

# Comparison of Perinatal Risk Factors Associated with Autism Spectrum Disorder (ASD), Intellectual Disability (ID), and Co-occurring ASD and ID

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Published online: 5 March 2015  
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**Abstract** While studies report associations between perinatal outcomes and both autism spectrum disorder (ASD) and intellectual disability (ID), there has been little study of ASD with versus without co-occurring ID. We compared perinatal risk factors among 7547 children in the 2006–2010 Autism and Developmental Disability Monitoring Network classified as having ASD + ID, ASD only, and ID only. Children in all three groups had higher rates of preterm birth (PTB), low birth weight, small-for-gestational-age, and low Apgar score than expected based on the US birth cohort adjusted for key socio-demographic factors. Associations with most factors, especially PTB, were stronger for children with ID only than children with ASD + ID or ASD only. Associations were similar for children with ASD + ID and ASD only.

**Keywords** Autism spectrum disorder · Intellectual disability · Preterm birth · Low birth weight · Intrauterine growth retardation · Risk factors

## Introduction

Autism spectrum disorder (ASD) and intellectual disability (ID) are both serious, pervasive neurodevelopmental disorders with lifelong impacts. In addition to the functional impacts associated with the core features of each disability, individuals with both ASD and ID also have increased rates of many co-occurring health and developmental conditions (Matson and Cervantes 2014; Kohane et al. 2012; Schieve et al. 2012). Recent prevalence estimates for both ASD and ID in US populations are between 1 and 2 % (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators 2014; Blumberg et al. 2013; Bhasin et al. 2006). Moreover, co-occurrence of the two conditions is common. Although the rate of co-occurrence has decreased over time, in 2010 an estimated 31 % of children with ASD had co-occurring ID and an additional 23 % had IQs in the borderline range (71–84) (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators 2014).

Previous studies report that suboptimal perinatal environment and adverse birth outcomes including preterm birth (PTB) and fetal growth restriction (as measured by small-for-gestational age, SGA), are associated with both ASD (Abel et al. 2013; MacKay et al. 2013; Singh et al. 2013; Langridge et al. 2013; Lampi et al. 2012; Schieve et al. 2011; Boulet et al. 2011) and ID (Bildler et al. 2013; Singh et al. 2013; MacKay et al. 2013; Langridge et al. 2013; Boulet et al. 2011; Drews-Botsch et al. 2011; de Bie et al. 2010; Moster et al. 2008). However, whether

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease and Control and Prevention.

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associations between perinatal outcomes and ASD are differential according to the presence or absence of co-occurring ID is not well studied.

Two recent studies suggest associations between adverse perinatal outcomes and ASD may be limited to (Langridge et al. 2013) or stronger among (Abel et al. 2013) children with ASD and ID rather than ASD only. We previously analyzed data from the 2002 Autism and Developmental Disabilities Monitoring (ADDM) Network and found that among children with ASD, both ID and low mean IQ score were significantly associated with term SGA, suggesting the associations that have been previously documented between sub-optimal perinatal environment and ASD might partially be a reflection of associations between perinatal risk factors and cognitive impairment rather than the core ASD symptomatology (Schieve et al. 2010).

There is also sparse study comparing risk factors for ID with and without ASD. Although a few studies have examined associations between perinatal risk factors and the two disabilities side by side, they did not account for the co-occurrence between the two disabilities (Boulet et al. 2011; MacKay et al. 2013; Singh et al. 2013).

Because in the US adverse perinatal outcomes as well as ASD and ID are associated with socio-demographic factors, it is also important to consider whether and the degree to which associations between perinatal factors and developmental disabilities reflects confounding. Additionally, in the US the relationships between socioeconomic status (SES) and ID and ASD are in opposite directions. The prevalence of ID increases with socioeconomic disadvantage (Christensen et al. 2014; Drews-Botsch et al. 2011), while the prevalence of ASD shows the opposite SES gradient (Windham et al. 2011; Durkin et al. 2010). While studies suggest the underlying reason for the association between increased ASD prevalence and high family SES likely relates to ASD ascertainment differences among low versus high SES families (Mazumdar et al. 2013; Durkin et al. 2010), the strong associations observed between ID and low maternal SES are possibly related to underlying causative factors. Studies suggest that differential postnatal enrichment opportunities for low- versus high-SES children, such as availability of books in the home, participation in preschool programs, and other early educational opportunities explain some of the association observed between family SES and cognitive deficits (Christensen et al. 2014; Guo and Harris 2000).

In addition to the potential for confounding by SES, several studies suggest the impacts of perinatal factors on ID or low cognitive score are in fact differential by SES. Malacova et al. (2009) reported that among children born to mothers residing in higher SES areas in Western Australia, there was a strong, linear relationship between

birthweight and reading scores; however, among children from disadvantaged neighborhoods, reading scores were low for all groups, regardless of birthweight. Likewise, Drews-Botsch et al. (2011) found that among children from disadvantaged families born at a public hospital the prevalence of cognitive deficit was high overall and not further influenced by birthweight-for-gestational-age; however an association between SGA and subsequent cognitive deficit was evident among children born at a private hospital that served a much higher SES population. A likely explanation for these observed effect modifications is that in low SES populations, the high level of competing adverse postnatal enrichment effects masks the more moderate perinatal effects.

Given the increasing prevalence of identified ASD (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators 2014; Blumberg et al. 2013) and the high proportion of children with ASD who have co-occurring ID (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators 2014), it is important to further tease apart whether various etiologic risk factors are associated with each of the two disabilities independently and whether socio-demographic factors mediate the associations. The convergence or divergence between risk factors for different neurodevelopmental disorders is important in advancing our understanding about whether and the degree to which the underlying etiological pathways for different neurodevelopmental disorders (specifically ID and ASD) are distinct.

The current study expands on our earlier limited assessment of ASD cases reported in the 2002 ADDM surveillance year. In this analysis of 2006–2010 ADDM data, we specifically compared perinatal risk factors among children with ASD and co-occurring ID, children with ASD without co-occurring ID, and children with ID without ASD with careful consideration of socio-demographic differences between groups. The larger sample size in this study also allowed for a detailed assessment of the effects of perinatal risk factors within specific socio-demographic subgroups of the population. Finally, we compare all groups to expected perinatal risk factor prevalence estimates from the general population of US births corresponding to the birth cohorts covered in this study.

## Methods

### Surveillance Methodology

The ADDM Network is an ongoing biennial ASD surveillance program among 8-year-old children residing in selected US population-based sites. Fourteen sites

participated in the 2006 and 2008 ADDM surveillance years and 11 sites participated in the 2010 surveillance year. All sites conduct population-based surveillance of ASDs. Seven sites, located in Arizona, Georgia, Maryland, New Jersey, North Carolina, South Carolina, and Utah, additionally conducted population-based surveillance of IDs in one or more surveillance years.

The ADDM surveillance methodology for both disabilities involves detailed, systematic reviews of records from public school special education departments and healthcare providers who conduct developmental evaluations for children living in a defined geographic surveillance area. All ADDM sites conducting ASD and ID surveillance have agreements in place to access records at multiple healthcare and education sources in their respective communities. The initial target population base for each site includes children meeting birth year and residence eligibility criteria for a given surveillance year. Records pertaining to children meeting these eligibility criteria are fully abstracted if, upon initial screening, documentation of any the following are noted: an ASD or ID diagnosis; an ASD or ID special education classification; a developmental evaluation with a description of behavioral characteristics consistent with possible ASD; and/or psychometric test scores consistent with possible ID. Data abstracted include demographics; ASD, ID, and other disability diagnoses; special education classifications; behavioral descriptions from comprehensive developmental evaluations; and IQ scores. If multiple records for the same child are abstracted from different sources, they are concatenated.

Trained clinicians review the composite abstractions and classify children as having or not having ASDs using a standardized protocol. A child is classified as having ASD if the behaviors documented in the child's comprehensive developmental assessments at any time from birth through age 8 years are consistent with the *Diagnostic and Statistical Manual of Mental Disorders-4th edition-Text Revision* (DSM-IV-TR) criteria for autistic disorder, pervasive developmental disorder—not otherwise specified, or Asperger disorder (American Psychiatric Association, 2000). Annual blinded inter-rater reliability checks conducted on a random sample of records reviewed consistently document inter-rater agreement meeting the quality assurance standards established by the ADDM Network of 80 % or higher.

Likewise trained clinicians follow a standardized protocol to review IQ scores and other data to classify children as having or not having ID (defined as  $IQ \leq 70$ ). Because this population-based sample was drawn from a wide range of health and educational sources, there was variability in type of IQ test administered and age at most recent test. The most commonly administered tests were the Wechsler Intelligence Test for Children and Stanford-Binet (various

editions). However, a range of other tests were also cited including the Battelle, Cattell Culture Fair Intelligence Test, Differential Abilities Scales, Kaufman Assessment Battery for Children, Merrill-Palmer Scale, Pictorial Test of Intelligence, Slosson Intelligence Test, Woodcock Johnson, and Wide Range Intelligence Test. While the vast majority of children were classified as having or not having ID based on a composite IQ score recorded in their health or education records, for some children, a qualified examiner had recorded the child's estimated cognitive or age-equivalent range based on psychometric testing or indicated a child had reached the lowest measurable limit for a given IQ test (e.g. Battelle,  $\leq 65$  or Bayley  $\leq 50$ ). We further classified children based on their IQ score as above average/average IQ, borderline IQ, mild ID, moderate ID, severe/profound ID, or ID, not otherwise specified.

Sites link their final data for ASD and ID cases to state natality files; across sites 74 % of case children are born in-state, and match a birth record.

### Study Population

We initially selected from the ADDM data files, children who were identified as cases of ASD, ID, or both from: three sites that performed surveillance for both disabilities in all three surveillance years of interest—2006, 2008, and 2010; one site that performed surveillance for both disabilities in 2006 and 2008; one site that performed surveillance for both disabilities in 2008 and 2010; and two sites that performed surveillance for both disabilities in 2010. We pooled data from three consecutive surveillance cycles to maximize sample size. In all, 8651 children from the selected sites/surveillance years were classified as ASD, ID, or both and were born in the same state as their ADDM site (and thus were linked to their birth certificate file). Given ADDM surveillance is based on children aged 8 years, these children were thus born in 1998, 2000, and 2002. Because each ADDM surveillance year covers a single birth year, no child was inadvertently included multiple times due to pooling of the data across surveillance years. We excluded 620 children with ASD who were missing IQ/cognitive testing data and 50 children missing key perinatal data (plurality, gestational age, and/or birth weight). Because perinatal risk profiles are vastly different for infants born in singleton versus multiple births, we further limited our analysis to the 7547 singletons, of whom 2726 had ASD without ID (ASD only), 1585 had ASD with ID (ASD + ID), and 3236 had ID without ASD (ID only).

### Perinatal Risk Factors

Data on gestational age, birth weight, and 5-min Apgar score were obtained from natality files. Gestational age was

based on last menstrual period (LMP), or clinical estimate in cases of missing LMP data. Birth weight-for-gestational-age (BWGA) percentile outcomes were derived from comparison of children in the study population to sex-specific referent curves based on singleton live births to US resident mothers in 1999–2000 (Oken et al. 2003).

PTB and very PTB (VPTB) were defined as <37 and <32 completed weeks' gestation, respectively. Low birth weight (LBW), very LBW (VLBW), and high birth weight (HBW) were defined as <2500, <1500, and  $\geq$ 4000 g, respectively. SGA, very SGA (VSGA) and large-for-gestational-age (LGA) were defined as BWGA <10th, <5th and  $\geq$ 90th percentiles, respectively. Term LBW was defined as  $\geq$ 37 weeks' gestation and <2500 g and term SGA was defined as  $\geq$ 37 weeks' gestation and BWGA <10th percentile. Low Apgar score was defined as 5-min score <7. Although there is overlap between PTB, LBW, and SGA outcomes, we assessed all three separately in order to maximize comparability with other studies. However, we also derived distinct outcome measures to examine the most severe end of each outcome separately and to separately examine the effects of LBW and SGA in term infants.

#### Potential Confounders or Effect Modifiers

Child sex, birth order, maternal race-ethnicity, maternal educational level, age, and marital status at the time of the child's birth, and smoking during pregnancy were examined as potential confounders. All variables were ascertained from natality files. We also created a composite maternal race-ethnicity-education variable to look at more refined SES subgroups. However, we could only sub-divide NHW and NHB children into distinct maternal education groups ( $\leq$ high school vs. >high school education). There were insufficient numbers of Hispanic children and children of other race-ethnicities to examine maternal education subgroups separately.

#### Statistical Analysis

We compared the proportionate distributions of each perinatal risk factor and each potential confounder/effect modifier among children in our three study groups—ASD only, ASD + ID, and ID only—using Chi-square tests. We also describe the latter two study groups in terms of their IQ distributions.

We calculated adjusted odds ratios (aORs) for three sets of comparisons: ASD + ID versus ASD only; ID only versus ASD only; and ID only versus ASD + ID. For each set of comparisons, we calculated aORs and 95 % confidence intervals (CIs) for each of the perinatal risk factors using multivariable logistic regression to adjust for all potential confounders except marital status at birth, which

was not included because of a high percentage of missing values.

We conducted further in-depth analyses for two distinct perinatal factors, PTB and term SGA, to assess whether associations were differential according to two key SES factors found previously to be highly associated with ID and ASD prevalence (Bhasin et al. 2006; Christensen et al. 2014; Windham et al. 2011), namely, race-ethnicity and maternal education at birth (NHW/>high school, NHW/ $\leq$ high school, NHB/>high school, NHB/ $\leq$ high school). We did not include Hispanic children or children of other racial groups in these analyses because sample size constraints precluded us from sub-dividing these groups by maternal education.

Finally, we also computed standardized morbidity ratios in which we compared the observed numbers of each of the 11 perinatal risk factors for each of the three study groups to expected numbers based on the general population of US births during the same time period. Expected numbers were derived from the National Center for Health Statistics public-use natality files for US births. We used the birth cohort linked birth-infant death files for 1998, 2000, and 2002 and excluded births in which the infant died during the first year of life. We additionally adjusted our expected numbers to match the race-ethnicity and maternal education distributions for children in each of the study groups. We computed standardized ratios by dividing observed numbers by expected numbers and calculated 95 % CIs for each estimate.

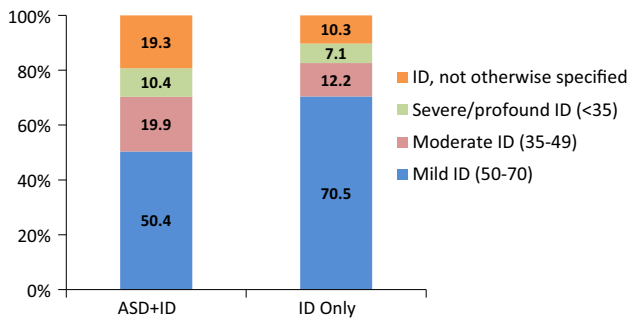
This study involved a secondary analysis of de-identified data. Each site met their local institutional review board requirements.

## Results

While by definition, none of the children with ASD only had ID, it was noteworthy that a considerable proportion (35 %) had an IQ score in the borderline range (71–85). Among children with ID, there was marked variability in the IQ distributions of children with ASD + ID and children with ID only (Fig. 1). Children with ASD + ID were more likely to have IQ scores in the moderate and severe/profound ID ranges and were more likely to be classified as ID, not otherwise specified, than children with ID only.

There were also notable statistically-significant differences between the three study groups on socio-demographic factors (Table 1). While all groups had a predominance of males, children with ASD only had the highest percentage, 86 % male. Over 60 % of children with ASD only were NHW, and nearly half were first-born children; the majority of their mothers were 30 years of age or older, married, and had completed more than a high school education by the time





**Fig. 1** IQ distribution among children with ASD + ID and ID only

of their births (with 39 % having attended college for four or more years). In contrast, only 35 % of children with ID only were NHW and 61 % were second or later births; at the time of their births nearly 70 % of their mothers were younger than 30 years of age, over 50 % were unmarried, and only 29 % had education beyond high school. Children with ID only also had a higher percentage of mothers who smoked during pregnancy than the other study groups. The distributions of characteristics of children with both ASD + ID fell roughly in between those for the other two groups. Also, for most characteristics, exceptions being sex, maternal race-ethnicity and smoking during pregnancy, the group of children with ASD + ID most resembled the general population of US children born during the same time period.

All three study groups of children had higher percentages of PTB, VPTB, LBW, VLBW, term LBW, SGA, VSGA, term SGA, and low Apgar score than the general US birth population (Table 2). In contrast, both HBW and LGA were notably lower among children with ID only than children in the general US population. There were also prominent differences *between* the three study groups on these risk factors. Among the three groups, children with ID only had the highest percentages of PTB, VPTB, LBW, VLBW, term LBW, SGA, VSGA, term SGA and low Apgar score, and children with ASD only had the lowest percentages for these factors. It is noteworthy that more than 20 % of children with ID only had PTB, LBW, and/or SGA, and more than 10 % had VPTB, VLBW, VSGA, term SGA, and/or low Apgar score; these estimates are 2.0–10.9 times as high as those for the general population and 1.6–4.3 times as high as those for children with ASD only. Children with ID only had the lowest percentages of HBW and LGA, while children with ASD only had the highest percentages for these factors. All differences between children with ID only and children with ASD only were statistically significant as were all differences between children with ID only and children with ASD + ID. The percentages of eight of the 11 risk factors were significantly different between children with ASD only and ASD + ID.

After adjustment for socio-demographic confounders, all differences between children with ID only and ASD only remained statistically significant; aORs ranged from 1.4 to 3.3 for PTB, VPTB, LBW, VLBW, term LBW, SGA, VSGA, term SGA and low Apgar score and 0.6–0.8 for HBW and LGA (Table 3). Additionally, after adjustment, the odds of having six risk factors (PTB, VPTB, LBW, VLBW, VSGA, and low Apgar score) remained significantly higher for children with ID only in comparison to ASD + ID, and the odds of LGA and HBW remained significantly lower. However, when comparing children with ASD + ID to those with ASD only, only four risk factors were significantly different; children with ASD + ID had higher odds of LBW, term LBW, SGA, and term SGA in comparison to children with ASD only.

Although there was variability and some imprecision in estimates, the differences observed between the three study groups for PTB were fairly consistent across the four race-ethnicity/maternal education subgroups we examined separately (Table 4). Likewise, the differences in term SGA between study groups were similar within most race-ethnicity/maternal education strata. Two exceptions were noted, however. The difference in term SGA for children with ID only versus ASD only was much stronger among NHW children with a maternal education > high school (aOR 2.7) than for the other three groups. Additionally, within this same subgroup, there was a significant difference in term SGA between children with ID only and ASD + ID (aOR 1.9) while no differences were observed in the other race-ethnicity maternal education strata.

After adjusting for both race-ethnicity and maternal education, PTB, VPTB, LBW, VLBW, SGA, VSGA, term SGA, and low Apgar score were all significantly higher among children with ASD only than expected based on the general population of US births (Table 5). All of the above perinatal factors plus term LBW were higher than expected among both children with ASD + ID and children with ID only. LGA and HBW were significantly lower than expected among children with ID only.

**Discussion**

We found that adverse perinatal outcomes were significantly associated with subsequent diagnoses of ASD only, ID only, or ASD + ID. In comparison to expected rates based on the general US birth cohort adjusted for two major SES factors, maternal race-ethnicity and maternal education, children with either ASD, ID, or both disabilities had higher rates of PTB, VPTB, LBW, VLBW, SGA, VSGA, term SGA, and low Apgar score.

**Table 1** Distribution of socio-demographic factors by whether a child has ASD only, ASD and ID, or ID only

Factor	ASD only (N = 2726) (A)	ASD + ID (N = 1585) (B)	ID only (N = 3236) (C)	Significant comparisons <sup>a</sup>	General US birth cohorts (1998, 2000, 2002) singletons <sup>b</sup>
Child sex					
Male	86.1	79.9	62.2	A versus B A versus C B versus C	51.2
Maternal race/ethnicity					
NHW	65.0	43.9	35.0	A versus B	58.8
NHB	17.0	34.0	43.7	A versus C	14.8
Hispanic	12.1	15.6	17.8	B versus C	20.6
Other NH race	5.9	6.5	3.4		5.8
Maternal education (birth)					
<High school	10.9	19.1	35.0	A versus B	21.9
High school	25.8	30.2	35.9	A versus C	31.9
Some college	24.2	23.4	17.0	B versus C	21.8
4+ years college	39.1	27.3	12.0		24.4
Race/maternal education group					
NHW, >high school	46.0	27.1	14.7	A versus B	33.4
NHW, ≤high school	19.6	17.2	20.7	A versus C	25.7
NHB, >high school	10.0	16.7	11.1	B versus C	5.1
NHB, ≤high school	7.2	17.3	32.9		9.6
Hispanic, >high school	4.1	3.3	1.8		4.3
Hispanic, ≤high school	8.0	12.2	15.7		16.2
Other NH race, >high school	3.2	3.7	1.5		3.3
Other NH race, ≤high school	1.9	2.6	1.7		2.4
Maternal age, years (birth)					
<20	5.5	9.6	16.5	A versus B	11.8
20–29	44.4	46.1	51.6	A versus C	52.2
30–34	30.5	23.9	18.1	B versus C	22.9
35+	19.7	20.4	13.7		13.2
Birth order					
First-born	49.0	43.4	38.6	A versus B A versus C B versus C	40.6
Mother unmarried at birth	24.1	35.5	51.8	A versus B A versus C B versus C	33.5
Mother smoked during pregnancy	8.3	7.7	11.7	A versus C B versus C	12.2

Missing values reduced sample sizes for some distributions. % missing was 0 for child sex, race and maternal age; <3 % for maternal education, birth order and maternal smoking; 11 % for maternal marital status

ASD autism spectrum disorder, ID intellectual disability, NHW non-Hispanic white, NHB non-Hispanic black

<sup>a</sup>  $p < 0.05$  for comparison of distributions between ADDM groups using Chi-square tests

<sup>b</sup> US birth cohort excluding infants who died within the first year of life

Associations for each disability group were strongest with the most severe perinatal indicators: VPTB, VLBW, and low Apgar score. Thus, the data are suggestive of a dose

response and generally supportive of causal associations. Nonetheless, we did not have the data to explore the specific causal pathways underlying these associations.

**Table 2** Prevalence of adverse perinatal outcomes by whether a child has ASD only, ASD and ID, or ID only

Perinatal outcome	ASD Only (N = 2726) (A)	ASD + ID (N = 1585) (B)	ID Only (N = 3236) (C)	Significant comparisons <sup>a</sup>	General US birth cohorts (1998, 2000, 2002) singletons <sup>b</sup>
PTB	13.3	15.5	25.2	A versus B A versus C B versus C	10.0
VPTB	2.7	3.9	10.5	A versus B A versus C B versus C	1.3
LBW	8.8	14.3	24.5	A versus B A versus C B versus C	5.7
VLBW	2.3	3.8	9.8	A versus B A versus C B versus C	0.9
Term LBW	2.6	4.8	7.1	A versus B A versus C B versus C	2.2
SGA	13.5	18.7	23.5	A versus B A versus C B versus C	9.9
VSGA	7.8	10.6	14.8	A versus C B versus C	5.0
Term SGA	11.7	15.8	18.2	A versus B A versus C B versus C	9.1
HBW	11.8	9.9	5.2	A versus C B versus C	10.1
LGA	9.9	8.7	6.5	A versus C B versus C	12.0
Low Apgar score	3.4	5.0	9.9	A versus B A versus C B versus C	1.0

% missing was 0 for all perinatal outcomes except Low Apgar Score, for which it was <1 %

ASD autism spectrum disorder, HBW high birth weight, ID intellectual disability, LGA large for gestational age, LBW low birth weight, PTB preterm birth, SGA small for gestational age, VLBW very low birth weight, VPTB very preterm birth, VSGA very small for gestational age

<sup>a</sup>  $p < 0.05$  for comparison of perinatal outcome across ADDM groups using Chi-square tests

<sup>b</sup> US birth cohort excluding infants who died within the first year of life

Initial analyses indicated that PTB, VPTB, LBW, VLBW, and low Apgar were more common among children who were subsequently identified as having ID only than children identified as having ASD (either with or without ID). Children with ID only were also much more likely than the other groups to have indications of low SES. These findings are in line with the known strong associations between mild, idiopathic ID and low SES, non-white race-ethnicity, and adverse perinatal outcomes (Leonard et al. 2005; Croen et al. 2001; Drews et al. 1995;

Mervis et al. 1995). However, even after adjustment for socio-demographic differences between the three study groups and stratification on race-ethnicity and maternal education, PTB remained a notably stronger risk factor among children with ID only than children in either of the ASD groups. Thus, the underlying mechanisms of effect might vary between the two conditions. Findings from animal studies suggest that early delivery during the third trimester at a time when neural migration is in progress renders an infant particularly vulnerable to poor cognitive

**Table 3** Adjusted odds ratios and 95 % confidence intervals for associations between adverse perinatal outcomes and ASD-ID group

Perinatal outcome	ASD + ID versus ASD only	ID only versus ASD only	ID only versus ASD + ID
PTB	1.1 (0.9–1.3)	<b>1.9 (1.6–2.2)</b>	<b>1.7 (1.5–2.0)</b>
VPTB	1.0 (0.7–1.5)	<b>3.1 (2.3–4.1)</b>	<b>2.8 (2.0–3.7)</b>
LBW	<b>1.5 (1.2–1.8)</b>	<b>2.7 (2.3–3.3)</b>	<b>1.7 (1.5–2.1)</b>
VLBW	1.1 (0.8–1.7)	<b>3.3 (2.4–4.4)</b>	<b>2.6 (1.9–3.5)</b>
Term LBW	<b>1.6 (1.1–2.3)</b>	<b>2.4 (1.7–3.3)</b>	1.2 (0.9–1.6)
SGA	<b>1.3 (1.1–1.6)</b>	<b>1.7 (1.4–2.0)</b>	1.2 (1.0–1.4)
VSGA	1.3 (1.0–1.6)	<b>1.8 (1.5–2.2)</b>	<b>1.3 (1.1–1.6)</b>
Term SGA	<b>1.3 (1.1–1.5)</b>	<b>1.4 (1.2–1.7)</b>	1.0 (0.9–1.2)
HBW	1.0 (0.8–1.2)	<b>0.6 (0.5–0.7)</b>	<b>0.6 (0.4–0.7)</b>
LGA	0.9 (0.7–1.2)	<b>0.8 (0.6–0.9)</b>	<b>0.7 (0.6–0.9)</b>
Low Apgar score	1.3 (0.9–1.8)	<b>2.8 (2.1–3.7)</b>	<b>2.2 (1.6–2.9)</b>

Odds ratios adjusted for child sex, birth order, maternal age, smoking, maternal race-ethnicity, and maternal education. Child sex, primiparous birth, and maternal smoking were entered into models as single dichotomous variables. Maternal age, race-ethnicity, and education were treated as categorical variables with multiple dummy variables entered into models. Maternal age 20–29, maternal race-ethnicity non-Hispanic white, and maternal education high school served as the referent categories

Risk estimates are presented in boldface to indicate the 95 % confidence interval does not include 1.0

ASD autism spectrum disorder, HBW high birth weight, ID intellectual disability, LGA large for gestational age, LBW low birth weight, PTB preterm birth, SGA small for gestational age, VLBW very low birth weight, VPTB very preterm birth, VSGA very small for gestational age

**Table 4** Associations between adverse perinatal outcomes and ASD-ID group within maternal race-ethnicity-education strata

Perinatal outcome/race-ethnicity-maternal education group	Adjusted odds <sup>a</sup> ratios and 95 % CI		
	ASD + ID versus ASD only	ID only versus ASD only	ID only versus ASD + ID
PTB	1.1 (0.9–1.3)	<b>1.9 (1.6–2.2)</b>	<b>1.7 (1.5–2.0)</b>
NHW, >high school	1.0 (0.7–1.4)	<b>1.7 (1.2–2.3)</b>	<b>1.8 (1.2–2.6)</b>
NHW, ≤high school	0.9 (0.6–1.4)	1.4 (1.0–2.0)	<b>1.6 (1.1–2.4)</b>
NHB, >high school	1.5 (0.9–2.4)	<b>2.6 (1.7–4.0)</b>	<b>1.7 (1.1–2.5)</b>
NHB, ≤high school	1.1 (0.7–1.7)	<b>2.0 (1.3–2.9)</b>	<b>1.8 (1.3–2.4)</b>
Term SGA	<b>1.3 (1.1–1.5)</b>	<b>1.4 (1.2–1.7)</b>	1.0 (0.9–1.2)
NHW, >high school	1.3 (0.9–2.0)	<b>2.7 (1.9–3.8)</b>	<b>1.9 (1.3–2.9)</b>
NHW, ≤high school	1.5 (1.0–2.3)	1.3 (0.9–1.9)	0.9 (0.6–1.3)
NHB, >high school	1.3 (0.8–2.1)	1.6 (1.0–2.6)	1.3 (0.8–2.0)
NHB, ≤high school	<b>1.8 (1.1–3.1)</b>	1.5 (0.9–2.3)	0.8 (0.6–1.1)

Risk estimates are presented in boldface to indicate the 95 % confidence interval does not include 1.0

ASD autism spectrum disorder, ID intellectual disability, NHB non-Hispanic black, NHW non-Hispanic white, PTB preterm birth, SGA small for gestational age

<sup>a</sup> Stratum specific odds ratios adjusted for child sex, birth order, maternal age, and smoking. Overall odds ratios adjusted for child sex, birth order, maternal age, smoking, maternal race-ethnicity, and maternal education. Child sex, primiparous birth, and maternal smoking were entered into models as single dichotomous variables. Maternal age, race-ethnicity, and education were treated as categorical variables with multiple dummy variables entered into models. Maternal age 20–29, maternal race-ethnicity non-Hispanic white, and maternal education high school served as the referent categories

outcomes (Luciana 2003); moreover, neuroimaging studies of preterm infants have documented a higher level of white matter damage than their term counterparts (Luciana 2003).

In contrast, in the total sample and in three of the four race-ethnicity-maternal-education strata we examined, there was only modest variation in term SGA between children with ID only and children in either ASD group.

However, we observed a more notable differential in one stratum; among NHW children whose mothers' had attained education beyond high school, term SGA was two or more times higher among children with ID only than among children in either of the ASD groups. One possible reason the term SGA differential was observed in only a single stratum is that in the other strata that included children who were NHB, had a lower maternal education,



**Table 5** Standardized morbidity ratios and 95 % confidence intervals for associations between each adverse perinatal outcome and ASD only, ASD and ID, and ID only in comparison to the US singleton birth cohorts for 1998, 2000, and 2002

	ASD only			ASD + ID			ID only		
	# Observed cases	# Expected cases <sup>a</sup>	O/E (95 % CI)	# Observed cases	# Expected cases <sup>a</sup>	O/E (95 % CI)	# Observed cases	# Expected cases <sup>a</sup>	O/E (95 % CI)
PTB	353	259.9	<b>1.4 (1.2–1.5)</b>	239	172.1	<b>1.4 (1.2–1.6)</b>	796	387.6	<b>2.1 (1.9–2.2)</b>
VPTB	72	34.0	<b>2.1 (1.6–2.6)</b>	57	25.6	<b>2.2 (1.6–2.8)</b>	330	61.5	<b>5.4 (4.8–5.9)</b>
LBW	230	148.2	<b>1.6 (1.4–1.8)</b>	220	104.2	<b>2.1 (1.8–2.4)</b>	776	242.4	<b>3.2 (3.0–3.4)</b>
VLBW	63	22.5	<b>2.8 (2.1–3.5)</b>	56	16.9	<b>3.3 (2.4–4.2)</b>	310	39.5	<b>7.8 (7.0–8.7)</b>
Term LBW	66	55.9	1.2 (0.9–1.5)	73	39.3	<b>1.9 (1.4–2.3)</b>	225	92.7	<b>2.4 (2.1–2.7)</b>
SGA	353	250.0	<b>1.4 (1.3–1.6)</b>	292	170.9	<b>1.7 (1.5–1.9)</b>	743	391.8	<b>1.9 (1.8–2.0)</b>
VSGA	204	125.6	<b>1.6 (1.4–1.8)</b>	164	87.6	<b>1.9 (1.6–2.2)</b>	469	204.6	<b>2.3 (2.1–2.5)</b>
Term SGA	306	229.6	<b>1.3 (1.2–1.5)</b>	245	156.6	<b>1.6 (1.4–1.8)</b>	575	359.1	<b>1.6 (1.5–1.7)</b>
HBW	318	283.3	1.1 (1.0–1.2)	155	141.5	1.1 (0.9–1.3)	164	256.6	<b>0.6 (0.5–0.7)</b>
LGA	268	325.5	0.8 (0.7–0.9)	137	173.2	0.8 (0.7–0.9)	206	332.4	<b>0.6 (0.5–0.7)</b>
Low Apgar score	91	25.3	<b>3.6 (2.9–4.3)</b>	73	16.3	<b>4.5 (3.4–5.5)</b>	312	36.5	<b>8.5 (7.6–9.5)</b>

Risk estimates are presented in boldface to indicate the 95 % confidence interval does not include 1.0

ASD autism spectrum disorder, HBW high birth weight, ID intellectual disability, LGA large for gestational age, LBW low birth weight, PTB preterm birth, SGA small for gestational age, VLBW very low birth weight, VPTB very preterm birth, VSGA very small for gestational age

<sup>a</sup> Expected values based on prevalence of perinatal outcomes within maternal race-ethnicity-education strata (NHW, ≥high school education; NHW, <high school education; NHB, ≥high school education; NHB, <high school education; Hispanic; other NH race-ethnicity). Number of observed cases excludes 181 cases for which data was missing on either education, race/ethnicity, or Apgar scores (<3 % of cases)

or both, the level of term SGA generally was fairly high overall, and thus, there was less likelihood for additional variation by disability status (data not shown). That is, the associations between maternal socio-demographic factors at birth and term-SGA might have masked the more distal associations between term-SGA and subsequent child neurodevelopment.

Although initially we observed higher rates of most adverse perinatal outcomes among children with both ASD + ID than ASD only, after adjustment for socio-demographic factors, the two groups were comparable on PTB, VPTB and VLBW. Modest differences remained between the two groups on term LBW and SGA. Nonetheless, the general perinatal risk factor profile for children with ASD + ID was more closely aligned with the ASD only group than the ID only group. The underlying causal pathways then might be inherently different for children with idiopathic ID versus ID secondary to or co-occurring with ASD. This is additionally supported in that the IQ distributions varied considerably between children with ID only versus children with ID + ASD. Over 70 % of children with ID only were classified as having mild ID versus 50 % of children with ID + ASD.

Our findings are consistent with numerous studies reporting associations between adverse perinatal outcomes and ASD (Abel et al. 2013; MacKay et al. 2013; Singh et al. 2013; Langridge et al. 2013; Lampi et al. 2012;

Schieve et al. 2011; Boulet et al. 2011) and ID (Bilder et al. 2013; Singh et al. 2013; MacKay et al. 2013; Langridge et al. 2013; Boulet et al. 2011; Drews-Botsch et al. 2011; de Bie et al. 2010; Moster et al. 2008). However, few studies have examined ASD and ID side by side in the same population and few studies have sub-divided ASD according to ID status. A recent US population-based study of children included in the National Survey of Children’s Health (NSCH) documented moderate to strong associations between, PTB, LBW, and VLBW and both ASD and ID (Singh et al. 2013). An earlier analysis based on similar data from the National Health Interview Survey (NHIS) reported strong associations between moderately LBW and VLBW and ID and moderate associations for these same factors and ASD (Boulet et al. 2011). However, neither study further sub-divided the ASD or ID groups to account for co-occurrence. The findings from these two survey-based studies are generally consistent with those from the current study; however, the NSCH study reported similar magnitudes of effect for both disabilities while the NHIS and current study reported stronger associations with ID than ASD. A population-based study from Scotland of various disabilities defined based on special education classifications, reported that both VPTB and PTB were strongly associated with ID, while only VPTB was associated with ASD (MacKay et al. 2013). Like the current study, the magnitude of the VPTB-ASD association was

lower than that for the VPTB-ID association. Additionally, the VPTB-ASD association was no longer statistically significant after adjustment; however, that finding might be the result of over-adjustment as the authors included other adverse perinatal outcomes such as low Apgar score and maternal complications in their models. In this same study, SGA was also associated with ID both before and after adjustment. However, there was no association between SGA and ASD. There was no assessment of subjects with both ASD and ID separate from those with ASD only.

Two recent studies included assessment of ASD with and without co-occurring ID. In a population-based study from Western Australia, Langridge et al. (2013) reported strong associations between ID and both PTB and SGA. In contrast, there were no associations between PTB and ASD, either with or without co-occurring ID, and SGA was associated only with ASD with co-occurring ID. In contrast, Abel et al. (2013) reported that SGA was associated with ASD both with and without co-occurring ID in their population-based study of children from Stockholm; as with the current study, the magnitude of the association was stronger for children with ASD + ID.

Several studies have also examined DSM-IV subtypes for ASD. Most recently, Lampi et al. (2012) showed similar associations between VLBW, LBW and VPTB, and SGA and autistic disorder and PDD but no associations between these perinatal factors and Asperger's disorder in their population-based study of children in Finland. Several small studies also suggested perinatal effects were more pronounced for autistic rather than Asperger's disorder (Glasson et al. 2004; Gillberg 1989). We lacked data to examine these sub-types, but our findings for ASD only versus ASD + ID suggest the differences between sub-types might not be very large in this US population-based sample.

The current study expands on our previous assessment of ADDM data (Schieve et al. 2010). Like the current study, the initial findings of our previous study suggested that both PTB and term SGA were more common among children with ASD + ID than ASD only. However, in both the previous and current studies, the PTB association differences were attenuated and no longer significant after adjustment for SES factors. The current analysis was more comprehensive and precise since the sample size was nearly four times as large as the previous sample. Moreover, reassessment was needed given that during the time period between the two studies, ASD prevalence overall has increased and the proportion of children with ASD who also have co-occurring ID has decreased (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators 2014). Thus we considered that the perinatal risk factor profiles for children with and without co-occurring ID might have also changed.

Finally, our current study included several noteworthy additional assessments; we separately examined children with ID only, and we compared all three case groups to expected numbers derived from the general population of US births.

This study must be interpreted in the context of several limitations. Children included in ADDM have all been previously identified and evaluated for developmental problems; thus, some children with ASD and ID are likely missing because they were never evaluated. Additionally, in this analysis we necessarily excluded children born out of state because they were missing birth certificate data. While, we have no reason to believe this difference is related to the specific relationships between perinatal factors and ASD and ID, it is nonetheless likely that immigration and emigration patterns within each state vary by socio-demographic characteristics and thus, this exclusion might impact the generalizability of our study population. Because our IQ variables were based on clinical testing results in children's health or education records, IQ was assessed at varying ages using a range of different tests; however, inconsistencies in testing procedures are unlikely to have resulted in major shifts in classification of ID. Although we controlled for a number of potential confounders, we cannot discount the possibility of residual confounding as we were limited to those socio-demographic characteristics that are collected on the birth certificate. Additionally, we could not control for study site (i.e. state of residence) due to small sample sizes for several sites. Both PTB and SGA are heterogeneous perinatal outcomes that reflect the end points of multiple underlying pathways. We lacked data to examine these pathways directly. Finally, we lacked data to assess any effects of specific developmental interventions on ID classification.

The study also has several strengths. Our large, population-based sample supported detailed analyses of perinatal risk factors and comparison of children with ASD, ID or both. Because both education and health records are reviewed in ADDM, population coverage includes children with a wide SES range. Finally, because ADDM includes review of children's evaluations up to 8 years of age, we were able to capture ASD and ID diagnoses that occurred later than those included in the samples used for several other studies of perinatal risk factors and ASD or ID.

This study adds to the growing literature demonstrating that suboptimal perinatal environment is associated with both ASD and ID, as evidenced by increases in numerous adverse perinatal outcomes. The current study further demonstrates that the ASD associations, while less prominent than the ID associations, are not simply driven by the high rate of co-occurring ID among children with ASD. Additionally, neither the ASD nor ID associations

are explained by key SES characteristics that vary among children with developmental disabilities and the general population. PTB and SGA both have complex, multifactorial etiologies. Thus, prevention efforts are not straightforward. Nonetheless, these findings highlight the need to reduce modifiable risk factors for PTB and SGA to the extent possible through comprehensive health care for women both prior to and during their pregnancies. Additionally infants with PTB, SGA, or other indications of adverse perinatal outcome need careful monitoring for many different developmental disabilities including behavioral disabilities such as ASD.

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