5.1	137,508	9.4
2008	1298	15.2	382	11.1	471	7.6	152,784	10.5
Maternal age, mean (SD)	29.2	(6.1)	28.5	(6.4)	26.5	(6.8)	27.4	(6.1)
Maternal education								
<12 years	1048	12.2	613	17.8	2122	34.5	309,869	21.3
12 years	2306	26.9	1059	30.7	2141	34.8	411,777	28.3
13–15 years	2035	23.8	828	24.9	1007	16.4	312,648	21.5
16 years	1847	21.6	583	16.9	555	9.0	258,320	17.7
>16 years	1196	14.0	308	8.9	230	3.7	142,496	9.8
Maternal race/ethnicity								
White, non-hispanic	5290	61.8	1473	42.8	2256	36.6	782,195	53.7
Black, non-hispanic	1465	17.1	1157	33.6	2497	40.5	266,816	18.3
Hispanic	1332	15.5	597	17.3	1152	18.7	320,706	22.0
Other (Pacific Islander, American Indian, Asian), non-hispanic	433	5.1	208	6.0	230	3.7	73,398	5.0

	ASD without ID		ASD and ID		ID without ASD		NCHS cohort	
Pre–/perinatal characteristic	***N* = 8566**	**% (SD)**	***N* = 3445**	**% (SD)**	***N* = 6158**	**% (SD)**	***N* = 1,456,914**	**% (SD)**
Parity, mean (SD)	1.8	(1.1)	2.0	(1.2)	2.2	(1.4)	2.1	(1.2)
Maternal smoking during pregnancy (*n*, %)	755	8.8	276	8.0	782	12.7	113,490	7.8
Gestational duration in weeks, mean (SD)	38.5	(2.4)	38.2	(2.9)	37.3	(3.9)	38.8	(2.5)
Birthweight in grams, mean (SD)	3317	(646)	3194	(715)	2893	(848)	3322	(583)
Breech/malpresentation presentation	367	4.3	136	3.9	334	5.4	46,124	3.2
Delivery method								
Vaginal birth (without prior C-section)	5587	65.2	2262	65.7	4109	66.7	1,095,562	75.2
Vaginal birth after prior C-section	124	1.4	63	1.8	117	1.9	27,227	1.9
Primary C-section	1886	22.0	728	21.1	1298	21.1	203,764	14.0
Repeat C-section	969	11.3	392	11.4	634	10.3	130,361	8.9

Note: Number and percent missing for the following categories *(n,* %): sex (1, <0.001%), maternal age (134, <0.001%), maternal education (22,095; 1.5%), maternal race/ ethnicity (13,878; 0.9%), parity (3544, 0.2%), gestational age (1835, 0.1%), maternal smoking (31,150; 2.1%), birthweight (927, 0.1%), breech presentation (2680, 0.2%). Abbreviations: ASD, autism spectrum disorder; C-section, cesarean section; ID, intellectual disability; NCHS, National Center for Health Statistics; SD, standard deviation.

TABLE 2

Adjusted associations[a] between autism spectrum disorder and/or intellectual disability and delivery method within all regions and in the Western, Southeastern, and Mid-Atlantic region of the United States.

	ASD without ID			ASD with ID			ID without ASD		
Delivery method	**OR[a]**	**95% CI**	***p***	**OR[a]**	**95% CI**	***p***	**OR[a]**	**95% CI**	***p***
All regions[b]									
Vaginal[c]	1			1			1		
Primary C-section	1.25	1.18–1.33	<0.001	1.32	1.20–1.45	<0.001	1.48	1.38–1.59	<0.001
Repeat C-section	1.17	1.09–1.27	<0.001	1.22	1.09–1.38	<0.001	1.29	1.18–1.41	<0.001
VBAC	0.99	0.81–1.20	0.901	1.12	0.85–1.46	0.430	1.02	0.84–1.24	0.825
Mid-Atlantic US[b]									
Vaginal[c]	1			1			1		
Primary C-section	1.24	1.13–1.37	<0.001	1.37	1.13–1.65	0.001	1.68	1.41–2.01	<0.001
Repeat C-section	1.21	1.08–1.35	0.001	1.19	0.95–1.49	0.126	1.35	1.09–1.66	0.006
VBAC	1.15	0.85–1.56	0.378	0.78	0.40–1.52	0.469	1.06	0.66–1.72	0.808
Southeastern US[b]									
Vaginal[c]	1			1			1		
Primary C-section	1.27	1.15–1.40	<0.001	1.21	1.06–1.38	0.004	1.39	1.27–1.52	<0.001
Repeat C-section	1.16	1.02–1.32	0.029	1.26	1.07–1.49	0.005	1.35	1.20–1.51	<0.001
VBAC	0.75	0.53–1.07	0.109	1.19	0.84–1.68	0.338	1.07	0.85–1.35	0.560
Western US[c]									
Vaginal[a]	1			1			1		
Primary C-section	1.25	1.09–1.42	<0.001	1.58	1.28–1.95	<0.001	1.60	1.36–1.88	<0.001
Repeat C-section	1.12	0.96–1.32	0.149	1.12	0.86–1.47	0.410	1.09	0.89–1.32	0.410
VBAC	1.11	0.76–1.62	0.587	1.25	0.72–2.18	0.430	0.88	0.54–1.45	0.619

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; C-section, cesarean section; ID, intellectual disability; OR, odds ratio; *p*, *p*-value; SD, standard deviation; US, United States; VBAC, vaginal delivery after cesarean section.

[a]Multinomial logistic regression adjusted for sex, birth year, gestational age, birthweight, parity, maternal age, maternal education, maternal race/ethnicity, breech presentation, and maternal smoking status. Overall model also adjusted for region.

[b] Overall model: *N* = 1,456,914 birth cohort, *N* = 8566 ASD only, *N* = 3445 ASD + ID, *N* = 6158 ID only; Western US (Arizona, Utah; *n* = 540,653 birth cohort, *n* = 2148 ASD only, *n* = 769 ASD + ID, *n* = 1306 ID only), Southeastern US (Georgia, North Carolina, South Carolina; *n* = 671,010 birth cohort, *n* = 3237 ASD only, *n* = 1865 ASD + ID, *n* = 3936 ID only), Mid-Atlantic US (New Jersey, Maryland; *n* = 186,478 birth cohort, *n* = 2838 ASD only, *n* = 721 ASD + ID, *n* = 831 ID only). Minnesota was also included in overall model (*n* = 58,773 birth cohort, *n* = 343 ASD only, *n* = 90 ASD + ID, *n* = 85 ID only).

[c] Vaginal delivery without prior cesarean section.