MALPRESENTATION AT DELIVERY AND ITS ASSOCIATION BETWEEN CHILD AUTISM SPECTRUM DISORDER AND COGNITIVE IMPAIRMENT

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ABSTRACT

Yitian Zhang: Malpresentation at Delivery and Its Association Between Child Autism Spectrum Disorder and Cognitive Impairment
(Under the direction of Julie Daniels)

The prevalence of autism spectrum disorder (ASD) has increased, and ASD causes substantial burden for individuals and their families. The prevalence of cognitive impairment also increased in children. ASD and cognitive function are neurodevelopmental disorders with multiple factors involved; however, specific risk factors remain unclear. Previous studies have shown associations between cesarean delivery and neurodevelopmental disorders; and limited studies focused on malpresentation at delivery, a common indication for cesarean delivery, and its association with ASD or cognitive function. The studies are limited by inconclusive results, by using outcome measurements with limited validity, or by not accounting for the gestational age-dependency prevalence of malpresentation.

To address these limitations, this study utilized data from the Study to Explore Early Development, a case-control study conducted in the United States. In Aim 1, we identified malpresentation and evaluated the association between malpresentation at delivery and ASD. In Aim 2, we evaluated the association between malpresentation and cognitive function in ASD and children from the general sample separately. In our study, we included 1371 children with ASD and 1576 population controls for Aim 1; and 1368 children with ASD and 1576 children from the general sample for Aim 2. We assessed whether the observed associations were modified by maternal pre-pregnancy body mass index (BMI) and gestational age. In Aim 1, we found an

association between malpresentation and ASD (ORa=1.36, 95% CI: 1.06, 1.74), after adjustment for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking. The association was similar for other malpresentations and breech. We did not find the association was modified by gestational age or pre-pregnancy BMI. We did not have evidence that malpresentation was associated with below average cognitive function, either in the ASD or the children from the general sample.

Our findings suggest that malpresentation is associated with ASD, but may not be associated with cognitive function. Future well-powered studies should investigate the role of gestational age or pre-pregnancy BMI in these associations. These results can help identify children at higher risk of ASD for whom developmental screening at younger ages may allow for early identification and potentially earlier intervention.

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
ACOG	The American College of Obstetrics and Gynecology
ADI-R	Autism Diagnostic Interview- Revised
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
CDC	Center of Disease Control and Prevention
CI	Confidence Interval
C-section/ CS	Cesarean Delivery/ Cesarean Section
DAG	Directed Acyclic Graph
DALY	Disability-adjusted life-year
DD	Children with Developmental Delays other than autism spectrum disorder
DMS-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECV	External Cephalic Version
EMM	Effect Measure Modification
HELLP	Hemolysis, Elevated Liver Enzymes and Low Platelets Syndrome
ICD	International Classification of Disease
IQ	Intelligence Quotient
MSEL	Mullen Scale of Early Learning
ORa	Adjusted Odds Ratio
POP	Population Control Group

PROM	Premature Rupture of Membranes
SCQ	Social Communication Questionnaire
SEED	the Study to Explore Early Development
US	United States

CHAPTER 1. INTRODUCTION AND SPECIFIC AIMS

A. Introduction

Autism spectrum disorder (ASD) is a severe behavioral disorder, characterized by a range of persistent deficits in social communication interaction across multiple contexts, as well as restricted, repetitive patterns of behavior, interests, or activities.[1] ASD is affecting 2.3% of US children.[2-4] As for cognitive impairment, a recent study on child population showed a high prevalence of intellectual disability of 18.30/1000[5]. ASD and cognitive impairment may lead to impairments in personal, social, academic, or occupational functioning throughout the lifetime,[6] causing substantial burden for individuals with such conditions and their families.[7, 8]

The etiology of ASD and cognitive impairment is complex, but recent evidence showed that it is a result of complex gene-environment interactions[9-11]. However, few environmental risk factors were identified. Brain development begins in early pregnancy,[12] and can be affected by prenatal and perinatal factors. Previous studies found that complications of pregnancy, including small gestational age at delivery[13, 14], mode of delivery[15, 16, 17, 18], and complications of high blood pressure[19, 20], have been associated with cognitive development and ASD.

Most fetuses with malpresentation are born by cesarean delivery, which has been shown to be associated with cognitive impairment[15, 16] and ASD[17, 18]. Fetal position continuously changes in the uterus throughout pregnancy, but the fetus typically settles with the head down (vertex position) as it approaches term. Malpresentation includes breech, and shoulder, compound, face, and brow presentations[21]. Breech presentation refers to a fetal position where the buttocks or lower extremity enters the maternal pelvis first. The probability of

malpresentation varies inversely with gestational age at delivery[22]. Malpresentation is more common at earlier gestational weeks, which may in part be related to fetal size. As gestational age increases, malpresentation is less common, and therefore is thought to be related to aberrant fetal development[23, 24]. A fetus begins turning to a vertex position as early as 32-week, but factors like fetal diseases[23, 25], insufficient intrauterine space[26, 27], maternal thyroid dysfunctions[28, 29], or fetal growth restriction[23] are associated with failure to turn, thus resulting in an abnormal presentation at delivery.

Few studies have investigated the role malpresentation may play in the observed associations between cesarean delivery and ASD, mostly focusing on breech presentation[18, 30-32]. These studies were record-based, and most did not account for the gestational age-dependency of malpresentation. Moreover, a few studies[33, 34] have investigated the association between malpresentation and educational achievements or intelligence quotient (IQ) at an older age, but have not considered the natural variation in probability of malpresentation over the course of pregnancy.

We posit that malpresentation at delivery is associated with ASD or cognitive function, perhaps as an independent risk factor for ASD or cognitive function and/or an early marker of adverse fetal development that subsequently manifests in ASD or cognitive impairment. (Figure 1.1)

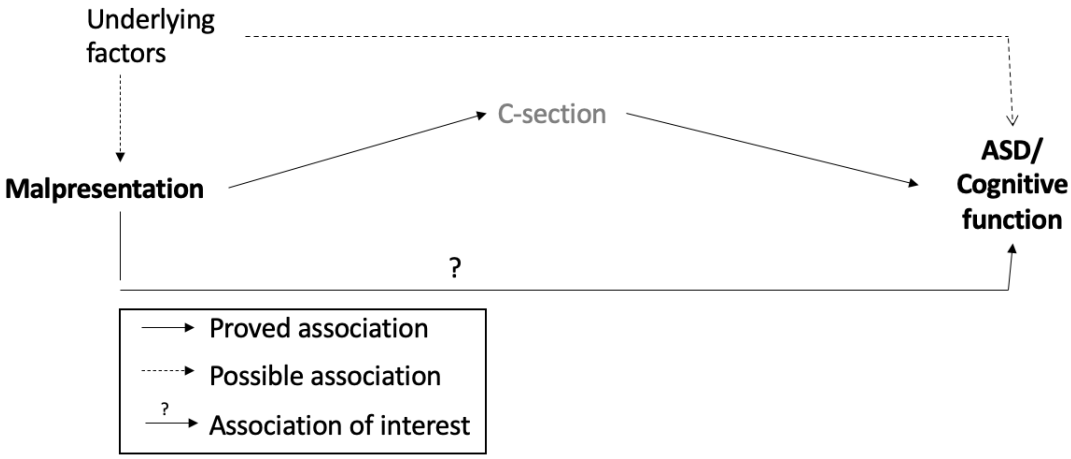


Figure 1.1 Conceptual Framework

We investigated the association between malpresentation at delivery and ASD and cognitive function in the Study to Explore Early Development (SEED),[35] a US multisite case-control study of 3 to 5-year-old children with ASD, children with developmental delays other than ASD, and children sampled from the general population (POP). SEED provides high-quality data on delivery from multiple sources and gold standard characterization of children's neurodevelopment for more than 7,000 mother-child pairs.[19, 36] We propose with the following specific aims:

B. Specific aims

Specific Aim 1: To examine the association between malpresentation at delivery and ASD in the offspring;

Specific aim 1a) Examine effect measure modification by gestational age.

Specific aim 1b) Examine effect measure modification by pre-pregnancy body mass index (BMI).

Hypothesis 1: Malpresentation at delivery is associated with an increased risk of ASD;

Hypothesis 2: Gestational age modifies the association between malpresentation and ASD, such that the association between malpresentation and higher risk of having ASD will be stronger among infants born at term than those born preterm. Pre-pregnancy BMI also modifies the association, as the association will be stronger among mothers with pre-pregnancy overweight or obesity.

Specific Aim 2: Examine the association between malpresentation at delivery and cognitive function. Cognitive function has been measured by the Mullen Scales of Early Learning (MSEL; 1995). The association will be evaluated separately for children with ASD and children from the general sample.

Specific aim 2a) Examine effect measure modification by gestational age.

Specific aim 2b) Examine effect measure modification by pre-pregnancy BMI.

We hypothesize that malpresentation at delivery will be associated with lower cognitive abilities in both groups and that this association may be stronger among infants born at or near term, and may be stronger among mothers with pre-pregnancy overweight or obesity.

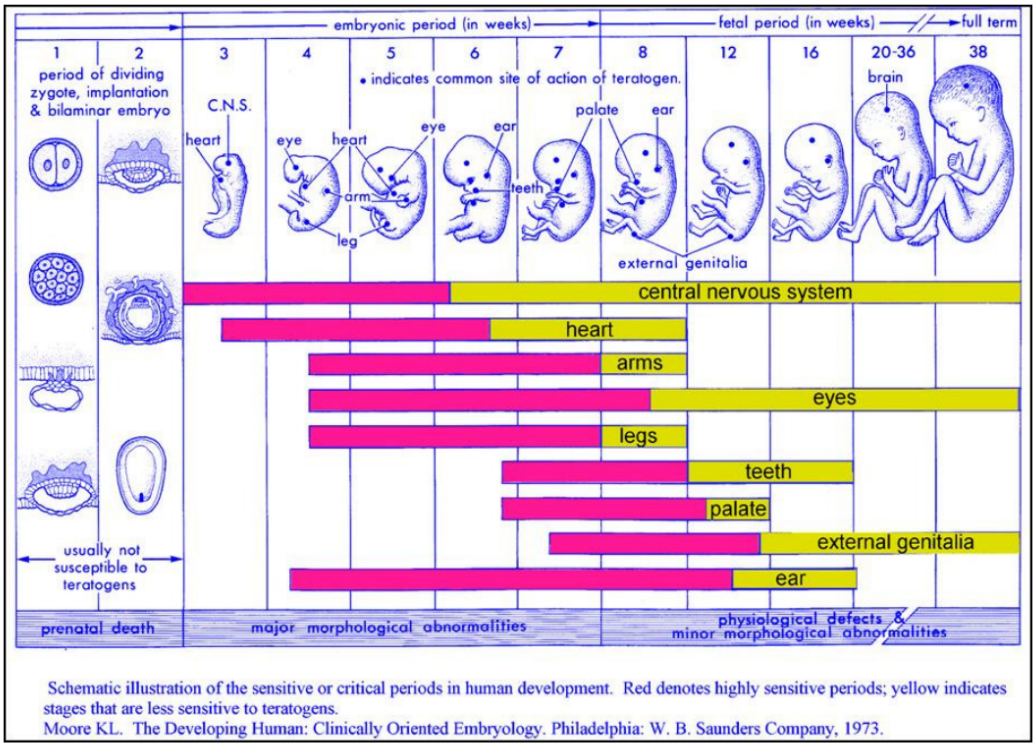
CHAPTER 2. BACKGROUND

A. Background

A.1 Overview of Child neurodevelopment

A1.1 Brain development

The fetal and neonatal periods are well known as critical stages in brain development. Rapid neurodevelopmental processes establish key functional neural circuits of the human brain. Human brain development is a protracted process that begins about 25 days after conception, when the neural tube begins to form.[37-40] Three to six weeks of gestation is a particularly sensitive period for central nervous system development. By the end of the embryonic period (gestational week 10), the basics of the neural system are established. However, the structures and function continue to develop throughout the fetal period and early childhood (Figure 2.1[41]). The processes that contribute to brain development range from the molecular events of gene



Schematic illustration of the sensitive or critical periods in human development. Red denotes highly sensitive periods; yellow indicates stages that are less sensitive to teratogens.
Moore KL. The Developing Human: Clinically Oriented Embryology. Philadelphia: W. B. Saunders Company, 1973.

Figure 2.1 Window of child development during pregnancy

expression to environmental input. Disruptions in this process during pregnancy may contribute to the development of neurodevelopment disorders.

A1.2 Neurodevelopmental disorders

Neurodevelopmental disorders are serious health problems impacting nearly 6% of children in the United States[42]**.** The nervous system develops over time along a continuum. Neurodevelopmental disorders can be defined as shifts in function across the distribution, especially towards the lower tail. Neurodevelopmental disorders can also be defined as discrete outcomes, referring to presence of specific traits or combinations of traits. They include impairments of the growth and development of the brain or central nervous system, or disorder of brain function that unfolds as the individual grows and affects emotion, learning ability, self-control, and memory.[43] In general, the group includes a very wide range of neurological and psychiatric problems that are clinically and causally heterogeneous, including rare genetic

syndromes, cerebral palsy, congenital neural anomalies, schizophrenia, attention deficit hyperactivity disorder, epilepsy, and autism spectrum disorders (ASD).[44, 45]

A.2 Autism spectrum disorder and cognitive function

A2.1 ASD and its prevalence

ASD is characterized by a range of persistent deficits in social communication interaction across multiple contexts, as well as restricted, repetitive patterns of behavior, interests, or activities.[1] The signs of ASD can be observed among infants and very young children, but diagnosis usually occurs between 3 to 5 years of age and many aspects of the disorder are life-long[46].

In 2018, the Center of Disease Control and Prevention (CDC) documented the prevalence of ASD to be 23.0 per 1,000 children in the United States, reflecting a continuous rise in documented prevalence over the past two decades[3, 4]. Studies in Asia, Europe, and North America have identified individuals with ASD with an average prevalence of between 1% and 2%.[47] ASD is much more prevalent in boys compared to girls (prevalence ratio approximately 4:1). The sex ratio is modified substantially by cognitive impairment; among cases without intellectual disability the sex ratio may be more than 5.5:1[48], whereas among those with intellectual disability the sex ratio may be closer to 2:1[49].

More than 70% of individuals with ASD have concurrent medical, developmental, or psychiatric conditions.[46] Globally, ASD accounts for more than 58 disability-adjusted life-year (DALYs) per 100,000 population.[50] The total costs per year for children with ASD in the United States were estimated to be between $11.5 billion – $60.9 billion (2011).[51] Another study[52] found ASD was associated with $3020 higher health care costs and $14,061 higher aggregate non-health care costs. Some estimates[53] suggest that children with ASD have 10 times the healthcare

expenditures of other Medicaid-eligible children and three times those of children with intellectual disabilities.

A2.2 Cognitive impairment and intellectual functioning

Cognition is the mental process of acquiring knowledge and understanding through thought, experience, and the senses. It encompasses various aspects of high-level intellectual functions and processes such as attention, memory, knowledge, decision-making, planning, reasoning, judgment, perception comprehension, language, and visuospatial function.[54] Cognitive impairment describes the impairment of different domains of cognition. It is not limited to any particular disease or condition but may be among the manifestations of a wide variety of underlying conditions.

Cognitive impairment sometimes is used to refer to intellectual disability, or low intellectual functioning.[55] In early childhood, incidence of child cognitive impairment or intellectual disability is challenging to be accurately measured as mild disabilities may be under-recognized until later in childhood. In the general population, the prevalence of intellectual disability in developing countries is estimated to range from 10 to 15 per 1000 children.[5] In the US, the prevalence of children ever diagnosed with intellectual disability was 1.48% among boys and 0.90% among girls during 2014-2016[42]. The prevalence of intellectual disability was lower among younger children than older children[42]. During the past decade, there was a significant increase in the prevalence of intellectual disability[56, 57], and the trend also existed in children with ASD.

Children with ASD vary widely in their verbal and cognitive abilities; approximately 33% of children with ASD have co-occurring intellectual disability, and 24% have cognitive impairment placing them in the intellectual disability borderline range[13]. Children also

experience challenges with social interaction and communication skills, ability to maintain attention, and sensory issues.[58] Cognitive impairment and other common developmental disabilities can impair personal, social, academic, or occupational functioning throughout lifetime.[6] Such disorders can cause substantial burdens for impacted individuals and their families.[7, 8]

A2.3 Etiology of ASD and cognitive function

The etiology of ASD and cognitive impairment is complicated and likely heterogeneous. Prior research on etiology has been on genetics and the child's experiences and exposures during delivery.[13, 59-62]

A2.3.1 Genetic basis

ASD are highly heritable.[9] Common variation refers to genetic variation from the reference genome, which is present in >1% of the population. Common variants with small effects are thought to act additively in the development of complex traits in ASD.[63] The most consistently reported genes among the common variants include the gamma-aminobutyric acid (GABA) A receptor, beta 3 (GABRB3); oxytocin receptor (OXTR); reelin (RELN); serotonin transporter (SLC6A4); N-methyl-D-aspartate receptor (NMDA; GRIN2B); arginine vasopressin receptor 1A (AVPR1A); engrailed homeobox 2 (EN2); integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61; ITGB3); met proto-oncogene (hepatocyte growth factor receptor; MET); and contactin-associated protein-like 2 (CNTCAP2) genes.[64] GWASs[65] (genome-wide association studies) found linkage in regions 2q21–33, 3q25–27, 3p25, 4q32, 6q14–21, 7q22, 7q31–36, 11p12–13, and 17q11–21, with a meta-analysis confirming 7q22–32 and showing suggestive evidence for regions 10p12–q11.1 and 17p11.2–q12. Rare variation, genetic variation at a frequency of ≤1% in population, are found in 3-5% of subjects with ASD. However, single

mutations account for no more than 1% of cases, mainly due to the presence of phenotypic heterogeneity and variable penetrance.[66] ASD is well known to have strong and clear genetic influences, but is now believed that ASD is a result of complex gene-environment interactions.[9-11]

Cognitive impairment may also arise from genetic abnormality, which can be a single gene mutation, copy number variation, or chromosomal abnormality that causes an inborn error of metabolism, neurodevelopmental defect, and neurodegeneration.[55]

Because neurodevelopment begins in early pregnancy and extend through the fetal period[12], it is also affected by environmental factors happening during pregnancy and at delivery.

A2.3.2 Prenatal and perinatal risk factors were found to be associated with ASD and cognitive function, including cesarean delivery.

Several obstetric conditions have been found to be associated with ASD and cognitive function. Preterm labor and delivery have been consistently associated with increases the risk of ASD.[13, 14, 67] Among preterm infants, organs such as the lungs and brain are still in their final weeks of development.

Prior epidemiological studies have also found cesarean delivery to be a modest, but consistent risk factor for cognitive impairment[15, 16] and ASD[17, 18]. However, the association is not verified to be causal, and the underlying mechanism for such association remain unclear. Other suboptimal obstetric conditions, such as preeclampsia[19, 20], hypertensive disorders[19], and PROM (premature rupture of membranes)[68] can lead to cesarean delivery and may also impact the infant's neurodevelopment. Few studies have distinguished neurodevelopmental risks associated with the indications for cesarean delivery from the cesarean delivery procedure.

The common indications for primary cesarean delivery include labor dystocia/ arrest (34%), abnormal or indeterminate fetal heart rate tracing (23%), fetal malpresentation (17%),

multiple gestation (7%), and suspected fetal macrosomia (4%).[69, 70] Other indications include preeclampsia and maternal request.[70] A cesarean delivery is medically indicated when a significant risk of adverse outcome for mother or baby is presented.[71] In the US, cesarean delivery is quite common (31.7% in 2019)[72]. For some medical indications such as placenta previa (placenta lying over the opening of the cervix) or malpresentation, cesarean delivery can be a life-saving operation.[73] According to The American College of Obstetrics and Gynecology (ACOG), there is a trend in the United States to perform cesarean delivery for term singleton fetuses in a breech presentation. In 2002, the rate of cesarean deliveries for women in labor with breech presentation was 86.9%,[74] suggesting that malpresentation is an important indication for cesarean delivery.

A.3 Malpresentation

A3.1 Malpresentation definition

Fetal malpresentation includes breech, shoulder, compound, face, and brow presentations[21]; among them, breech presentation is the most common form of malpresentation.[75] Breech presentation refers to the fetus lying longitudinally with the buttocks or lower extremity entering the pelvis first.

A3.2 Prevalence of malpresentation

The prevalence of malpresentation, especially breech presentation, changes with gestational age. Among malpresentation, breech presentation is the most common abnormal presentation at delivery. The prevalence of breech, along with other malpresentation, is 3-4% among term birth, and 25% among extremely preterm births.[76] Such prevalence differences across gestational ages is due to the continuous change in fetal position in the uterus during pregnancy.[22] Before the 25th week, the fetal presentation changes frequently, and the fetuses

with a malpresentation at this time does not affect the probability of malpresentation at delivery at a later gestational age. From 25 to 35 gestational week, the incidence of cephalic (vertex) presentation increases, and the probability of malpresentation is inversely associated with gestational age. After the 36th week, the probability of vertex and malpresentation changes in favor of vertex presentation. (See Figure 2.2[76])

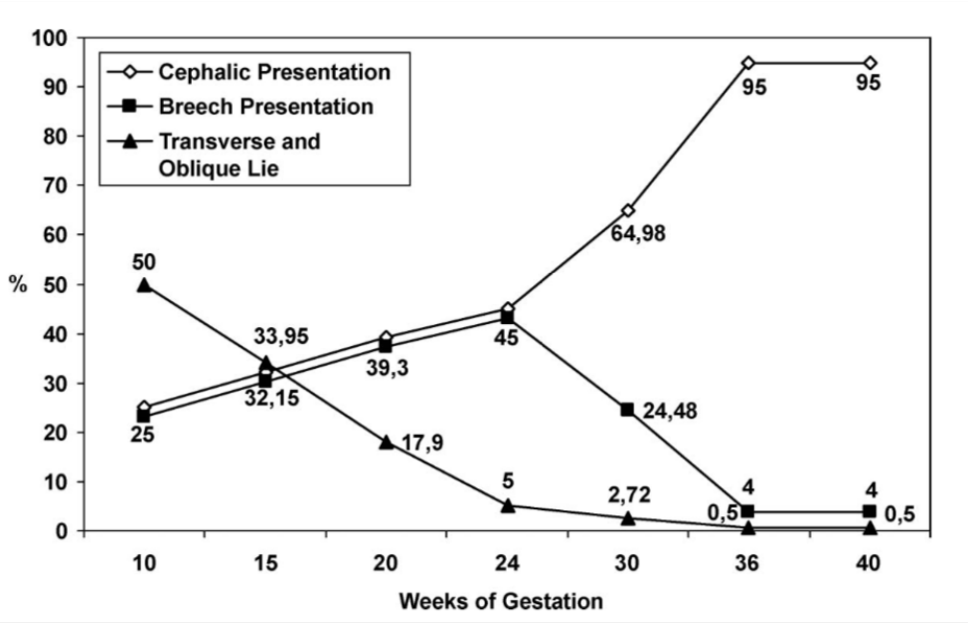


Figure 2.2 Probability of breech and other malpresentation in weeks of gestation

A3.3 Malpresentation and neurodevelopmental delay

Malpresentation, specifically breech presentation, is a strong indication for primary cesarean delivery[77] and may also impact the infant's neurodevelopment[19, 20, 68], but the research focusing on malpresentation was very limited. Studies[78-80] have suggested that among infants with malpresentation at delivery, neurodevelopmental risk did not differ by being delivered by cesarean delivery or by vaginal delivery. Another study found that the association between cesarean delivery and ASD was not significant after stratifying on breech presentation.[31] Therefore, it is possible that malpresentation is the underlying factor associated with ASD and cognitive impairment, or an indicator for other underlying factors, which could be linked with

neurodevelopment. Distinguishing the potential ramifications of malpresentation and cesarean delivery on ASD development may improve our understanding on ASD etiology.

Fetal malpresentation could be a sign of abnormal fetal brain development. Malpresentation is much more common in preterm births (i.e. with a small gestational age) where the fetus occupies a smaller proportion of the intrauterine capacity, and it could be fairly normal for an infant to be delivered with a malpresentation at a small gestational age. As gestational age increases, malpresentation is less typical and may be a sign of aberrant fetal development. A failure to successfully turn to the vertex presentation is a consequence of many endogenous and exogenous factors (e.g. fetal diseases[23, 25], fetal growth restriction[23], insufficient intrauterine space[26, 27], and maternal thyroid functions[28, 29]), which may have an impact on the brain development in the offspring. Malpresentation at birth increases the risk of deviation from normal parturition and causes incomplete engaging of the presenting part of the fetus in the isthmic part of the uterus. This could be followed by a delay in delivery and an increased incidence of birth asphyxia because of umbilical cord prolapse and head entrapment.[25]

External cephalic version (ECV) is a primary technique recommended by ACOG for turning the unborn baby into a cephalic (vertex) presentation to ease delivery using pressure through the mother's abdominal wall.[81] The preferred timing of ECV is controversial and success rate is 40-50%.[81-83]

A.4 Previous studies on malpresentation and ASD or cognitive function

Few population-based studies have looked at malpresentation and neurodevelopmental disorders such as cerebral palsy[84, 85], suggesting that malpresentation could be associated with aberrant fetal development or birth defects, or a sign of such developmental delays. But limited research investigated ASD or cognitive function. Moreover, previous studies on malpresentation

and ASD or cognitive function have methodological flaws. A few studies[86-89] examined the association between fetal presentation and ASD, and nearly all studies focused on breech presentation specifically, but not malpresentation more generally. Most studies concluded that malpresentation was associated with ASD. However, the studies were all record-based, without confirmation on ASD conditions, leading to conflicting results. Most studies used birth records; evidence has also suggested that the accuracy varied across different types of perinatal events in birth records, therefore may using birth records may result in malpresentation misclassification.[90, 91] Most studies also have not accounted for the gestational age-dependency of malpresentation. And there is little research available for other malpresentations and ASD. A detailed description of the literature on malpresentation and ASD could be found in Table 2.1.

Table 2.1 Summary of studies that have looked at the association between malpresentation and ASD

First author, year	Study design	Study population and period	Exposure	Outcome	Finings
Eaton, 2001[86]	Case-control using Danish Psychiatric Central Register, and the Danish Medical Birth Register	Records from all births in Denmark from 1973 through 1993 were linked to records of all psychiatric hospitalizations. Diagnoses were grouped into seven broad categories. A reference population of 10% of births in Denmark from 1973 to 1990 was used for comparison. They identified 116 children with ASD, and 102,905 from the general population.	Back of head presentation, head presentation, and other presentation from Medical Birth Registrer	ASD identified using ICD codes 299.00, 299.01, 299.03	After adjusted for gender and birth, the point estimate of risk ratio (RR) was 1.47 for back of head presentation, and 1.89 for other presentation (no CI provided, the authors concluded it was not significant).
Larsson, 2005[32]	Case-control using Danish Psychiatric Central Register, the Danish Medical Birth Register, and the Integrated Database for Longitudinal Labor Market Research	The study was nested within a cohort of all children born in Denmark after 1972 and at risk of being diagnosed with autism until December 1999. Prospectively recorded data were obtained from nationwide registries in Denmark. Cases totaled 698 children with a diagnosis of autism; each case was individually matched by gender, birth year, and age to 25 controls.	Breech presentation and other presentation from Medical Birth Registrer	ASD identified using ICD codes: ICD-8 diagnosis codes 299.00–299.01 or ICD-10 diagnosis codes F84.0–F84.1x	Adjusted analyses showed that the risk of autism was associated with breech presentation (risk ratio [RR]= 1.63, 95% confidence interval [CI]: 1.18, 2.26), and the RR for other malpresentation was 1.92 (95% CI: 0.48, 6.36). Adjustment set included perinatal factors, parental psychiatric history,

					and socioeconomic characteristic.
Bilder, 2009[31]	Nested case-control design using the birth certificate database	The targeted population was 8-year-old children born in 1994 and residing in 1 of the 3 most populous counties in Utah. Of those identified, 132 children (115 boys, 17 girls) had birth certificate records available. Each child was matched by gender and birth year to 100 controls (11 500 boys, 1700 girls) from the birth certificate database in a nested case-control design.	Breech presentation and cesarean section identified by birth certificates	ASD identified on the basis of methodology used by the 2002 Autism and Developmental Disabilities Monitoring Network	Significant perinatal factors included breech presentation, adjusting for maternal age, gestational length, and parity; adjusted OR: 2.10 [95% CI: 1.11–3.98]. When corrected for breech presentation, a known indication for cesarean delivery, the association between primary cesarean delivery and autism spectrum disorder was eliminated.

Burstyn, 2010[92]	Cohort study using provincial delivery records	Provincial delivery records identified the cohort of 218,890 singleton live births in Alberta, Canada, between January 1, 1998, and December 31, 2004. These were followed-up for ASD via ICD-9 diagnostic codes assigned by physician billing until March 31, 2008.	Breech/ shoulder presentation from delivery records	ASD identified using ICD codes: ICD-9 codes 299.0, 299.8	RR for ASD in breech/ shoulder presentation compared to cephalic presentation was 1.31, 95% CI was (1.02 - 1.69), adjusted for clustering of births with mother

Two[33, 34] of four population-based studies[33, 34, 93, 94] have reported an association between breech presentation and cognitive function when investigating children without known neurodevelopmental delays. Important limitations include lack of adjustment for important confounding. Moreover, none of these studies considered the changing prevalence of malpresentation across gestational weeks, thus ignoring the possible correlation between malpresentation and gestational age. Those studies were dated and focused more on older children, and the measurement of cognitive function relied on intelligence quotient (IQ) or educational achievement. A detailed description can be found in Table 2.2.

Table 2.2 Summary of studies that have looked at the association between malpresentation and cognitive function

First author, year	Study design	Study population and period	Exposure	Outcome	Finings
Sorensen, 1999[33]	Cohort study linking birth registry data with data collected during evaluation for military service	The study enrolled 4,298 conscripts born between 1973 and 1976 residing in the study area during 1993 and 1994	Breech presentation identified using information from Danish birth registry	Cognitive function was measured by Boerge Prien IQ. Low cognitive was identified by IQ test score <38.	The breech presentation was negatively associated with low cognitive (OR=2.31, 95% CI: 1.16, 4.59), after adjustment for maternal age, parity, civil status, and employment status. It also persisted when we restricted the analyses to term singleton pregnancies.
Langridge, 2013[94]	Retrospective cohort study using Midwives' Notification System, birth records and population-based disability databases	All live singleton births in Western Australia (WA) between January 1984 and December 1999 (N=383,153), with >20 weeks gestation and/or >400 g birthweight	Breech presentation identified using information from Midwives' Notification System	Children with intellectual disability were identified from the Intellectual Disability Exploring Answers Database, a WA population-based register. The diagnostic codes are assigned by physicians using the American Association on	Among children with mild-moderate intellectual disability, the ORa was 1.33 (95% CI: 1.13, 1.56), and the ORa for severe ID was 0.90, 95% CI (0.46, 1.77), after adjusting for birth year and

				Mental Retardation classification system. All cases with a biomedical cause (e.g. Down syndrome, Rett syndrome, etc) were excluded.	socioeconomic status.
Mackay, 2015[34]	Cohort study linking three Scotland-wide administrative databases at an individual level: the ScotXed school census; Scottish Qualifications Authority examination results; and Scottish Morbidity Record maternity database.	The linkage provided information on singleton children, born at term, attending Scottish schools between 2006 and 2011	Breech presentation identified by medical records	Academic achievement was measured using the Scottish Credit and Qualifications Framework, which has produced a unified points scale which allocates a tariff for each examination result based on the level at which it was sat and the grade achieved. The SCQF summates these tariffs for each child and then categorizes the total into: low, basic, broad general and high attainment.	Children born by vaginal breech delivery had lower levels of attainment than those born by cephalic vaginal delivery (ORa: 1.14, 95% CI: 1.01-1.28). Children delivered by planned caesarean section for breech presentation achieved better attainment levels on univariate analysis, but were no different from children born by vaginal cephalic

					delivery following adjustment for potential confounders: infant sex, maternal age, maternal height, marital status, area deprivation index, parity, birthweight centile, previous spontaneous and therapeutic abortions, estimated gestational age, smoking during pregnancy and year of delivery.
Azria, 2016[93]	Prospective population-based cohort that included all births occurring from 22 to 32 completed weeks of gestation in 1997 in 9 French regions	Singletons infants without congenital malformations born from 27 to 32 completed weeks of gestation enrolled in France in 1997 in the EPIPAGE cohort	Breech presentation identified by medical records	Cognitive function, along with other neurodevelopmental function, was measured by a standardized medical examination, including a short version of the Touwen neurologic examination and a developmental assessment with the Kaufman	There was no difference according to fetal presentation in cognitive deficiencies/learning disabilities or overall deficiencies, after adjusting first for gestational age, sex, and antenatal corticosteroid use, then adding SGA

		Assessment Battery for Children, at 5 years of age, performed by trained examiners in special centers set up for the study.	and PROM, and thirdly, maternity unit level and mode of delivery, and further adjusted for parental SES, maternal age at delivery, and maternal country of birth.

A.5 Significance

Our study shed light on potential in utero etiology of ASD and cognitive function. ASD is a severe neurodevelopmental disorder, and its prevalence is increasing both in the US and globally. Despite the strong genetic basis of ASD and cognitive function, the etiology still remains unclear, suggesting that non-genetic factors could be an important part in understanding the development of ASD and cognitive function. We hypothesized that malpresentation is associated with ASD or cognitive impairment and/or is an early marker of adverse neurodevelopment. Finding an association between malpresentation and ASD or cognitive function could prompt research to further distinguish whether malpresentation is a risk factor or a sign of aberrant fetal development- perhaps resulting from other underlying endogenous and exogenous influences during pregnancy. This knowledge may help inform early monitoring for neurodevelopment among children born with malpresentation.

To address limitations of prior research, we proposed to use the rich data from the Study to Explore Early Development (SEED) to distinguish associations between malpresentation, combining breech and other malpresentation, while considering for potential effect measure modification by gestational age and pre-pregnancy body mass index (BMI). We also controlled for confounding such as demographic characteristics, maternal smoking, and pregnancy complications. As malpresentation, gestational age, and neurodevelopment are intertwined, understanding how these factors interact with each other is crucial to advance our understanding of the etiology for ASD and cognitive impairment.

B. Innovation

This study (1) addressed methodological limitations related to the interaction malpresentation and other conditions (gestational age and pre-pregnancy BMI); (2) provided a better measurement for cognitive function and ASD ascertainment; and (3) had a sufficient power to control for confounding.

1. We addressed the probability of malpresentation during pregnancy by looking at the modification of gestational age. Previous studies failed to consider malpresentation in light of gestational age. Due to variation in the probability in malpresentation across gestational ages, there may be heterogeneity in associations between malpresentation and ASD or cognitive function, such that malpresentation at term gestation may be indicative of pathology. None of the prior studies investigated malpresentation at different gestational ages. In SEED, we have high quality information on gestational age using multiple sources (birth records, maternal interviews, and medical records).

2. We measured ASD and cognitive function using validated and well-established assessments. By leveraging the validated assessment tools to classify ASD and cognitive function, the study provided gold standard measurements of ASD and valid measurement for cognitive function.

3. Our study also had a large sample size and had the ability to better control for confounding using detailed information. Previous studies were not able to sufficiently control for confounding. In SEED, detailed information on medical history, pregnancy complications, labor and delivery process, and infant health was well documented in three sources: maternal interviews, medical records, and birth records, making it possible for us to identify all potential confounders.

CHAPTER 3. METHODS

We examined the relationship between malpresentation at delivery and ASD/ cognitive function in children, and how the association is modified by gestational age or pre-pregnancy BMI. We leveraged the extant data from SEED. With an efficient study design and a large study population, we addressed many limitations from previous studies and provide insight for further studies on ASD etiology and clinical practice.

A. Study design

SEED is a US multisite case-control study with multiple-source ascertainment of children with ASD, children with developmental delays other than ASD (DD), and children sampled from the general population (POP). SEED focused on children aged from 3 to 5 years of age. Children residing in six states in the US were enrolled in the study. Children with ASD were identified as case group, and two different control groups were defined for SEED: POP and DD. The study had data available for 7400 children born from 2003 to 2011.

SEED collected data retrospectively on family medical history, maternal reproductive health, and pregnancy outcomes. Child-oriented data collection was focused on assessing child development and behavioral characteristics, through channels including telephone interviews, self-administered forms, and in-person child developmental assessments. Biosamples and maternal and child medical records were also gathered. Data collection was standardized across six sites and subject to uniform standards for quality data checks. It is currently the largest study

in the United States to help identify factors that may put children at risk for ASD and other developmental disabilities.[35]

B. Study population

Children eligible for SEED were required to have: 1) been born in the study catchment area during the period from 2003 to 2011; 2) resided in one of six multi-county catchment areas in California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania at the time of the first study contact; 3) live with a caregiver (family member or caregiver at least 18 years of age at enrollment; who had resided with and consistently cared for the child since he or she was 6 months of age or younger). The caregivers were required to communicate in English (or Spanish for some sites) and give consent; and 4) the children were required to be between 30-68 months of age at the completion of the in-person clinical developmental assessment. We further restricted this analysis to the children whose biological mothers were the caregiver completing the interview (>95% of participants). Children for whom birth certificates or legal consent was inaccessible (e.g., adoption) were excluded.[35]

Of the original 7,271 SEED participants, we added the following inclusion and exclusion criteria.

The participants were included in the study if: 1) were singleton, 2) index children, and 3) could be clearly classified into a final classification of autism spectrum disorder (ASD) or population control group (POP) based on a clinical assessment.

We excluded DD group in our study analysis. Comparisons between the ASD and POP groups were designed to identify risk factors in children with ASD relative to children among the general population. The DD group was enrolled as controls to investigate whether the risk factors found are specific to ASD, or common among all neurodevelopmental delays. It was used to cast

a wide net to screen children with developmental disabilities and identify children who may not already have a diagnosis for ASD. As such, the DD group captured a lot of different conditions therefore was also very heterogeneous. In our study, as we were interested in how malpresentation was associated with ASD compared to the general population, we restricted the control group only to the POP population. We also excluded multiples, or those who did not complete clinical assessment so that their ASD/ POP status could not be confirmed.

Though not a national study, SEED took several approaches to increase the representativeness of the study population to the children in the rest of the country. SEED selected children with ASD and other developmental problems from a number of clinics and schools in the study areas to increase the representative of all children with these types of developmental problems and not just children who might be seen at a single clinic or school. The POP group was sampled at random from all of the children born in each community during the same time.

C. Outcome assessment

C.1 Cognitive function

Cognitive function measurement: cognitive function was measured by the Mullen Scales of Early Learning (MSEL) (Mullen, 1995; 1995 AGS/Pearson Version). MSEL is a standardized assessment commonly used in clinical psychology as a measurement of cognitive development; and had been demonstrated to be an effective tool to measure the cognitive and developmental functioning for children with neurodevelopmental concerns. The MSEL was organized into 5 subscales: (a) gross motor, (b) fine motor, (c) visual reception (or non-verbal problem solving), (d) receptive language, and (e) expressive language. In SEED, only fine motor, visual reception (or non-verbal problem solving), receptive language, and expressive language were administered

in-person to children from 30 to 68 months. The t-score for each subscale was standardized on age, and reported as mean of 50 and standard deviation of 10[95]. An early learning composite score can be derived from subscales (b), (c), (d), and (e). For young children this early learning composite score is considered equivalent to a more traditional IQ score or a developmental standard score. The MSEL composite standard score was reported as standard scores with a mean of 100 and SD of 15. Children with early learning composite standard score at 15 percentile or below (score of 84) in MSEL was categorized as below average abilities[95].

MSEL can be administered to infants and children up to 68 months of age.[96] In the general population, the internal consistency for the MSEL composite score was high, suggesting that the composite score could be used as an as overall measure of cognitive functioning.[97] The MSEL has good internal, test-retest, and interrater reliabilities, as well as good convergent validity with the Bayley Scales of Infant Development.[98]

Children with ASD varied widely in verbal and cognitive abilities. Their limited social interaction and communication skills further interfered with the accurate assessment of a young child's cognitive abilities.[58] Normal tests IQ were frequently invalid for the assessment of children with very low IQ, as the development and standardization samples rarely included substantial representation of this segment of the population.[99] Although the MSEL subscales that make-up this composite score have not been standardized specifically in young children with ASD, the non-verbal problem solving of MSEL has been considered a better representation of IQ for young children with ASD, given ASD deficits in language.[98] Many studies of children with ASD use the MSLE as its primary measure of cognition.[100] Among children with ASD, MSEL showed to have high convergent validity with Differential Ability Scales, a tool that has been used to assess cognitive abilities in several studies of children with ASD.[101]

C.2 Ascertainment of ASD and POP

Ascertainment of ASD: In SEED, children with potential ASD were ascertained through multiple sources, including early intervention, special education, and related service programs for toddlers and young children, hospitals, clinics, and individual providers. Potential participants had to have received an ASD or related diagnosis (e.g., conduct disorder, intellectual disability, or significant developmental delay) from a clinical provider, or received early intervention or special education services for an ASD or related condition (e.g., intellectual disability or severe emotional disorder). Parents who had a child with a documented ASD or ASD-related diagnosis could also have contacted the study directly and the child was enrolled if eligible. All children were screened for autism symptoms using social communication questionnaire (SCQ), and those who screened positive (SCQ ≥11) received a more extensive assessment, Autism Diagnostic Observation Schedule (ADOS). The caregivers also completed Autism Diagnostic Interview- Revised (ADI-R). Those with final ASD classification meet either 1) ASD criteria on the ADOS algorithms and autism criteria on the ADI-R; or 2) ASD criteria on the ADOS algorithms and one of the three relaxed criteria on the ADI-R. Untestable children or those who refused to take ADOS or ADI-R would be classified as possible ASD, and were excluded in our study.

Table 3.1 Instruments administered in SEED and criteria for ASD classification

Instrument	Domains	Criteria
Autism Diagnostic Observation Schedule-2 (ADOS) [102, 103]	Social effect Restricted interests and repetitive behaviors (RRB)	Module 1 with no words=11 Module 1 with some words=8 Module 2 less than 59 months=7 Module 2 more than 59 months=8 Module 3=7
Autism Diagnostic Interview- Revised (ADI-R) [104]	Social Communication RRB	Standard: Social=10; Communication=8 for verbal children or 7 for nonverbal children; RRB=3 Relaxed (when child meets the ADOS criteria but not standard ADI-R) Social=10 and Communication=6 for verbal children or 5 for nonverbal children; Communication=8 for verbal children or 7 for nonverbal children and RRB=8; Social=10 and RRB=2

ADOS/ ADI-R package was a validated and reliable measurement for ASD, and was consider the gold standard for ASD diagnosis. Sensitivity of the tool had been reported to range from 86 to 100 percent and specificity with other developmental disabilities was 73 to 100 percent.[105]

A detailed flowchart of ASD and POP ascertainment is showed in Figure 3.1.

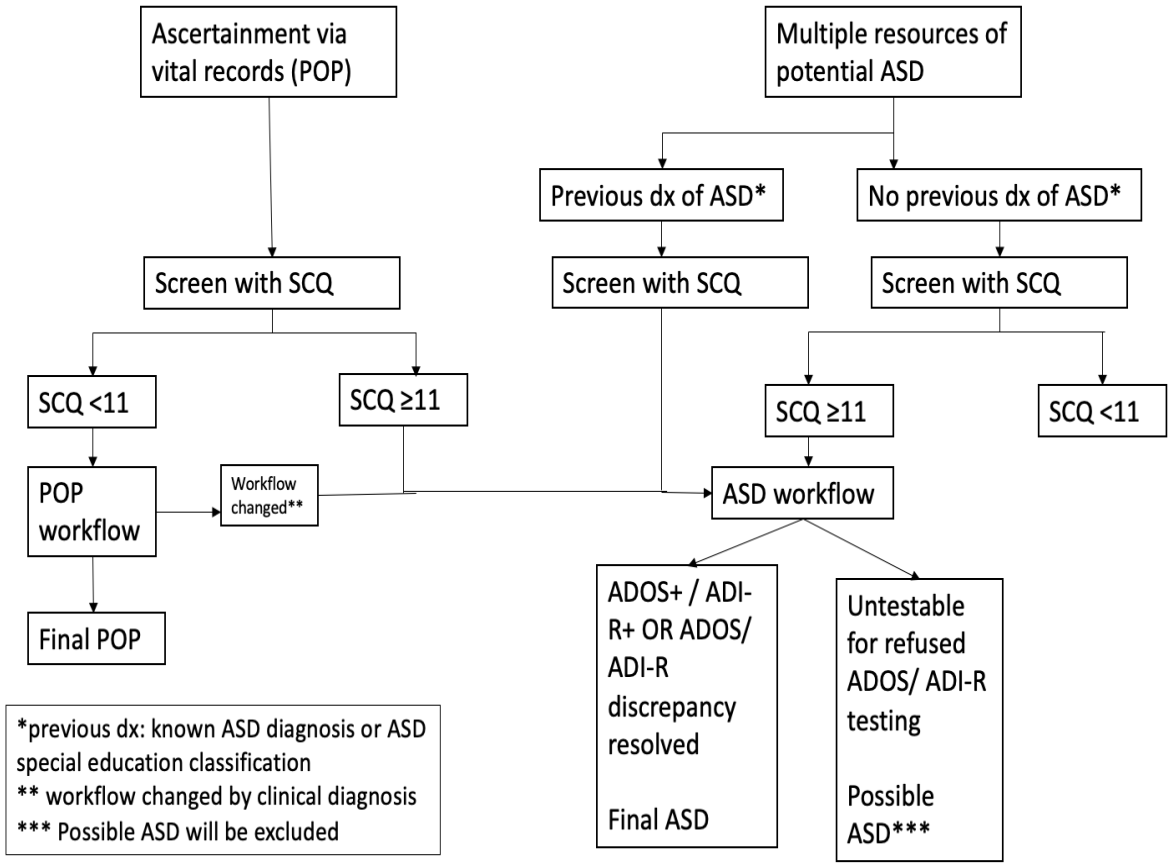


Figure 3.1 Classification of ASD and POP participants

Ascertainment of POP children: POP children were identified by randomly sampling state vital records of children born in the specified birth date range to mothers' resident in a study catchment area at delivery. Birth records were linked to state death certificate files to remove deceased children from the contact list. All children who participated the study were initially screened using the SCQ by a trained clinician, and those screened with negative results on SCQ (SCQ <11) or screened positive on the SCQ but did not meet ASD criteria based on ADOS and ADI-R assessments were classified as POP.

C.3 Exposure assessment

In SEED, information regarding presentation at delivery could be obtained from multiple sources: medical records, maternal interviews, and birth records. (1) Maternal medical records were abstracted. Information on prenatal, perinatal, and postnatal medical information related to risk factors of interest was gathered. Information regarding presentation at delivery was classified as vertex, transverse lie (shoulder presentation), face, breech, other, and not reported. (2) Maternal interview was conducted with the caregiver of the index child, and our study restricted it to biological mothers. The mother was interviewed by telephone and asked, "Was the baby breech?" (3) Birth records were linked to the index child. Information regarding breech/ malpresentation was included on the birth records as "breech/ malpresentation".

Overall, labor and delivery medical record data were available for 76.8% of our study sample, and maternal self-report data were available for 98.7%.

Table 3.2 Distribution of presentation in each source

	Maternal interview	Medical records	Birth records
Vertex	2804 (95.15%)	1999 (67.85%)	2011 (68.24%)
Malpresentation	103 (3.50%)	264 (8.96%)	94 (3.19%)
Missing	40 (1.36%)	684 (23.21%)	842 (28.57%)*

* Most of the missing was due to administrative problems with birth records in two states (CA and CO).

When comparing different sources of information on presentation at birth, we found that medical records had more detailed information for other malpresentations other than breech, while birth records did not distinguish breech from other malpresentations. Maternal interviews only captured breech presentation, and were completed after 3 to 5 years of child birth.

Furthermore, generally, studies suggested medical record was a more valid source for delivery information compared to birth record.[106, 107] There were two main issues with identifying presentation at delivery: 1. in birth record, two study sites reported "missing" (blank) as "No" to "Breech /malpresentation". 2. The inconsistency of malpresentation categorization among different sources. We addressed both issues.

1) Missing information in birth records: Two sites (CA and CO) recorded only the presence of malpresentation, where "missing" indicated the absence of malpresentation or the information was missing on malpresentation. Among the observations with the information missing in birth records (n=842), only 9 observations were also missing fetal presentation information on both maternal interview and medical records. As such, we left missing as it was.

Table 3.3 Report on fetal malpresentation on medical record and maternal interview among children with birth record showing as missing (N=842)

Medical record	Maternal interview	N (%)
Yes	Yes	15 (1.78)
Yes	No	41 (4.87)
No	Yes	3 (0.36)
No	No	599 (71.14)
No	Missing	11 (1.31)
Missing	Yes	1 (0.12)
Missing	No	163 (19.36)
Missing	Missing	9 (1.07)

2) Inconsistency in classification of presentation at birth across sources: medical record had the most detailed information on presentation (vertex, breech, face, shoulder, etc.), where maternal interview reported breech presentation (Y/N), and birth records recorded breech/ malpresentation (Y/N). We evaluated the agreement based on comparison between maternal

interviews and medical records, and birth records with medical records. We found strong agreement for breech presentation (κ=0.61 [95% CI: 0.53, 0.69] between maternal interviews and medical records comparing breech presentation only, n=2100 for participants with both sources available). As discussed, in birth record, some sites report No as missing. After recoding missing to "No", we found κ=0.57 (95% CI 0.49, 0.66) between birth records and medical records. Furthermore, we restricted this comparison to sites that did not mix missing with "No" to compare the agreement between medical records and birth records, and found κ=0.57 (95% CI: 0.47, 0.68) for malpresentation (n=2062 for participants with both sources available), suggesting a robust result for the recoding approach in birth records.

Thus, final classification of malpresentation and breech presentation was determined using the following approach: breech presentation was classified as having the condition ('Yes') if it was reported in the medical record when medical record was available; when medical record was not available, the presentation was classified if it was reported by either maternal interview or birth record. If medical record reported other malpresentation than breech presentation, then the final presentation will be classified as other malpresentation. Due to the low prevalence of other malpresentation, information from birth records were identified as breech presentation. (Figure 3.2) The final classification of fetal presentation was 'vertex', and 'malpresentation'; 'malpresentation' was further categorized into two subgroups 'breech presentation' and 'other malpresentation than breech'.

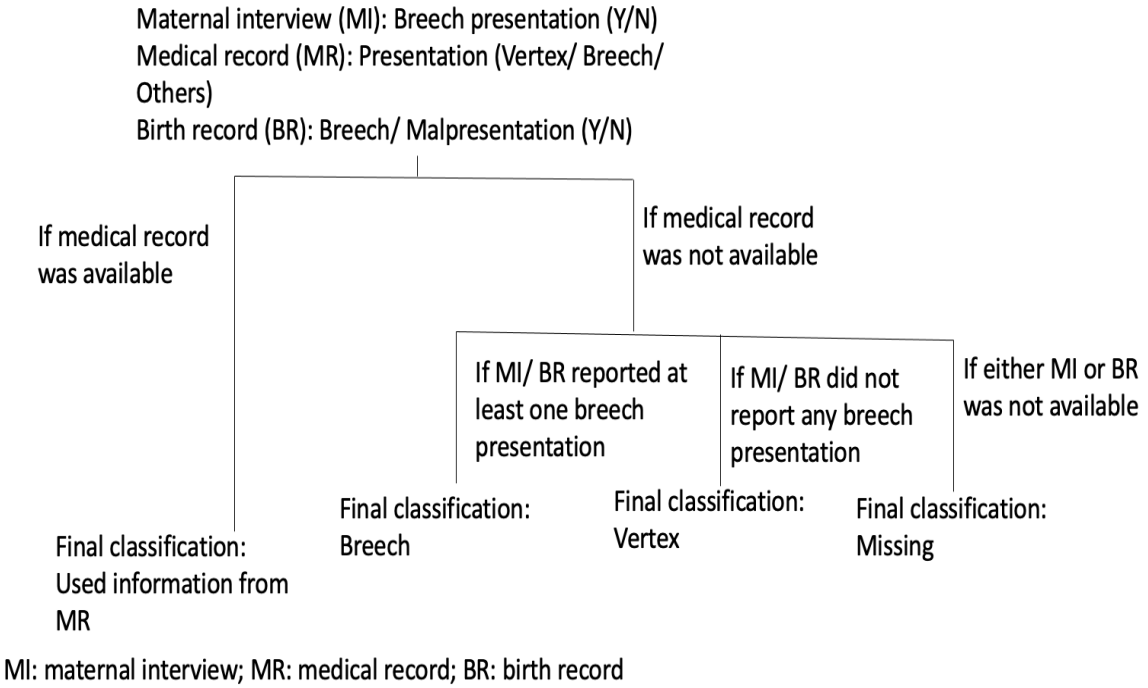


Figure 3.2 Final classification of presentation

C.4 Covariates

We considered the following variables to be potential confounders or effect measure modifiers: maternal age (from birth record, continuous), parity (from medical record, continuous), pre-pregnancy BMI (from maternal interview, categorical), maternal race/ ethnicity (from maternal interview, categorical: Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian/ Pacific Islander, American Indian, and others), maternal education (from maternal interview, categorical: some high school, high school diploma, some college, college degree, >college), maternal smoking (from maternal interview, binary: yes/ no), maternal hypertensive disorder (from medical record, binary: yes/ no), uterine malformation (from medical record, poorly measured, binary: yes/ no), and maternal thyroid dysfunction (from medical record, poorly measured, binary: yes/ no).

We used a directed acyclic graph (DAG) (Figure 3.3) to identify potential confounders based on review of the literature[19, 108-110]. For potential confounding, the minimally sufficient adjustment covariate set included maternal age, smoking, hypertensive disorders of pregnancy, and the family poverty index. Maternal age at delivery was derived from the mother's date of birth and child's date of birth, on birth records. Maternal smoking was categorized as 'ever smoked during pregnancy', using information from maternal interviews. Indications of hypertensive disorders included pre-existing chronic hypertension, pregnancy-induced hypertension, preeclampsia, eclampsia, and HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets) from maternal interviews and medical records. The poverty index was derived by applying the federal thresholds to parent reported income 12 months prior to child's birth from maternal interviews using federal poverty threshold. Poverty index was categorized as the following 4 groups, 'Less than or equal to 138%', 'Greater than 138 to less than or equal to 250', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

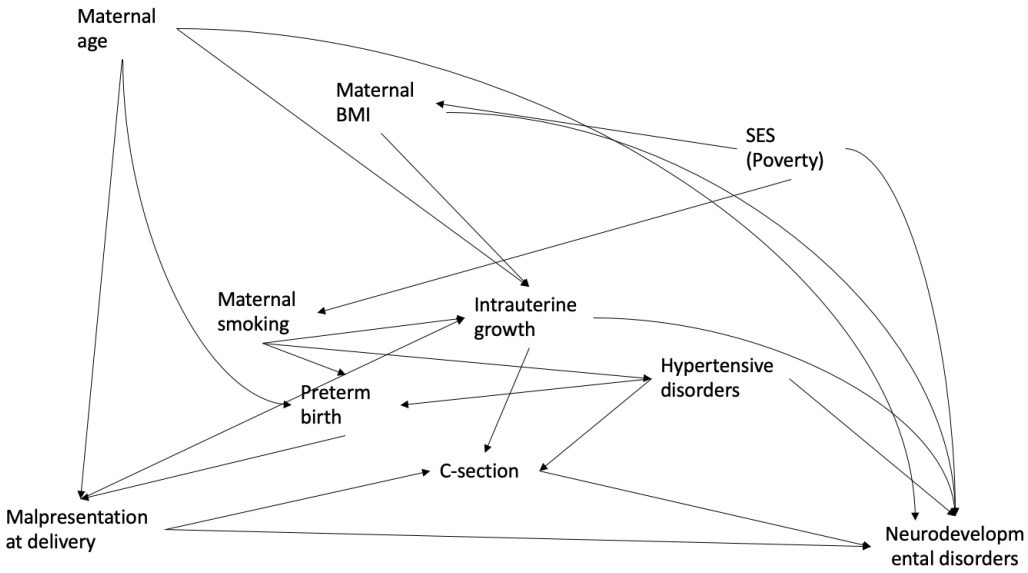


Figure 3.3 DAG for malpresentation and neurodevelopmental delay

Gestational age at delivery and pre-pregnancy body mass index (BMI) were also derived to explore whether they modify the association between malpresentation and ASD or cognitive function. Gestational age at delivery based on best clinical estimate was retrieved from birth records. Gestational age was categorized into preterm (<37 weeks) or term birth (>=37 weeks). Infant's presentation is settled near term, thus any malpresentation at or after term may reflect aberrant development during pregnancy. Because study suggested endocrinologic and/or immunologic correlates of maternal obesity[111] and could affect child neurodevelopment, we also analyzed the potential for pre-pregnancy BMI to modify the association between malpresentation and ASD/ cognitive function. Pre-pregnancy BMI was derived from medical records. Pre-pregnancy BMI was originally categorized as 'low BMI', 'Health BMI', 'Overweight', and 'Obese'.

Though factors like parity, race, or ethnicity could be potential confounders in other studies, they were not included in the covariate set for analysis. Parity was very weakly associated with malpresentation in our study population; moreover, parity was not shown to be a risk factor for ASD by meta-analysis results[18]. The distributions of race and ethnicity were similar between malpresentation and vertex presentations in the general sample (POP). Race and ethnicity are social constructs that could be a proxy for socioeconomic status and associated with access to healthcare; however, in our study, we had the information on household income and education, which could serve as a better indicator for socioeconomic status and health care access.[112]

Table 3.4 Summary of covariates associated with malpresentation or ASD/ cognitive function

Covariate	Primary Data Source	Potential confounding	Potential EMM
Maternal race/ethnicity	Maternal interview	N	N
Maternal education	Maternal interview	N	N
Maternal poverty	Birth record	Y	N
Maternal age at delivery	Birth record	Y	N
Parity	Maternal interview	N	N
pre-pregnancy BMI	Maternal interview	N	Y
Maternal hypertensive disorder	Prenatal medical record, maternal interview	Y	N
Maternal smoking	Maternal interview	Y	N
Preterm birth	Derived from gestational age in prenatal and delivery medical record	N	Y
Child sex	Birth certificate	N	N
C-section	Delivery medical record	N	N
Birthweight Z-score (Proxy for fetal intrauterine growth)	Birth record	N	N
Uterine malformation	Prenatal medical record	N	N

C.5 Statistical analysis

Specific Aim 1: to examine the association between malpresentation and ASD in the offspring; 1a) determine if the association is modified by gestational age; 1b) determine if the association is modified by pre-pregnancy BMI.

Specific Aim 2: to examine the association between malpresentation and cognitive function, in the ASD and children sampled from general population (POP) separately; 2a) determine if the association is modified by gestational age; 2b) determine if the association is modified by pre-pregnancy BMI.

A descriptive analysis was conducted first. We described distribution of maternal characteristics (malpresentation, gestational age, maternal age, race/ ethnicity, education, parity, etc.) and information on child after delivery (child sex, birth weight Z-score) in both ASD and POP groups. A description of MSEL composite score in ASD and POP groups was further conducted.

Because cumulative missing was more than 5% for both aims, we further conducted multiple imputation to address potential bias. We assumed missing at random and conducted multiple imputations (chained equations with a logistic regression imputation model for missing binary data and a multinomial imputation model for missing categorical data). We generated 20 independent imputed datasets.

For specific aim 1, multivariable logistic regression was conducted to estimate the adjusted odds ratio (ORa) of the association, using the minimally sufficient adjusted covariate set. Exposure of fetal presentation was identified, with subgroups of breech presentation and other malpresentation other than breech. Reference group will be ‘vertex presentation’. We explored the association by first comparing all malpresentation to vertex presentation, then

compared breech presentation and other malpresentation to vertex presentation, separately. Effect modification of gestational age or pre-pregnancy BMI was estimated. For gestational age, we stratified on preterm births and term births, using subgroup analysis. For pre-pregnancy BMI, due to the low prevalence of malpresentation in the study population, we re-categorized BMI as 'low/ healthy BMI' and "overweight/ obese', and conducted subgroup analysis.

For continuous variables like maternal age, the functional form was determined by Akaike information criterion (AIC)- the smaller the AIC value, the better the model fitted. We also evaluate linearity in the logit regression using indicator variables, generalized linear models, or other flexible form to see natural distribution of data.

For Specific aim 2, we modeled the outcome in two ways, as MSEL subscale and composite score were reported as linear, but a below average cognitive function was identified in SEED. First, we fit a logistic regression to below average cognitive function using the covariate set in ASD and POP children separately. By modelling the outcome as a dichotomous variable, we were able to make it easier to interpret the results to the general population with more typical development. To ensure power, an additional linear regression using linear MSEL subscale or composite score as the outcome was conducted. However, as the MSEL composite score was skewed towards the low tail in children with ASD, our ability to evaluate the relationship between presentation and cognitive development across the range of the distribution was limited due to violation in assumptions about data distribution.[113] As such, we conducted a linear regression on MSEL composite score and subscale score only in the POP children.

Effect modification of gestational age or pre-pregnancy BMI was estimated. For gestational age, we stratified on preterm births and term births, using subgroup analysis. For pre-pregnancy BMI, due to the low prevalence of malpresentation in the study population, we re-

categorized BMI as ‘low/ healthy BMI’ and “overweight/ obese’. For continuous variables like maternal age, the functional form was determined by AIC- the smaller the AIC value, the better the model fitted. We also evaluated linearity in the logit regression using indicator variables, generalized linear models, or other flexible form to see natural distribution of data.

C.6 Sensitivity analysis

A small evaluation of one SEED site with supplemental data showed that maternal education was differently distributed between the participation of POP and ASD groups[114], which could reflect bias in our study. Therefore, we conducted sensitivity analysis to evaluate if maternal education could impact our results, by adding maternal education into the adjustment set and comparing the results.

C.7 Power/ Sample Size

We conducted power calculation using a one-sided Type 1 error rate of $\alpha=0.05$[115, 116]. For the whole population, we had 286 children with malpresentation, 1365 children with ASD, and 1573 POP children. The probability of being exposed was $Pr(X=1)=256/2938=0.097$ and the probability of having the outcome of ASD in the unexposed group was $Pr(Y=1|X=0)=1211/2652=0.45$. Several studies on breech presentation and ASD reported an association with an OR of 1.2 to 2.2 after adjustment. For specific aim 1, at a power of 80%, a minimum detectable odds ratio was around 1.35.

Table 3.5 Statistical power obtained to detect an association with ASD by effect size for malpresentation

Minimum Effect Size	Pr(x=1)	Pr (Y=1lX=0)	Statistical Power
OR=1.1	0.097	0.45	19%
OR=1.2	0.097	0.45	45%
OR=1.3	0.097	0.45	72%
OR=1.35	0.097	0.45	82%
OR=1.4	0.097	0.45	89%
OR=1.5	0.097	0.45	97%
OR=1.6	0.097	0.45	99%
OR=1.7	0.097	0.45	99%
OR=1.8	0.097	0.45	99%

To detect the potential effect modification of gestational age (specific aim 1a), if we treat gestational age as a continuous variable, we used Quanto Power Calculator (Ver 1.2.4) to estimate the study power. Previous studies observed a dose-response-like relationship in which each week of shorter gestation was associated with an increased risk of ASD[117]. Therefore, we conservatively estimated the main effect of malpresentation on ASD to be 1.2, main effect of gestational age on ASD to be 0.9. With our study sample size, the power to detect an interaction at OR=1.4 was 66.5%, and the power to detect an OR=1.5 for the interaction term was 81.6%. If gestational age is categorized as preterm/ term, at a power of 80%, a minimum detectable odds ratio was 1.27 in preterm infants; 1.56 in infants born term.

For specific aim 2, we calculated power for logistic regression when modelling MSEL score as binary outcome. In POP children, 132 children reported having malpresentation, and 180 children had with below average cognitive function, and 1384 children with average or above cognitive function. The probability of being exposed was Pr(X=1)=132/1573=0.084 and the probability of having the outcome of below average cognitive function in the children with

vertex presentation was Pr(Y=1 | X=0)=167/1441=0.12. At a power of 80%, a minimum detectable odds ratio was around 1.9 for POP children.

In children with ASD, we had 154 children with malpresentation, 1073 children with below average cognitive function, and 274 children with average or above cognitive function. The probability of being exposed was Pr(X=1)=154/1362=0.113 and the probability of having the outcome of below average cognitive function in the children with vertex presentation was Pr(Y=1 | X=0)=953/1208=0.80. At a power of 80%, a minimum detectable odds ratio was around 1.7 for children with ASD.

At some effect sizes, the statistical power was below adequate. This is common when studying rare exposures. While we may be limited in making causal inferences at this level, the associations that are detected and patterns in the data can still be very informative.

Table 3.6 Statistical power obtained to detect an association with below average cognitive function in children with ASD or POP children, by effect size for malpresentation

	POP			ASD		
Minimum Effect Size	Pr(x=1)	Pr (Y=1lX=0)	Statistical Power	Pr(x=1)	Pr (Y=1lX=0)	Statistical Power
OR=1.1	0.084	0.12	10%	0.113	0.80	11%
OR=1.2	0.084	0.12	18%	0.113	0.80	21%
OR=1.3	0.084	0.12	28%	0.113	0.80	34%
OR=1.4	0.084	0.12	39%	0.113	0.80	49%
OR=1.5	0.084	0.12	50%	0.113	0.80	64%
OR=1.6	0.084	0.12	60%	0.113	0.80	76%
OR=1.7	0.084	0.12	70%	0.113	0.80	86%
OR=1.8	0.084	0.12	77%	0.113	0.80	92%
OR=1.9	0.084	0.12	84%	0.113	0.80	96%
OR=2.0	0.084	0.12	88%	0.113	0.80	98%

CHAPTER 4. MALPRESENTATION AND AUTISM SPECTRUM DISORDERS IN THE STUDY TO EXPLORE EARLY DEVELOPMENT

A. Background

Autism spectrum disorder (ASD) is characterized by a range of persistent deficits in social communication and interaction across multiple contexts, as well as restricted, repetitive patterns of behavior, interests, or activities. In 2018, the Center of Disease Control and Prevention documented the prevalence of ASD to be 23.0 per 1,000 children in the United States.[3, 4] ASD can result in enormous health and economic burden on individuals with ASD and their families.[7, 8]

ASD is likely a result of complex gene-environment interactions impacting development during gestation and early life.[9-11] The fetal and neonatal periods are critical stages in brain development vulnerable to adverse events. Some epidemiological studies have found sub-optimal labor events, including cesarean delivery, to be risk factors for ASD[17, 18]; however, findings are mixed. Sub-optimal conditions at delivery are complicated and interconnected. It is not clear that observed associations for a given condition of pregnancy such as cesarean delivery are causal, as most studies did not adjust for confounding by the indication for cesarean delivery or other important factors. Upstream indications for cesarean delivery[77, 118] include labor dystocia[119], abnormal fetal heart rate[120, 121], fetal malpresentation[77], and hypertensive disorders during the pregnancy period, each of which has been associated with adverse neurodevelopmental outcomes in the offspring[19, 20, 68].

Malpresentation at delivery, or failure to turn, could be a result of fetal disorders[23, 25], insufficient intrauterine space[26, 27], abnormal maternal thyroid functions[28, 29], or fetal growth restriction[23]. These conditions could also be associated with child neurodevelopment. Thus malpresentation could be an early marker of problems in fetal development that ultimately manifest in ASD during childhood. Yet the association between malpresentation and child neurodevelopment has not been well studied.

Most infants present in a vertex (head down) position at delivery[22]. Fetal malpresentation includes breech (where the buttocks or lower extremity enters the maternal pelvis first) and shoulder, compound, face, and brow presentations[21]; among these, breech presentation is most common[75]. The probability of a fetus turning into a vertex presentation increases as gestation progresses[22] so malpresentation is less common in term births.

Two large registry-based studies suggested malpresentation was associated with adverse fetal development such as congenital anomaly[23, 24] and two other large studies found an association between breech presentation and ASD[31, 32]. Another registry-based study[86] concluded that breech presentation was not associated with ASD, but lacked power due to the low prevalence of ASD and breech presentation. Most studies focused only on breech presentation and have not accounted for the gestational age-dependency of malpresentation.

To address limitations in prior research, we used detailed information on pregnancy, delivery, and the child's ASD diagnosis from the Study to Explore Early Development (SEED) to disentangle associations between malpresentation and ASD, while considering potential effect measure modification by gestational age. Understanding how malpresentation, gestational age, and neurodevelopment interact is crucial to advance our understanding of the etiology of ASD.

B. Methods

B.1 Study population

SEED is a United States-based multi-site, case-control study aimed at identifying risk factors for ASD and other developmental disabilities. Children with potential ASD were ascertained through multiple sources, including early intervention, special education, and related service programs for toddlers and young children in hospitals and health clinics. Potential participants were identified and recruited based on evaluation or treatment for ASD or a related developmental condition from a clinical or special education program. Children enrolled as controls were identified by randomly sampling state vital records of children born in the specified birth date range according to mothers' residence in a study catchment area at delivery.

Children eligible for SEED Phases 1 and 2 were required to have been: 1) born in the study catchment area during the period from 2003 to 2011; 2) between 30-68 months of age during study participation; 3) resident in the multi-county catchment areas of California, Colorado, Georgia, Maryland, North Carolina, or Pennsylvania at the time of the first study contact; and 4) lived with a knowledgeable caregiver (defined as family member or caregiver at least 18 years of age at enrollment who was able to legally consent to the child's participation and birth certificate access, and has resided with and consistently cared for the child since he or she was 6 months of age or younger, and could communicate in English or Spanish in California or Colorado). We restricted this analysis to: singleton children, children whose biological mothers were the caregivers completing the interview (>95% of participants) [35], and children who could be clearly classified into a an ASD case group or population control group (POP) based on completion of the developmental evaluation.

B.2 Case status

All children who participated in the study were initially screened for possible ASD using the social communication questionnaire (SCQ)[122]. All children with a previous indication of ASD and those who screened positive on the SCQ (SCQ score ≥11) received an extensive ASD-specific assessment. Children participated in the Autism Diagnostic Observation Schedule (ADOS) and their caregivers completed the Autism Diagnostic Interview- Revised (ADI-R)[123]. The ADOS/ ADI-R package is a validated and reliable measurement for ASD and is considered the gold standard for ASD diagnosis. The instruments' sensitivity ranges from 86 to 100 percent and specificity with other developmental disabilities is 73 to 100 percent.[105] Classification of ASD for this study required children to meet either 1) ASD criteria on the ADOS algorithms and autism criteria on the ADI-R; or 2) ASD criteria on the ADOS algorithms and one of the three relaxed criteria on the ADI-R[35]. Untestable children or those who refused to complete the ADOS or ADI-R were classified as possible ASD and excluded from this analysis.

Children randomly sampled from birth records who either screened negative on the SCQ (SCQ score <11) or screened positive on the SCQ but did not meet ASD criteria based on ADOS and ADI-R assessments were classified as population controls (POP).

B.3 Exposure

Information regarding presentation at delivery was obtained from multiple sources: medical records for maternal labor and child's delivery, maternal interviews, and birth records. Medical records provided detailed information that allowed us to distinguish breech and other malpresentations, but other sources did not. Malpresentation at the time of delivery was identified based on the medical records when available (77%); when medical record was not available, presentation was classified from maternal interviews (7%) or birth records (17%). We

found strong agreement for breech presentation between maternal interviews and medical records (κ=0.61, 95% CI: 0.53, 0.69) and similar agreement for overall malpresentation between medical records and birth records (κ=0.57, 95% CI: 0.49, 0.66). Final classification of presentation at delivery was vertex and malpresentation, with malpresentation subgroups of breech presentation and other malpresentations.

B.4 Covariates

We used a directed acyclic graph (DAG) to identify potential confounders based on review of the literature[19, 108-110]. For potential confounding, the minimally sufficient adjustment covariate set included maternal age, smoking, hypertensive disorders of pregnancy, and the family poverty index. Maternal age at delivery was derived from birth records. Maternal smoking was categorized as 'ever smoked during pregnancy', using information from maternal interviews. Indications of hypertensive disorders included pre-existing chronic hypertension, pregnancy-induced hypertension, preeclampsia, eclampsia, and HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets) from maternal interviews and medical records. Poverty index was derived by applying the federal thresholds to parent reported income during 12 months prior to child's birth from maternal interview. Poverty index was categorized into 4 groups, 'Less than or equal to 138%', 'Greater than 138 to less than or equal to 250', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

We assessed the potential for gestational age at delivery and pre-pregnancy body mass index (BMI) to modify the association between malpresentation and ASD. Infants typically turn before term, thus any malpresentation at or after term may reflect aberrant development during pregnancy. Gestational age at delivery was based on best clinical estimate from birth records and categorized into preterm (<37 weeks) or term (>=37 weeks). Endocrinologic and/or

immunologic correlates of maternal obesity could affect child neurodevelopment[111]. Pre-pregnancy BMI was obtained from medical records and dichotomized to low/ healthy BMI vs overweight/ obese.

Though factors like parity, race, or ethnicity were considered as potential confounders in other studies, they were not included in the covariate set for analysis. Parity was very weakly associated with malpresentation in our sample and not shown to be a risk factor for ASD by results from a recent meta-analysis[18]. The distribution of race and ethnicity was also similar among case and control groups. Race and ethnicity are social constructs that could be a proxy for socioeconomic status and associated with access to healthcare; however, in our study, we had information on household income, which may better capture socioeconomic status and health care access.[112]

B.5 Statistical analysis

We described the distribution of maternal characteristics, delivery and labor details, and the child's development for both ASD and POP groups. We fit logistic regression models to model the probability of ASD compared to POP by fetal presentation, estimating the adjusted odds ratios (ORa) and computed the 95% Wald confidence intervals (CI). We used the minimally sufficient adjustment covariate set. We did not adjust for cesarean delivery to avoid potential bias as it being a descendent of malpresentation[124] (Figure 4.1). We chose the functional form of each covariate with the smallest Akaike information criterion (AIC) value. Model diagnostic plots were also used to check the model performance.

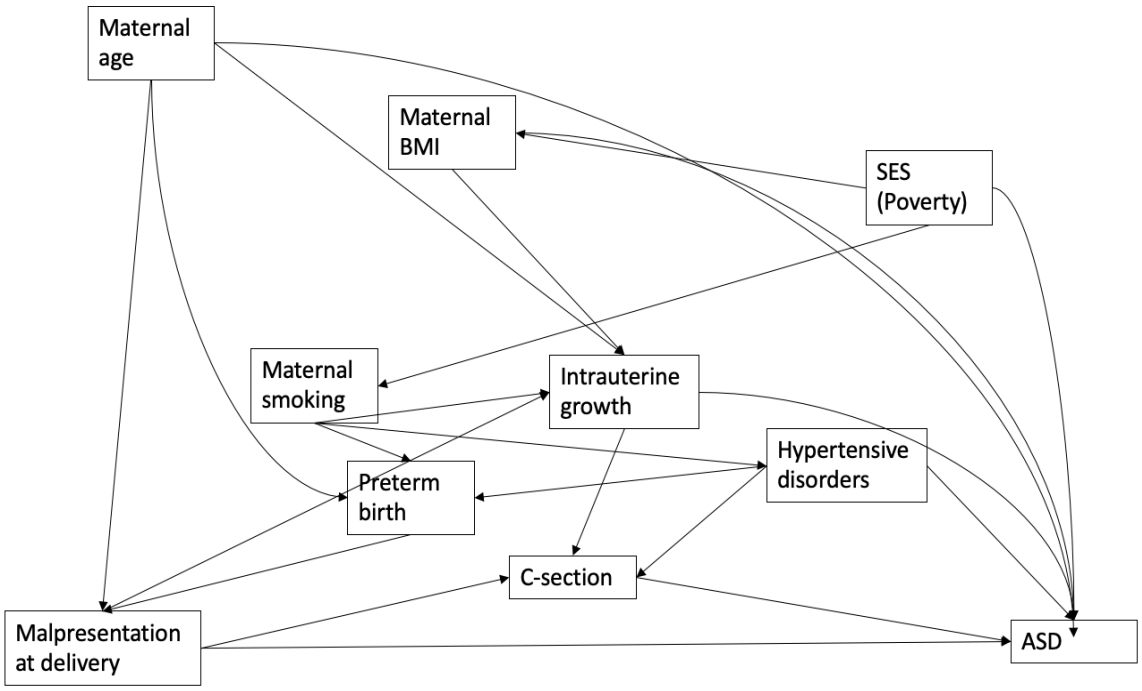


Figure 4.1 DAG on malpresentation and ASD

To further distinguish the effect of breech from other malpresentations, we analyzed the association between malpresentation and ASD separately for breech presentation and other malpresentation. We used stratified models to examine the potential for the association between malpresentation and ASD to be modified by preterm or pre-pregnancy BMI.

Finally, because one SEED site with supplemental data found that maternal education was differently distributed in the participation of POP and ASD groups, and may lead to participation or selection bias[114], we conducted sensitivity analyses to evaluate the potential for maternal education to impact our results.

B.6 Multiple imputation on missing data

Missing data for individual variables included: poverty (3.9%), maternal smoking (1.3%), maternal hypertensive disorders (0.4%), pre-pregnancy BMI (3.1%), and gestational age (0.4%). Because cumulative missing was 9.1%, we assumed missing at random and conducted multiple imputations (chained equations with a logistic regression imputation model for missing binary data and a multinomial imputation model for missing categorical data). We generated 20 independent imputed datasets. All analyses were conducted in SAS v9.4 software (SAS Institute, Inc., Cary, NC, USA).

B.7 Ethics approval

The study was approved by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill, Chapel Hill, United States of America (No. 21-1775). The SEED study was approved by the Institutional Review Board of the US Centers for Disease Control and Prevention as well as that of each participating site.

C. Results

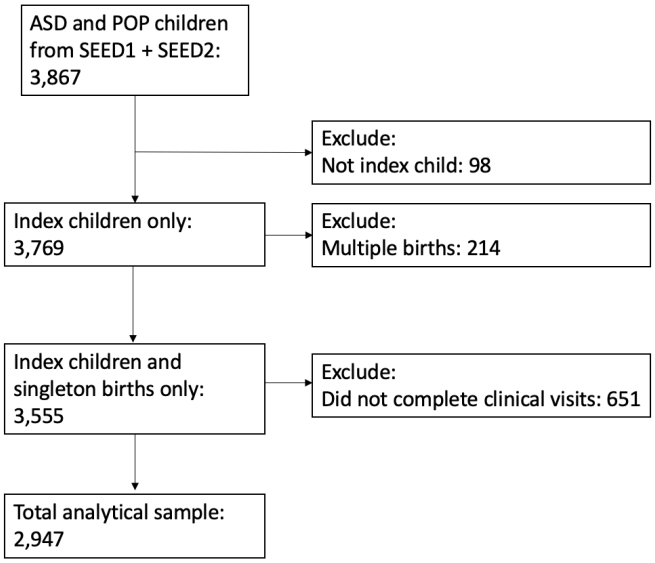


Figure 4.2 Study flowchart

From the total SEED sample (n = 3,867), we included 2,947 participants in our analysis (Figure 4.2), 1,371 with ASD and 1,576 as population controls (POP). Overall, 59.3% mothers were 30-39 years old at delivery, and the proportion was higher among mothers with children with ASD (Table 4.1). Most mothers were college graduates or higher, 60% were Non-Hispanic White, and 18.0% were Non-Hispanic Black. Most families had above or equal to 400% of the ratio of total household pre-tax income to poverty threshold in the year before pregnancy.

Compared to the POP group, fewer mothers of children with ASD had a college degree or above, had higher income, or were non-Hispanic White; and more were overweight or obese before pregnancy, reported smoking during pregnancy or having a hypertensive disorder. More children with ASD were delivered preterm (<37 weeks) than from the POP group.

Most children were vertex at the time of delivery. Malpresentation at delivery occurred more frequently among children with ASD compared to POP and more children with ASD were delivered by cesarean delivery compared to POP children.

More children with malpresentation were non-Hispanic White, especially among POP controls. Children with ASD and malpresentation were more likely to be preterm and also have mothers reporting smoking, pre-pregnancy obesity or hypertensive disorders. Most children with a non-vertex/malpresentation were delivered by cesarean delivery, with 64 (91.4%) of children presenting breech delivered by cesarean.

Table 4.1 Maternal and child characteristics among infant presentation in SEED from 2003 to 2011 (N=2938, Missing =9 for fetal presentation)

	ASD Cases N=1365 (%)			POP Controls N=1573 (%)			Total n=2938 (%)		
	Malpresen-tation n= 154	Vertex n= 1211	Total	Malpresen-tation n= 132	Vertex n= 1441	Total	Malpresen-tation n= 286	Vertex n= 2652	Total
Maternal age (years)									
<20	1 (0.7)	28 (2.3)	29 (2.1)	3 (2.3)	43 (3.0)	46 (2.9)	4 (1.4)	71 (2.7)	75 (2.6)
20-29	51 (33.1)	439 (36.3)	490 (35.9)	44 (33.3)	434 (30.1)	478 (30.4)	95 (33.2)	873 (32.9)	968 (33.0)
30-39	86 (55.8)	680 (56.2)	766 (56.1)	76 (57.6)	899 (62.4)	975 (62.0)	162 (56.6)	1579 (59.5)	1741 (59.3)
40 and above	16 (10.4)	64 (5.3)	80 (5.9)	9 (6.8)	65 (4.5)	74 (4.7)	25 (8.7)	129 (4.9)	154 (5.2)
Missing	0	0	0	0	0	0	0	0	0
Maternal education									
≥College	65 (42.2)	637 (52.6)	702 (51.5)	93 (70.5)	978 (67.9)	1071 (68.1)	158 (55.2)	1615 (60.9)	1773 (60.4)
Some college	61 (39.6)	351 (29.0)	412 (30.2)	21 (15.9)	290 (20.1)	311 (19.8)	82 (28.7)	641 (24.2)	723 (24.6)
≤High school	28 (18.2)	222 (18.4)	250 (18.3)	18 (13.6)	172 (11.9)	190 (12.1)	46 (16.1)	394 (14.9)	440 (15.0)
Missing	0	1	1	0	1	1	0	2	2
Maternal race/ ethnicity									
Non-Hispanic, White	85 (55.2)	601 (49.7)	686 (50.3)	93 (70.5)	982 (68.2)	1075 (68.4)	178 (62.2)	1583 (59.7)	1761 (60.0)

N=2938, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

*: Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%' and 'Greater than or equal to 400%'.

	ASD Cases N=1365 (%)			POP Controls N=1573 (%)			Total n=2938 (%)		
	Malpresen-tation n= 154	Vertex n= 1211	Total	Malpresen-tation n= 132	Vertex n= 1441	Total	Malpresen-tation n= 286	Vertex n= 2652	Total
Non-Hispanic, Black or African American	28 (18.2)	285 (23.6)	313 (23.0)	21 (15.9)	195 (13.5)	216 (13.7)	49 (17.1)	480 (18.1)	529 (18.0)
Hispanic	25 (16.2)	170 (14.1)	195 (14.3)	8 (6.1)	136 (9.4)	144 (9.2)	33 (11.5)	306 (11.6)	339 (11.6)
Non-Hispanic, American Indian or Alaska Native	0	2 (0.2)	2 (0.2)	0	1 (0.1)	1 (0.1)	0	3 (0.1)	3 (0.1)
Asian or Pacific Islander	11 (7.1)	110 (9.1)	121 (8.9)	7 (5.3)	82 (5.7)	89 (5.7)	18 (6.3)	192 (7.3)	210 (7.2)
Non-Hispanic, >1 Race	5 (3.3)	42 (3.5)	47 (3.5)	3 (2.3)	44 (3.1)	47 (3.0)	8 (2.8)	86 (3.3)	94 (3.2)
Missing	0	1	1	0	1	1	0	2	2
Poverty*									
≤ 138%	28 (18.4)	223 (19.3)	251 (19.2)	16 (12.3)	175 (12.6)	191 (12.6)	44 (15.6)	398 (15.6)	442 (15.6)
139 - 250%	16 (10.5)	157 (13.6)	173 (13.2)	8 (6.2)	118 (8.5)	126 (8.3)	24 (8.5)	275 (10.8)	299 (10.6)

N=2938, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

*: Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%' and 'Greater than or equal to 400%'.

	ASD Cases N=1365 (%)			POP Controls N=1573 (%)			Total n=2938 (%)		
	Malpresen -tation n= 154	Vertex n= 1211	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2652	Total
251-399%	24 (15.8)	206 (17.8)	230 (17.6)	16 (12.3)	232 (16.7)	248 (16.3)	40 (14.2)	438 (17.2)	478 (16.9)
400%									
≥ 400%	84 (55.3)	569 (49.3)	653 (50.0)	90 (69.2)	866 (62.3)	956 (62.9)	174 (61.7)	1435 (56.4)	1609 (56.9)
Missing	2	56	58	2	50	52	4	106	110
Pre-pregnancy BMI									
Low BMI	2 (1.3)	42 (3.6)	44 (3.3)	4 (3.1)	48 (3.4)	52 (3.4)	6 (2.1)	90 (3.5)	96 (3.4)
Healthy BMI	72 (47.7)	586 (50.3)	658 (50.0)	71 (54.2)	859 (61.1)	930 (60.5)	143 (50.7)	1445 (56.2)	1588 (55.6)
Overweight	39 (25.8)	287 (24.6)	326 (24.8)	31 (23.7)	312 (22.2)	343 (22.3)	70 (24.8)	599 (23.3)	669 (23.4)
Obese	38 (25.2)	251 (21.5)	289 (21.9)	25 (19.1)	188 (13.4)	213 (13.9)	63 (22.3)	439 (17.1)	502 (17.6)
Missing	3	45	48	1	34	35	4	79	83
Maternal smoking									
Yes	28 (18.3)	131 (10.9)	159 (11.8)	9 (6.9)	85 (6.0)	94 (6.0)	37 (13.0)	216 (8.2)	253 (8.7)
No	125 (81.7)	1067 (89.1)	1192 (88.2)	122 (93.1)	1341 (94.0)	1463 (94.0)	247 (87.0)	2408 (91.8)	2655 (91.3)
Missing	1	13	14	1	15	16	2	28	30
Maternal hypertensive disorder									

N=2938, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

*: Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%' and 'Greater than or equal to 400%'.

	ASD Cases N=1365 (%)			POP Controls N=1573 (%)			Total n=2938 (%)		
	Malpresen-tation n= 154	Vertex n= 1211	Total	Malpresen-tation n= 132	Vertex n= 1441	Total	Malpresen-tation n= 286	Vertex n= 2652	Total
Yes	35 (22.7)	214 (17.7)	249 (18.3)	21 (15.9)	191 (13.3)	212 (13.5)	56 (19.6)	405 (15.3)	461 (15.7)
No	119 (77.3)	993 (82.3)	1112 (81.7)	111 (84.1)	1247 (86.7)	1358 (86.5)	230 (80.4)	2240 (84.7)	2470 (84.3)
Missing	0	4	4	0	3	3	0	7	7
Gestational age									
Preterm	29 (18.8)	131 (10.9)	160 (11.8)	16 (12.2)	102 (7.1)	118 (7.5)	45 (15.8)	233 (8.8)	278 (9.5)
Term	125 (81.2)	1072 (89.1)	1197 (88.2)	115 (87.8)	1335 (92.9)	1450 (92.5)	240 (84.2)	2407 (91.2)	2647 (90.5)
Missing	0	8	8	1	4	5	1	12	13
Parity (including index child)									
1 previous livebirth	90 (60.0)	575 (50.0)	665 (50.8)	66 (51.2)	638 (45.7)	704 (46.2)	156 (55.9)	1213 (47.5)	1369 (48.3)
2 previous livebirths	41 (27.3)	385 (33.3)	426 (32.6)	33 (25.6)	520 (37.3)	553 (36.3)	74 (26.5)	905 (35.4)	979 (34.6)
≥3 previous livebirths	19 (12.7)	198 (17.1)	217 (16.6)	30 (23.3)	238 (17.1)	268 (17.6)	49 (17.6)	436 (17.1)	485 (17.1)
Missing	4	53	57	3	45	48	7	98	105
Delivery mode									

N=2938, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

*: Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%' and 'Greater than or equal to 400%'.

	ASD Cases N=1365 (%)			POP Controls N=1573 (%)			Total n=2938 (%)		
	Malpresen-tation n= 154	Vertex n= 1211	Total	Malpresen-tation n= 132	Vertex n= 1441	Total	Malpresen-tation n= 286	Vertex n= 2652	Total
Vaginal	49 (31.8)	805 (66.5)	854 (62.6)	34 (25.8)	1065 (74.0)	1099 (69.9)	83 (29.0)	1870 (70.5)	1953 (66.5)
Cesarean delivery	105 (68.2)	406 (33.5)	511 (37.4)	97 (73.5)	375 (26.0)	472 (30.0)	202 (70.6)	781 (29.5)	983 (33.5)
Breech extraction	0	0	0	1 (0.8)	0	1 (0.1)	1 (0.4)	0	1 (0.0)
Missing	0	0	0	0	1	1	0	1	1
Birthweight (grams)									
Mean (SD)	3033.0 (897.2)	3317.7 (623.8)	3285.7 (665.8)	3256.4 (730.6)	3372.3 (560.4)	3362.6 (577.2)	3136.4 (830.4)	3347.4 (590.6)	3326.9 (621.0)
Median	3175.0	3345.0	3345.0	3373.0	3401.9	3401.9	3316.9	3374.0	3373.0
Missing	2	10	12	1	8	9	3	18	21
Child sex									
Male	122 (79.2)	994 (82.1)	1116 (81.8)	62 (47.0)	756 (52.5)	818 (52.0)	184 (64.3)	1750 (66.0)	1934 (65.8)
Female	32 (20.8)	217 (17.9)	249 (18.2)	70 (53.0)	685 (47.5)	755 (48.0)	102 (35.7)	902 (34.0)	1004 (34.2)
Missing	0	0	0	0	0	0	0	0	0
Birthweight z-score[125]									
Male (n=1934)									

N=2938, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

*: Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%' and 'Greater than or equal to 400%'.

	ASD Cases N=1365 (%)			POP Controls N=1573 (%)			Total n=2938 (%)		
	Malpresen -tation n= 154	Vertex n= 1211	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2652	Total
Mean	-0.23	-0.08	-0.10	-0.12	-0.02	-0.03	-0.20	-0.05	-0.07
Median	-0.17	-0.07	-0.09	-0.28	0.00	-0.01	-0.18	-0.04	-0.07
Missing	2	16	18	0	8	8	2	24	26
Female (n=1004)									
Mean	-0.35	-0.08	-0.12	0.11	0.00	0.01	0.03	-0.02	-0.02
Median	-0.38	-0.08	-0.12	0.09	-0.02	-0.02	-0.08	-0.04	-0.04
Missing	0	1	1	2	4	6	2	5	7

N=2938, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

*: Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%' and 'Greater than or equal to 400%'.

Table 4.2 Malpresentation at delivery and odds ratio of ASD in ASD and POP children in SEED, Birth years 2003-2011

	ASD n (%)	POP n (%)	Odds ratio	Confidence interval	CLR
Vertex	1211 (88.7)	1441 (91.6)	1.00	-	
Malpresentation	154 (11.3)	132 (8.4)	1.36	1.06, 1.74	1.65
Breech	75 (5.5)	70 (4.5)	1.28	0.91, 1.80	1.98
Other malpresentation	79 (5.8)	62 (3.9)	1.45	1.02, 2.06	2.00

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking;
CLR: Confidence limit ratio

Malpresentation at the time of delivery was associated with a higher odds of ASD (ORa 1.36, 95% CI: 1.06, 1.74) (Table 4.2). The association was similar when examining breech presentation (ORa: 1.28, 95%CI: 0.91, 1.80) separately from other malpresentation (ORa: 1.45; 95% CI: 1.02, 2.06), with a higher point estimate for other malpresentation.

Table 4.3 Malpresentation at delivery and odds ratio of ASD, separately among subgroups of preterm and term births comparing ASD and POP children in the US, 2003, 2011

	ASD n (%)	POP n (%)	Odds ratio	Confidence interval	CLR
Term					
Vertex	1072 (89.6)	1335 (92.1)	1.00	-	
Malpresentation	125 (10.4)	115 (7.9)	1.32	1.01, 1.74	1.72
Breech	52 (4.3)	56 (3.9)	1.17	0.79, 1.73	2.19
Other Malpresentation	73 (6.1)	59 (4.1)	1.49	1.04, 2.13	2.05
Preterm					
Vertex	131 (81.9)	102 (86.4)	1.00	-	
Malpresentation	29 (18.1)	16 (13.6)	1.40	0.70, 2.79	3.97
Breech	23 (14.4)	13 (11.0)	1.38	0.65, 2.96	4.56
Other malpresentation	6 (3.8)	3 (2.5)	NEP	NA	NA

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking
NEP: no OR estimate presented due to small number of cases
NA: Not applicable
CLR: Confidence limit ratio

We stratified the analysis by term status (Table 4.3). For all malpresentations together, the association between malpresentation and ASD was similar among preterm and term births. When we further evaluated breech presentation separately from other malpresentations, among term births, the association for other malpresentation and ASD was similar as that for breech; but results were very imprecise among preterm births. We did not find the association to be markedly different by pre-pregnancy BMI overall or when breech presentation was separated from other malpresentation (Table 4.4). Additional adjustment for maternal education did not change the results for the overall association between malpresentation and ASD (ORa: 1.33, 95%

CI: 1.04, 1.72). The education-adjusted results were also similar for subgroup analysis of gestational age and maternal pre-pregnancy BMI (Supplemental Table 4.3).

Table 4.4 Breech and other malpresentations at delivery and odds ratio of ASD, within subgroups of pre-pregnancy BMI in ASD and POP children in the US, 2003, 2011

	ASD n (%)	POP n (%)	Odds ratio	Confidence interval	CLR
Low or healthy BMI					
Vertex	628 (89.5)	907 (92.4)	1.00	-	
Malpresentation	74 (10.5)	75 (7.6)	1.43	1.02, 2.00	1.98
Breech	35 (5.0)	36 (3.7)	1.49	0.92, 2.40	2.61
Other malpresentation	39 (5.6)	39 (4.0)	1.38	0.87, 2.19	2.52
Overweight or obese					
Vertex	538 (87.5)	500 (89.9)	1.00	-	
Malpresentation	77 (12.5)	56 (10.1)	1.22	0.84, 1.78	2.12
Breech	39 (6.3)	33 (5.9)	1.02	0.62, 1.67	2.68
Other malpresentation	38 (6.2)	23 (4.1)	1.53	0.89, 2.64	2.96

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking
CLR: confidence limit ratio

D. Comment

D.1 Principal findings

Overall, we found that malpresentation at delivery was associated with a 36%-increased odds of ASD. This association was constant across gestational age and pre-pregnancy BMI. When further separating breech presentation and other malpresentation, the associations were similar, but potentially stronger for other malpresentation and ASD, than for breech.

D.2 The association between malpresentation and ASD

Limited literature is available on the association between malpresentation and ASD and is mainly focused on breech presentation. The findings we report here are consistent with most previous studies[31, 32, 92]. In a nested case-control study among 8-year-olds born in 1994 in Utah[31] that included 132 cases of ASD and 13,200 matched controls, researchers reported an association between breech presentation and ASD. In a Danish nested case-control study[32] among children between 1973 and 1999 that included 698 children with ASD and 25 controls per case, the authors also reported an association between breech presentation and ASD. Finally, in a cohort study of 218,890 singleton live births from 1998 to 2015 in Canada[92], researchers reported a crude risk ratio of 1.31 for the association between breech presentation and ASD. Another Danish registry study[86] reported an autism risk of 1.47 for infants presenting as back of head and 1.89 for 'other' malpresentation, with no information about precision, which they interpreted as showing no association. However, these risk estimates were in line with both the current study and other previous studies.

Several upstream determinants of malpresentation could be associated with child neurodevelopment, such as maternal hormones or fetal disorders. Distinguishing the potential influence of these factors on the development of ASD might be helpful in future studies.

However, SEED did not have information on maternal hormone levels or fetal disorders to allow us to distinguish the potential influence of these underlying factors on ASD.

We found an association between other malpresentations and ASD, with a higher point estimate compared to the association among children with breech presentation. In our study population, nearly all children with a breech presentation were delivered by cesarean; however, approximately half of children with malpresentation other than breech were delivered by cesarean. When comparing subgroups of vaginal delivery and cesarean delivery, we found a stronger association among non-vertex children born by a vaginal delivery (See supplemental tables 4.1 and 4.2). Vaginal delivery of non-vertex infants can be challenging and convey injury[126]. The Term Breech Trial in 2000 demonstrated a decreased risk of perinatal and neonatal mortality, or serious morbidity, with planned cesarean delivery compared with vaginal delivery for breech presentation[127, 128]; and caesarean rates for breech presentation increased substantially after publication of that trial. However, little published information is available regarding developmental risks associated with mode of delivery for other malpresenting babies. Like breech, other malpresentation is associated with a lower Apgar score at 1 and 5 minutes[129] and could be associated with a higher risk of neonatal asphyxia[130] if delivered vaginally. Malpresentation, as well as complications resulting from delivering malpresenting children vaginally, deserve additional consideration as potential risk factors for ASD. Malpresentation could be among multiple factors upstream of cesarean delivery that could be associated with ASD[17, 18].

D.2.1 Effect measure modification by gestational age

We did not find evidence that preterm status modified the association between malpresentation and ASD, but had limited power to explore associations across gestational age. In a trial of vaginal breech delivery for preterm delivery, researchers found no increase in risk of neurodevelopmental outcomes among extremely preterm and very preterm gestations with breech presentation; but among moderate to late preterm births, breech was associated with an increased risk of ASD compared to children born in cephalic presentation[131]. The study used the Finland Medical Birth Register and the Hospital Discharge Register with the information on all surgical procedures and diagnoses in inpatient care and outpatient care using ICD codes. However, because of the low prevalence of extremely preterm and very preterm, breech presentation, and ASD, the study results were very imprecise and should be interpreted with caution. Larger studies are needed to explore this important question.

D.2.2 Effect measure modification by pre-pregnancy BMI

In the subgroup analysis, pre-pregnancy BMI did not modify the association between malpresentation with ASD. Other studies have reported that higher pre-pregnancy BMI, especially overweight and obesity, could be a sign of maternal hormonal dysregulation and child inflammatory biomarkers[132-134]. For example, isolated thyroid autoimmunity, a maternal thyroid dysfunction, was associated with gestational diabetes mellitus[135] and a higher pre-pregnancy BMI[136]. Maternal thyroid dysfunction, as studies have suggested[28, 29], could prevent the fetus from turning to a vertex presentation, and could also impact the child's neurodevelopment[137]. However, BMI is an imperfect biomarker of maternal thyroid hormone dysregulation or other hormonal dysregulation that could impact a child neurodevelopment. Alternately, BMI might have an impact on fetal presentation through a different mechanism due to small uterine space.

BMI is correlated with uterine size[138] and failure to turn is associated with intra-uterine space[26, 27], thus the association between malpresentation and ASD could differ for those with mothers of low-BMI. In our study, we did not have evidence that pre-pregnancy BMI modified the association between malpresentation and ASD. However, such modification might only show in extreme cases like low pre-pregnancy BMI or obesity, which we were underpowered to examine. Future research powered to separate different BMI groups is needed.

D.3 Strengths

This study improves on previous investigations in several ways. SEED conducted standardized high-quality evaluation of ASD using gold standard assessment tools to confirm developmental status. SEED also collected detailed information on obstetric conditions, as well as health information on the infant's health at and after delivery. Many prior registry-based studies lacked confirmation of ASD diagnosis and details on potential confounding factors. SEED's detailed data provided confidence in ASD classification and allowed control for critical covariates, like maternal smoking and hypertensive disorders. Information on malpresentation was available in multiple sources; we prioritized information from the medical records because medical records are considered a more valid source for delivery information compared to birth records.[106, 139, 140] But, we also evaluated the quality of each source and found the agreement between sources was generally high; thus, we expect the bias due to misclassification of conditions related to labor and delivery to be small. Our results were robust to the adjustment sets, and was not strongly biased by differential participation by maternal education.

D.4 Limitations

The ability to draw clear inferences from this investigation has some limitations. First, while we had robust adjustment for confounding, the potential remains for residual confounding by unmeasured upstream factors that might cause malpresentation, lead to cesarean delivery, and may also be associated with ASD. Medical records were collected 3-5 years after the child's birth from numerous hospital systems and were not available for all children (missing rate approximately 30%). The maternal interview was conducted 3-5 years after pregnancy and subject to recall bias, thus data on obstetric complications and the specificity of the malpresentation may be incomplete. Moreover, due to the small sample with malpresentation and preterm delivery, we did not have sufficient power to identify the potential for effect measure modification by gestational age or pre-pregnancy BMI.

E. Conclusions

Malpresentation at delivery was modestly associated with ASD in these data. While prior reports have focused on the association between cesarean and ASD, these data suggest that factors upstream of cesarean delivery, like malpresentation or its antecedents, could be contributing to that association with ASD. Future well-powered studies should explore whether gestational age or pre-pregnancy BMI modifies these association, and whether malpresentation is a risk factor or an early sign of aberrant fetal development– perhaps resulting from other underlying endogenous and exogenous influences during pregnancy. Despite the need for additional research, early monitoring of neurodevelopment among children born with malpresentation could identify children with ASD sooner and enhance opportunities for early intervention.

Supplement tables and materials

The majority of our investigation focused on whether malpresentation was associated with ASD. However, as much of previous literature focused on the association between cesarean delivery and ASD, readers interested in ASD may be interested to know whether the association between malpresentation and ASD differs by vaginal delivery and cesarean delivery. While most (91%) breech presentations were delivered by cesarean delivery, precluding examination of differences by mode of delivery. However, among those with other malpresentations, 45% were delivered by cesarean delivery, allowing comparison by mode of delivery. From supplement Tables 4.1 and 4.2, we observed a stronger association between malpresentation and ASD among children born by vaginal delivery (ORa: 1.93, 95% CI: 1.23, 3.05) than by cesarean delivery (ORa: 0.97, 95% CI: 0.70, 1.33). These differences could support concerns that malpresentation delivered vaginally could cause brain injury and later development delay[141, 142]. However, we acknowledge that stratifying on mode of delivery, which temporally occurs after malpresentation at delivery, may introduce bias to our study results and extra caution is necessary for causal interpretation.

Supplement table 4.1 Malpresentation at delivery and odds ratio of ASD, among vaginal delivery, within subgroups of preterm and pre-pregnancy BMI in ASD and POP children in the US, 2003-2011

	ASD (n, %)	POP	OR	Confidence interval	CLR
vertex	805 (84.3)	1065 (96.9)	1.00	-	
malpresentation	49 (5.7)	34 (3.1)	1.93	1.23, 3.05	2.49
Gestational age					
Term					
Vertex	772 (94.0)	999 (96.8)	1.00	-	
malpresentation	46 (6.0)	33 (3.2)	1.93	1.21, 3.08	2.55
Preterm					
Vertex	78 (96.3)	62 (98.4)	1.00	-	
Malpresentation	3 (3.7)	1 (1.6)	3.00	0.29, 31.10	107.44
Pre-pregnancy BMI					
Low or healthy BMI					
Vertex	453 (94.8)	715 (96.5)	1.00	-	
Malpresentation	25 (5.2)	26 (3.5)	1.49	0.84, 2.64	3.14
Overweight or obese					
Vertex	317 (93.2)	323 (97.6)	1.00	-	
Malpresentation	23 (6.8)	8 (2.4)	3.05	1.32, 7.01	5.30

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking

Supplemental table 4.2 Malpresentation at delivery and odds ratio of ASD, among cesarean delivery, within subgroups of preterm and pre-pregnancy BMI in ASD and POP children in the US, 2003-2011

	ASD (n, %)	POP	OR	Confidence interval	CLR
vertex	406 (79.5)	375 (79.5)	1.00	-	
malpresentation	105 (20.6)	97 (20.6)	0.97	0.70, 1.33	1.88
Gestational age					
Term					
Vertex	350 (81.6)	335 (80.5)	1.00	-	
malpresentation	79 (18.4)	81 (19.5)	0.90	0.63, 1.28	2.02
Preterm					
Vertex	53 (67.1)	40 (72.7)	1.00	-	
Malpresentation	26 (32.9)	15 (27.3)	1.35	0.62, 2.98	4.85
Pre-pregnancy BMI					
Low or healthy BMI					
Vertex	175 (78.1)	192 (79.7)	1.00	-	
Malpresentation	49 (21.9)	49 (20.3)	1.43	1.02, 2.00	1.97
Overweight or obese					
Vertex	221 (80.4)	177 (79.0)	1.00	-	
Malpresentation	54 (19.6)	47 (21.0)	1.11	0.70, 1.73	2.46

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking

Supplemental table 4.3 Malpresentation at delivery and odds ratio of ASD, among all modes of delivery in ASD and POP children in the US, 2003, 2011, considering potential bias by maternal education

Birth presentation	ASD n (%)	POP n (%)	ORa*	Confidence interval	CLR
vertex	1211 (88.7)	1441 (91.6)	1.00	-	
malpresentation	154 (11.3)	132 (8.4)	1.33	1.04, 1.72	1.65
Gestational age					
Term					
Vertex	1072 (89.6)	1335 (92.1)	1.00	Referent	
malpresentation	125 (10.4)	115 (7.9)	1.29	0.99, 1.70	1.73
Preterm					
Vertex	131 (81.9)	102 (86.4)	1.00	Referent	
Malpresentation	29 (18.1)	16 (13.6)	1.39	0.69, 2.77	3.99
Pre-pregnancy BMI					
Low or healthy BMI					
Vertex	628 (89.5)	907 (92.4)	1.00	Referent	
Malpresentation	74 (10.5)	75 (7.6)	1.42	1.01, 2.00	1.98
Overweight or obese					
Vertex	538 (87.5)	500 (89.9)	1.00	Referent	
Malpresentation	77 (12.5)	56 (10.1)	1.20	0.82, 1.75	2.12

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, maternal education, and maternal smoking

CHAPTER 5. MALPRESENTATION AT DELIVERY AND COGNITIVE FUNCTION IN THE STUDY TO EXPLORE EARLY DEVELOPMENT

A. Background

The probability of a fetus being in vertex presentation increases with gestational age,[22] and the prevalence of malpresentation (a presentation other than vertex) is nearly 25% among preterm infants. The fetus starts to turn head down around 32 weeks, and only 3-4% remain non-vertex at term[22, 76]. Many factors could result in a fetus' failure to turn at the proper gestational age, such as fetal disorders[23, 25], insufficient intrauterine space[26, 27], maternal thyroid dysfunction[28, 29], or fetal growth restriction[23]. These conditions, especially maternal hormonal dysfunction and fetal disorders, could also be associated with child neurodevelopment[143, 144].

Neurodevelopment begins in early pregnancy[12] and can be affected by prenatal and perinatal factors. Previous studies have found that complications during pregnancy like hypertensive disorders are associated with child cognitive function[15, 16]. Fetal malpresentation includes breech, shoulder, compound, face, and brow presentations[21]; among them, breech presentation is the most common form of malpresentation.[75] Malpresentation, specifically breech presentation, is an indication for primary cesarean delivery[77] and may also be associated with the infant's neurodevelopment[19, 20, 68], but the research focusing on malpresentation and cognitive function has been limited. Results of the few studies focused on malpresentation and subsequent cognitive function have been inconclusive- some reported that malpresentation was associated with cognitive impairment while some did not find an association[33, 34, 93, 94]. Important limitations

of the extant literature included lack of adjustment for important confounders such as maternal hypertensive disorders, as well as stratifying on factors that are not confounders such as cesarean delivery, which could potentially introduce bias. The prevalence of malpresentation changes across gestational weeks, thus the association between malpresentation and neurodevelopment may vary by gestational age. Moreover, all studies were conducted outside of the United States and dated, which may not reflect modern clinical practices during labor and delivery or measures of neurodevelopmental outcomes. Finally, a variety of measurements have been used to assess cognitive function, including academic achievement, which is only modestly correlated with cognitive function, and can be affected by factors like social or economic factors[145] . We used the rich data from the Study to Explore Early Development (SEED) to evaluate the associations between malpresentation and cognitive function.

B. Methods

B.1 Study population

SEED was designed as a multi-site, case-control study in the United States conducted to identify factors that may put children at risk for ASD and other developmental disabilities. For this analysis, the primary investigation is focused on the relationship between malpresentation and cognitive function among children sampled from the general population (POP); however, we also investigate the association among children with ASD.

POP children were identified by randomly sampling state vital records of children born in the specified birth date range to mothers' resident in a study catchment area at delivery. Children with potential ASD were ascertained through multiple sources, including early intervention, special education, and related service programs for toddlers and young children from hospitals and health clinics. Children eligible for SEED Phases 1 and 2 were required to

have been: 1) born in the study catchment area during the period from 2003 to 2011; 2) between 30-68 months of age during study participation; 3) resident in the multi-county catchment areas of California, Colorado, Georgia, Maryland, North Carolina, or Pennsylvania at the time of the first study contact; and 4) lived with a knowledgeable caregiver (defined as family member or caregiver at least 18 years of age at enrollment who was able to legally consent to the child's participation and birth record access; has resided with and consistently cared for the child beginning on or before age 6 months of age; and could communicate in English or Spanish (only in California or Colorado).

Our study is nested within the larger SEED case-control study. Specifically, we restricted this analysis to the singleton children whose biological mothers were the caregiver completing the interview (>95% of participants) [35], and excluded siblings of the index children and children who could not be clearly classified into an ASD case group or POP based on completion of the developmental evaluation.

B.2 Outcome measurement: cognitive function

Cognitive function was measured using the Mullen Scales of Early Learning (MSEL) (Mullen, 1995; 1995 AGS/Pearson Version). MSEL is a standardized assessment that is commonly used in clinical psychology to measure cognitive development and has been demonstrated to be an effective tool to measure the cognitive and developmental functioning for children with neurodevelopmental concerns.[58, 99, 146] In SEED, research-reliable clinicians administered the 4 MSEL subscales to children with 30 to 68 months of age that comprise the composite score: fine motor, visual reception (or non-verbal problem solving), receptive language, and expressive language[35]. The subscale age-standardized t-scores were reported as mean of 50 and standard deviation of 10. For young children this early learning composite score

is considered equivalent to a more traditional IQ score or a developmental standard score.[97] The MSEL composite standard score was age-standardized and was reported as standard scores with a mean of 100 and SD of 15[95]. SEED also derived MSEL composite categories as: very high, above average, average, below average, and very low. We combined the original MSEL composite categories to create two MSEL composite categories. Children who had very high, above average, and average cognitive function were re-categorized as 'average and above cognitive function'; children with below average or very low MSEL composite score were re-categorized as 'below average cognitive function'.

Because the original goals of the SEED study were to examine risk factors for ASD, all children who participated in the study were screened for possible ASD using the Social Communication Questionnaire (SCQ)[122]. Children who were randomly sampled from population birth records and either screened negative on the SCQ (SCQ score <11) or screened positive on the SCQ but did not meet ASD criteria based on ADOS and ADI-R assessments were classified as POP.

All children with a previous diagnosis of ASD from a community provider and those who screened positive on the SCQ (SCQ ≥11) received an extensive ASD-specific assessment. Children participated in the Autism Diagnostic Observation Schedule (ADOS) for children and their caregivers completed the Autism Diagnostic Interview- Revised (ADI-R)[123] . The ADOS/ ADI-R package is a validated and reliable measurement for ASD and is considered the gold standard for ASD diagnosis.[105] Children met final classification of ASD for this study by meeting either 1) ASD criteria on the ADOS algorithms and autism criteria on the ADI-R; or 2) ASD criteria on the ADOS algorithms and one of the three relaxed criteria on the ADI-R.

Untestable children or those who did not complete the ADOS or ADI-R were classified as possible ASD and excluded from this analysis.

B.3 Exposure assessment: Malpresentation

Information regarding presentation at delivery was obtained from multiple sources: medical records for maternal labor and child's delivery, maternal interviews, and birth records. Medical records are considered a more valid source for delivery information compared to birth records.[106, 139, 140] Malpresentation at the time of delivery was based on the medical records when available (77%); when medical record is not available, the presentation was classified by report from maternal interviews (7%) or on the birth records (17%). We found the agreement for breech presentation between maternal interviews and medical records to be κ=0.61, (95% CI: 0.53, 0.69) and similar agreement for overall malpresentation between medical records and birth records (κ=0.57, 95% CI: 0.49, 0.66). The final classification of presentation at delivery included vertex and malpresentation, with the malpresentation subgroups of breech presentation and other malpresentations.

B.4 Covariates

We used a directed acyclic graph (DAG) to identify potential confounders based on a review of the literature. For potential confounding, the minimally sufficient adjustment covariate set included maternal age, smoking, hypertensive disorders of pregnancy, and the family poverty index. Maternal age at delivery was derived from birth records. Maternal age was categorized as '<29 years', '30-39 years', and '≥ 40 years'. Maternal smoking was categorized as 'ever smoked during pregnancy', using information from maternal interviews. Hypertensive disorders were identified from maternal interviews and medical records, including conditions of pre-existing chronic hypertension, pregnancy-induced hypertension, preeclampsia, eclampsia, and HELLP

syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets). We derived the poverty index by calculating the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138%', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

Gestational age at delivery was based on best clinical estimate noted in birth records. Gestational age was categorized into preterm (<37 weeks completed gestation) or term birth (>=37 weeks completed gestation). We evaluated the potential for associations to be modified by gestational age (term/preterm). We also evaluated the potential for pre-pregnancy BMI to modify the association between malpresentation and cognitive function, because endocrinologic and/or immunologic are associated with maternal obesity[111, 132-134, 137] and could affect child neurodevelopment. Pre-pregnancy BMI was derived from medical records.

Though factors like parity, race, or ethnicity could be considered potential confounders, they were not included in the covariate set for analysis for the following reasons. Parity was weakly associated with malpresentation and was not associated with cognitive function in our study population; moreover, parity was not shown to be a risk factor for developmental delay in a recent meta-analysis[18]. The distributions of race and ethnicity were similar between malpresentation and vertex presentations in the general sample (POP children). We also note that race and ethnicity are social constructs that could be a proxy for socioeconomic status and be associated with access to healthcare. In this study, we had information on household income, which is another strong indicator of socioeconomic status and health care access.[112]

B.5 Statistical analysis

We first described the distribution of maternal characteristics, delivery and labor details, MSEL composite and subscale t-scores for children in the ASD and POP groups. Since children with ASD are likely to have cognitive impairment[13] and the distribution of MSEL composite score was skewed in ASD children in our population, all analyses were conducted separately for the ASD and POP groups. We fit logistic regression models to estimate the probability of below average cognitive function in relation to presentation at delivery, estimating the adjusted odds ratios (ORa) and 95% Wald confidence intervals (CI). Moreover, as MSEL composite standard score is normally distributed among children without identified neurodevelopment delays, we estimated the effect of malpresentation on change in the continuous MSEL score and 95% Wald CI by fitting linear regression models and estimating 95% Wald CI. We adjusted for maternal age, smoking, hypertensive disorders of pregnancy, and the family poverty index, and did not adjust for caesarean delivery because cesarean delivery is a descendant of malpresentation and could mediate the association between malpresentation and cognitive function according to the DAG informed by our literature review (Figure 5.1). For linear regression model, as child biological sex at birth is strongly associated with cognitive function[42], we additionally adjusted for child sex. The functional form of each covariate was determined by Akaike information criterion (AIC)- the smaller the AIC value, the better the model fits. Model diagnostic plots were also used to check the model performance.

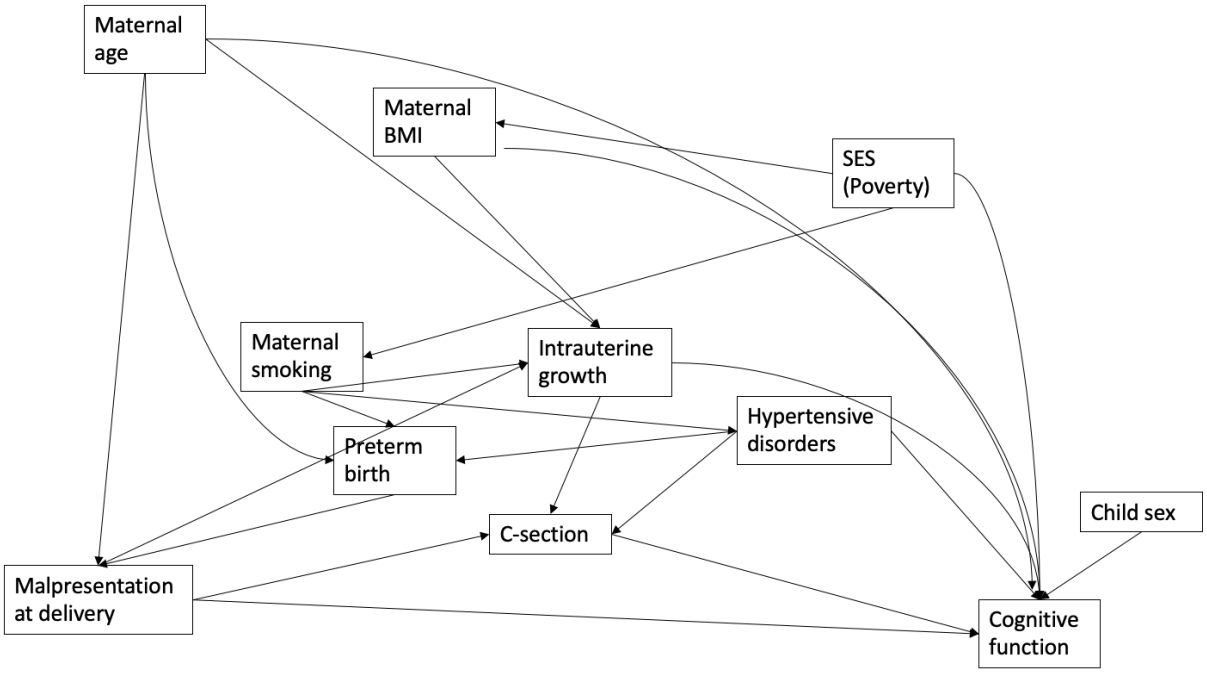


Figure 5.1 DAG for malpresentation and cognitive function

We examined the potential for gestational age to modify the association between malpresentation and cognitive function by stratifying on term births and preterm births (subgroup analysis). We also analyzed the potential modification of the association by pre-pregnancy BMI by stratifying on pre-pregnancy BMI groups (collapsed to low/ healthy BMI vs overweight/ obese because of small samples in more refined BMI categories). Finally, we conducted a sensitivity analysis to determine whether our results were sensitive to additional adjustment for maternal education, which was identified as a factor associated with participation in one site in SEED[114].

Missing data for individual variables included: MSEL score (0.8%), poverty (3.9%), maternal smoking (1.3%), maternal hypertensive disorders (0.4%), pre-pregnancy BMI (3.1%), and gestational age (0.4%). Because cumulative missing was 9.9%, we used multiple imputation

(chained equations with a logistic regression imputation model for missing binary data and a multinomial imputation model for missing categorical data) to impute the missing data. We utilized m=20 imputation datasets. This technique assumes data was missing at random, an assumption that appeared to be supported by descriptive analyses. All analyses were completed using with SAS v9.4 software (SAS Institute, Inc., Cary, NC, USA).

B.6 Ethics approval

The study was approved by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill, Chapel Hill, United States of America (No. 21-1775). SEED was approved by the Institutional Review Board of the US Centers for Disease Control and Prevention as well as that of each participating site.

C. Results

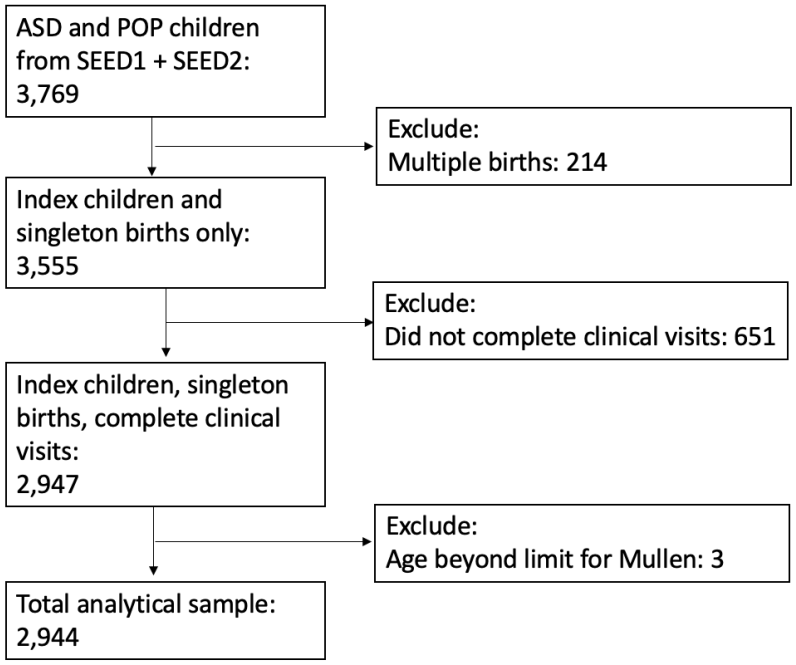


Figure 5.2 Study flowchart

Among the total SEED population (n = 3,769), we included 2,944 participants into our analysis (Figure 5.2): 1,368 children with ASD and 1,576 POP children. Information on presentation at delivery was available for 2,935 children (2,649 [90.2%] vertex presentation and 286 [9.7%] malpresentation, with 145 breech presentation and 141 malpresentation other than breech presentation). Table 5.1 showed the distribution of infants' malpresentation across demographic and health-related variables. For the 651 patients who did not complete clinical visits, the distribution of malpresentation was similar to the study sample (29 children with malpresentation, 5.7%).

Table 5.1 Child cognitive function among infant presentation in SEED from 2003 to 2011*

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen-tation n= 154	Vertex n= 1208	Total	Malpresen-tation n= 132	Vertex n= 1441	Total	Malpresen-tation n= 286	Vertex n= 2649	Total
Cognitive function Category									
Very high	1 (0.7)	3 (0.3)	4 (0.3)	9 (6.8)	62 (4.3)	71 (4.5)	10 (3.5)	65 (2.5)	75 (2.6)
Above average	0	13 (1.1)	13 (1.0)	27 (20.5)	245 (17.1)	272 (17.4)	27 (9.5)	258 (9.8)	285 (9.8)
Average	30 (19.9)	227 (18.9)	257 (19.1)	83 (62.9)	958 (66.9)	1041 (66.6)	113 (39.9)	1185 (45.0)	1298 (44.6)
Below average	27 (17.9)	192 (16.1)	219 (16.3)	7 (5.3)	121 (8.5)	128 (8.2)	34 (12.0)	313 (11.9)	347 (11.9)
Very low	93 (61.6)	761 (63.6)	854 (63.4)	6 (4.6)	46 (3.2)	52 (3.3)	99 (35.0)	807 (30.7)	906 (31.1)
Missing	3	12	15	0	9	9	3	21	24
Cognitive function (binary)									
Average and above	31 (20.5)	243 (20.3)	274 (20.3)	119 (90.2)	1265 (88.3)	1384 (88.5)	150 (53.0)	1508 (57.4)	1658 (57.0)
Below average	120 (79.5)	953 (79.7)	1073 (79.7)	13 (9.9)	167 (11.7)	180 (11.5)	133 (47.0)	1120 (42.6)	1253 (43.0)
Missing	3	12	15	0	9	9	3	21	24
MSEL composite score									
Mean (SD)	67.1 (19.0)	66.6 (19.7)	66.7 (19.6)	103.7 (18.0)	103.2 (15.8)	103.3 (16.0)	84.2 (26.1)	86.6 (25.4)	86.3 (25.5)

N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen -tation n= 154	Vertex n= 1208	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2649	Total
median	62.0	59.0	59.0	105.0	104.0	104.0	87.0	92.0	91.0
Q1: Q3	49.0: 81.0	49.0: 81.0	49.0: 81.0	93.5: 117.0	94.0: 113.0	94.0: 113.0	58.0: 105.0	61.0: 106.0	61.0: 106.0
Min: max	49.0: 132.0	49.0: 132.0	49.0: 132.0	49.0: 139.0	49.0: 149.0	49.0: 149.0	49.0: 139.0	49.0: 149.0	49.0: 149.0
Missing	3	12	15	0	9	9	3	21	24
Visual reception t-score									
Mean (SD)	36.0 (15.7)	34.7 (15.4)	34.8 (15.5)	52.1 (11.8)	52.4 (10.1)	52.4 (10.2)	43.4 (16.1)	44.3 (15.5)	44.2 (15.6)
median	35.0	31.0	31.0	53.0	53.0	53.0	47.0	47.0	47.0
Q1: Q3	20.0: 48.0	20.0: 47.0	20.0: 47.0	44.5: 59.0	45.0: 58.0	45.0: 59.0	29.0: 55.0	33.0: 56.0	32.0: 56.0
Min: max	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0
Missing	1	6	7	0	7	7	1	13	14
Fine motor t-score									
Mean (SD)	29.4 (11.5)	29.6 (11.7)	29.6 (11.7)	50.0 (12.0)	49.9 (10.1)	49.9 (10.2)	39.0 (15.6)	40.7 (14.8)	40.5 (14.9)
median	25.0	23.0	24.0	49.0	49.0	49.0	39.0	43.0	43.0
Q1: Q3	20.0: 37.0	20.0: 39.0	20.0: 39.0	44.0: 58.0	43.0: 56.0	43.0: 56.0	20.0: 49.0	25.0: 53.0	25.0: 52.0
Min: max	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0	20.0: 80.0
Missing	3	7	10	0	7	7	3	14	17
Receptive language t-score									
Mean (SD)	30.9 (12.8)	30.1 (13.0)	30.2 (13.0)	52.1 (11.8)	52.3 (10.8)	52.3 (10.9)	40.8 (16.3)	42.2 (16.2)	42.1 (16.2)
median	24.0	21.0	22.0	54.0	53.0	53.0	43.0	44.0	44.0

N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen -tation n= 154	Vertex n= 1208	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2649	Total
Q1: Q3	20.0: 43.0	20.0: 39.0	20.0: 39.0	44.0: 60.0	46.0: 60.0	46.0: 56.0	20.0: 54.0	24.0: 54.0	24.0: 54.0
Min: max	20.0: 65.0	20.0: 73.0	20.0: 73.0	20.0: 74.0	20.0: 80.0	20.0: 80.0	20.0: 74.0	20.0: 80.0	20.0: 80.0
Missing	3	10	13	0	8	8	3	18	21
Expressive language t-score									
Mean (SD)	29.0 (10.9)	29.2 (11.5)	29.2 (11.4)	52.4 (10.5)	51.4 (10.3)	51.5 (10.3)	39.9 (15.9)	41.3 (15.5)	41.2 (15.5)
median	24.0	23.0	23.0	53.5	52.0	52.0	40.0	43.0	43.0
Q1: Q3	20.0: 36.0	20.0: 37.0	20.0: 37.0	46.0: 60.0	45.0: 58.0	45.0: 58.0	20.0: 54.0	25.0: 54.0	25.0: 54.0
Min: max	20.0: 60.0	20.0: 74.0	20.0: 74.0	20.0: 71.0	20.0: 80.0	20.0: 80.0	20.0: 71.0	20.0: 80.0	20.0: 80.0
Missing	3	10	13	0	9	9	3	19	22

N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

Table 5.2 Maternal and infant characteristic among fetal presentation in SEED, 2003-2011

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen-tation n= 154	Vertex n= 1208	Total	Malpresen-tation n= 132	Vertex n= 1441	Total	Malpresen-tation n= 286	Vertex n= 2649	Total
Maternal age (years)									
<20	1 (0.7)	28 (2.3)	29 (2.1)	3 (2.3)	43 (3.0)	46 (2.9)	4 (1.4)	71 (2.7)	75 (2.5)
20-29	51 (33.1)	438 (36.3)	489 (35.9)	44 (33.3)	434 (30.1)	478 (30.4)	95 (33.2)	872 (32.9)	967 (33.0)
30-39	86 (55.8)	679 (56.2)	765 (56.2)	76 (57.6)	899 (62.4)	975 (62.0)	162 (56.6)	1578 (59.6)	1740 (59.3)
40 and above	16 (10.4)	63 (5.2)	79 (5.8)	9 (6.8)	65 (4.5)	74 (4.7)	25 (8.7)	128 (4.8)	153 (5.2)
Missing	0	0	0	0	0	0	0	0	0
Maternal education									
≥College	65 (42.2)	634 (52.5)	699 (51.4)	93 (70.5)	978 (67.9)	1071 (68.1)	158 (55.2)	1612 (60.9)	1770 (60.4)
Some college	61 (39.6)	351 (29.1)	412 (30.3)	21 (15.9)	290 (20.1)	313 (19.8)	82 (28.7)	641 (24.2)	723 (24.7)
≤High school	28 (18.2)	222 (18.4)	250 (18.4)	18 (13.6)	172 (11.9)	190 (12.1)	46 (16.1)	394 (14.9)	440 (15.0)
Missing	0	1	1	0	1	1	0	2	2

*: N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

**Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen -tation n= 154	Vertex n= 1208	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2649	Total
Maternal race/ ethnicity									
Non-Hispanic, White	85 (55.2)	599 (49.6)	684 (50.3)	93 (70.5)	982 (68.2)	1075 (68.4)	178 (62.2)	1581 (59.7)	1759 (60.0)
Non-Hispanic, Black or African American	28 (18.2)	284 (23.5)	312 (22.9)	21 (15.9)	195 (13.5)	216 (13.7)	49 (17.1)	479 (18.1)	528 (18.0)
Hispanic	25 (16.2)	170 (14.1)	195 (14.3)	8 (6.1)	136 (9.4)	144 (9.2)	33 (11.5)	306 (11.6)	339 (11.6)
Non-Hispanic, American Indian or Alaska Native	0	2 (0.2)	2 (0.2)	0	1 (0.1)	1 (0.1)	0	3 (0.1)	3 (0.1)
Asian or Pacific Islander	11 (7.1)	110 (9.1)	121 (8.9)	7 (5.3)	82 (5.7)	89 (5.7)	18 (6.3)	192 (7.3)	210 (7.2)
Non-Hispanic, >1 Race	5 (3.3)	42 (3.5)	47 (3.5)	3 (2.3)	44 (3.1)	47 (3.0)	8 (2.8)	86 (3.3)	94 (3.2)

*: N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

**Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen -tation n= 154	Vertex n= 1208	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2649	Total
Missing	0	1	1	0	1	1	0	2	2
Poverty**									
≤ 138%	28 (18.4)	223 (19.3)	251 (19.2)	16 (12.3)	175 (12.6)	191 (12.6)	44 (15.6)	398 (15.6)	442 (15.6)
139 - 250%	16 (10.5)	157 (13.6)	173 (13.3)	8 (6.2)	118 (8.5)	126 (8.3)	24 (8.5)	275 (10.8)	299 (10.6)
251-399%									
400%	24 (15.8)	206 (17.9)	230 (17.6)	16 (12.3)	232 (16.7)	248 (16.3)	40 (14.2)	438 (17.2)	478 (16.9)
≥ 400%	84 (55.3)	567 (49.2)	651 (49.9)	90 (69.2)	866 (62.3)	956 (62.9)	174 (61.7)	1433 (56.3)	1607 (56.9)
Missing	2	55	57	2	50	52	4	105	109
Pre-pregnancy BMI									
Low BMI	2 (1.3)	42 (3.6)	44 (3.4)	4 (3.1)	48 (3.4)	52 (3.4)	6 (2.1)	90 (3.5)	96 (3.4)
Healthy BMI	72 (47.7)	585 (50.3)	657 (50.0)	71 (54.2)	859 (61.1)	930 (60.5)	143 (50.7)	1444 (56.2)	1587 (55.7)
Overweight	39 (25.8)	286 (24.6)	325 (24.7)	31 (23.7)	312 (22.2)	343 (22.3)	70 (24.8)	598 (23.3)	668 (23.4)
Obese	38 (25.2)	250 (21.5)	288 (21.9)	25 (19.1)	188 (13.4)	213 (13.9)	63 (22.3)	438 (17.0)	501 (17.6)
Missing	3	45	48	1	34	35	4	79	83
Maternal smoking									
Yes	28 (18.3)	131 (11.0)	159 (11.8)	9 (6.9)	85 (6.0)	94 (6.0)	37 (13.0)	216 (8.2)	253 (8.7)
No	125 (81.7)	1064 (89.0)	1189 (88.2)	122 (93.1)	1341 (94.0)	1463 (94.0)	247 (87.0)	2405 (91.8)	2652 (91.3)

*: N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

**Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen-tation n= 154	Vertex n= 1208	Total	Malpresen-tation n= 132	Vertex n= 1441	Total	Malpresen-tation n= 286	Vertex n= 2649	Total
Missing	1	13	14	1	15	16	2	28	30
Maternal hypertensive disorder									
Yes	35 (22.7)	213 (17.7)	248 (18.3)	21 (15.9)	191 (13.3)	212 (13.5)	56 (19.6)	404 (15.3)	460 (15.7)
No	119 (77.3)	991 (82.3)	1110 (81.7)	111 (84.1)	1247 (86.7)	1358 (86.5)	230 (80.4)	2238 (84.7)	2468 (84.3)
Missing	0	4	4	0	3	3	0	7	7
Gestational age									
Preterm	29 (18.8)	130 (10.8)	159 (11.7)	16 (12.2)	102 (7.1)	118 (7.5)	45 (15.8)	232 (8.8)	277 (9.5)
Term	125 (81.2)	1070 (89.2)	1195 (88.3)	115 (87.8)	1335 (92.9)	1450 (92.5)	240 (84.2)	2405 (91.2)	2645 (90.5)
Missing	0	8	8	1	4	5	1	12	13
Parity (including index child)									
1 previous livebirth	90 (60.0)	573 (49.6)	663 (50.8)	66 (51.2)	638 (45.7)	704 (46.2)	156 (55.9)	1211 (47.5)	1367 (48.3)
2 previous livebirths	41 (27.3)	385 (33.3)	426 (32.6)	33 (25.6)	520 (37.3)	553 (36.3)	74 (26.5)	905 (35.5)	979 (34.6)

*: N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

**Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen -tation n= 154	Vertex n= 1208	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2649	Total
≥3 previous livebirths	19 (12.7)	197 (17.1)	216 (16.6)	30 (23.3)	238 (17.1)	268 (17.6)	49 (17.6)	435 (17.1)	484 (17.1)
Missing	4	53	57	3	45	48	7	98	105
Delivery mode									
Vaginal	49 (31.8)	802 (66.4)	851 (62.5)	34 (25.8)	1065 (74.0)	1099 (69.9)	83 (29.0)	1867 (70.5)	1950 (66.5)
Cesarean delivery	105 (68.2)	406 (33.6)	511 (37.5)	97 (73.5)	375 (26.0)	472 (30.0)	202 (70.6)	781 (29.5)	983 (33.5)
Breech extraction	0	0	0	1 (0.8)	0	1 (0.1)	1 (0.4)	0	1 (0.0)
Missing	0	0	0	0	1	1	0	1	1
Birthweight (grams)									
Mean (SD)	3033.0 (897.2)	3320.1 (619.8)	3287.8 (662.7)	3256.4 (730.6)	3372.3 (560.4)	3362.6 (577.2)	3136.4 (830.4)	3348.6 (588.6)	3328.0 (619.3)
Median	3175.1	3345.0	3345.0	3373.0	3401.9	3401.9	3316.9	3374.0	3373.0
Missing	2	10	12	1	8	9	3	18	21

*: N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

**Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

	Children with ASD N=1362 (%)			Children from the population (POP) N=1573 (%)			Total n=2935 (%)		
	Malpresen -tation n= 154	Vertex n= 1208	Total	Malpresen -tation n= 132	Vertex n= 1441	Total	Malpresen -tation n= 286	Vertex n= 2649	Total
Birthweight z-score									
Male (n=1934)									
Mean	-0.23	-0.08	-0.10	-0.12	-0.02	-0.03	-0.20	-0.05	-0.07
Median	-0.17	-0.07	-0.09	-0.28	0.00	-0.01	-0.18	-0.04	-0.07
Missing	2	16	18	0	8	8	2	24	26
Female (n=1001)									
Mean	-0.35	-0.08	-0.12	0.11	0.00	0.01	0.03	-0.02	-0.02
Median	-0.38	-0.08	-0.12	0.09	-0.02	-0.02	-0.08	-0.04	-0.04
Missing	0	1	1	2	4	6	2	5	7
Child sex									
Male	122 (79.2)	992 (82.1)	1114 (81.8)	62 (47.0)	756 (52.5)	818 (52.0)	184 (64.3)	1748 (66.0)	1932 (65.8)
Female	32 (20.8)	216 (17.9)	248 (18.2)	70 (53.0)	685 (47.5)	755 (48.0)	102 (35.7)	901 (34.0)	1003 (34.2)
Missing	0	0	0	0	0	0	0	0	0

*: N=2935, Missing =9 for fetal presentation; however, the missing fetal presentation was imputed in the regression analysis.

**Poverty levels: the ratio of parent reported household pre-tax income during the 12 months prior to child's birth and the federal poverty threshold, then categorized poverty relative to the national threshold: 'Less than or equal to 138% ', 'Greater than 138 to less than or equal to 250%', 'Greater than 250 to less than 400%', and 'Greater than or equal to 400%'.

Overall, cognitive function was higher among POP children compared to children with ASD (Table 5.1). The MSEL composite score among POP children was normally distributed with a mean of 103.3 and a standard deviation of 16.0. However, the composite score for ASD children was skewed toward low cognitive function, with a mean and standard deviation of 66.7 and 19.6. Nearly 70% of children with malpresentation were delivered by cesarean section.

Among POP children, 8.4% (n=132) children had malpresentation at delivery. In total, 9.9% of the POP children born with malpresentation had below average cognitive function. POP children with malpresentation had a similar mean MSEL subscale score for visual reception, fine motor, receptive language, and expressive language, compared to POP children with a vertex presentation. Among the POP group who had children with malpresentation, mothers were more likely to report smoking, be overweight or obese before pregnancy, have hypertensive disorders, and deliver preterm or by cesarian section.

Among children with ASD, the prevalence of malpresentation at delivery was 11.3%. The proportion of children with below average cognitive function was similar for children with malpresentation and vertex presentation (79.5% for malpresentation; 79.7% for vertex presentation). Similar to POP children, among children with ASD with malpresentation at delivery, there was a higher prevalence of maternal pre-pregnancy overweight or obesity, maternal smoking, hypertensive disorders, and preterm delivery compared to children with ASD who had a vertex presentation at delivery.

Table 5.3 Malpresentation at delivery and odds ratio of below average cognitive function among POP children in SEED, birth years 2003-2011

	Below average n (%)	>=Average n (%)	Odds Ratio	95% Confidence interval	CLR
vertex	167 (92.8)	1265 (91.4)	1.00	-	
malpresentation	13 (7.2)	119 (8.6)	0.89	0.47, 1.68	3.57
Gestational age					
Term					
vertex	144 (94.1)	1184 (91.8)	1.00	-	
malpresentation	9 (5.9)	106 (8.2)	0.70	0.33, 1.49	4.47
Preterm					
vertex	22 (84.6)	78 (86.7)	1.00	-	
malpresentation	4 (15.4)	12 (13.3)	NEP	NA	NA
Pre-pregnancy BMI					
Low/ healthy BMI					
vertex	87 (92.6)	817 (92.3)	1.00	-	
malpresentation	7 (7.5)	68 (7.7)	0.93	0.39, 2.20	5.64
Overweight/ obese					
vertex	74 (92.5)	422 (89.4)	1.00	-	
malpresentation	6 (7.5)	50 (10.6)	0.83	0.32, 2.15	6.72

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking
NEP: no OR estimate presented due to small number of cases
NA: Not applicable
CLR: Confidence limit ratio

Table 5.4 Malpresentation at delivery and MSEL composite score and subscale t-scores among POP children in SEED, Birth years 2003-2011

	Malpresentation (n)	Vertex (n)	Mean difference (SE)	95% CI	p-value
MSEL Composite	Mean=103.70; n=283	Mean=103.23; n=2628	-0.09 (1.33)	(-2.66, 2.48)	0.95
Gestational age					
Term	Mean=105.28; n=237	Mean=103.53; n=2388	1.20 (1.38)	(-1.50, 3.91)	0.38
preterm	Mean=92.19; n=45	Mean=99.26; n=229	-9.20 (4.02)	(-17.08, -1.32)	0.02
Pre-pregnancy BMI					
Low or healthy BMI	Mean=106.00; n=146	Mean=104.45; n=1525	1.70 (1.70)	(-1.62, 5.02)	0.32
Overweight or obesity	Mean=100.80; n=133	Mean=101.33; n=1026	-2.24 (2.07)	(-6.29, 1.82)	0.28
MSEL Subscale t-score					
Visual reception	Mean=52.05; n=285	Mean=52.38; n=2636	-0.44 (0.89)	(-2.18, 1.30)	0.62
Fine motor	Mean=49.95; n=283	Mean=49.92; n=2635	-0.23 (0.88)	(-1.97, 1.50)	0.79
Receptive language	Mean=52.12; n=283	Mean=52.26; n=2631	-0.52 (0.90)	(-2.28, 1.24)	0.56
Expressive language	Mean=52.36; n=283	Mean=51.40; n=2630	0.58 (0.87)	(-1.12, 2.29)	0.50

All models adjusted for maternal age, poverty level, child sex, maternal hypertensive disorder, and maternal smoking

Among the general sample (POP children), malpresentation at delivery was not associated with below average cognitive function (ORa: 0.89, 95% CI: 0.47, 1.68) when modeled as below average vs average or above. The association among term births was similar to the overall association, and was imprecise for preterm. Despite imprecision, the association was similar across pre-pregnancy BMI groups (Table 5.3). In linear models, malpresentation was not associated with mean MSEL composite score (-0.09, 95% CI: [-2.65, 2.48]) (Table 5.4). Though

imprecise, malpresentation was associated with a lower MSEL composite score among children born preterm (mean change -9.20, 95% CI: -17.08, -1.32). None of the changes in subdomain scores were associated with malpresentation.

Table 5.5 Malpresentation at delivery and odds ratio of below average cognitive function in children with ASD in SEED, with subgroups of term and preterm births, birth years 2003-2011

	Below average n (%)	>=Average n (%)	Odds ratio	Confidence interval	CLR
vertex	956 (88.9)	243 (88.7)	1.00	-	
malpresentation	120 (11.2)	31 (11.3)	1.00	0.66, 1.54	2.34
Gestational age					
Term					
vertex	842 (89.7)	220 (89.8)	1.00	-	
malpresentation	97 (10.3)	25 (10.2)	1.03	0.64, 1.65	2.56
Preterm					
vertex	108 (82.4)	22 (78.6)	1.00	-	
malpresentation	23 (17.6)	6 (21.4)	NEP	NA	NA
Pre-pregnancy BMI					
Low or healthy BMI					
vertex	469 (88.8)	153 (92.7)	1.00	-	
malpresentation	59 (11.2)	12 (7.3)	1.65	0.87, 3.14	3.60
Overweight/ obese					
vertex	445 (88.5)	87 (82.1)	1.00	-	
malpresentation	58 (11.5)	19 (17.9)	0.61	0.34, 1.20	3.24

All models adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking
NEP: no OR estimate presented due to small number of cases
NA: Not applicable
CLR: Confidence limit ratio

Among children with ASD, results generally indicated no association between malpresentation and the probability of below average cognitive function, either overall or in

subgroups of gestational age or pre-pregnancy BMI. Models additionally adjusted for maternal education produced similar results (Supplemental Table 5.1).

D. Discussion

D.1 The association between malpresentation and cognitive function

In this study of children living in 6 states in the US, we explored whether malpresentation at delivery was associated with below average cognitive function measured by MSEL among children 3-5 years of age. Overall, we did not find evidence that malpresentation at delivery was associated with cognitive function, either for the general population or among children with ASD. Our results are largely consistent with the limited existing literature; yet limited study power does not allow complete dismissal of the probability of failing to detect an underlying association between malpresentation and cognitive function in our study.

The limited existing research on malpresentation and cognitive function is focused only on breech presentation and inconclusive. Two studies[93, 94] reported results similar to ours, that breech presentation was not associated with cognitive deficiency. One study[93] only focused on children born at an early gestational age. The study enrolled singleton infants without congenital malformations born from 27 to 32 completed weeks of gestation in France in 1997 and followed children's cognitive development up to 8 years of age using ICD diagnosis and/ or Kaufman Assessment Battery for Children. This study followed children born preterm, when non-vertex fetal position is more common, and reported no association after applying multiple adjustment sets. Another study[94] used data from birth records from all live singleton births (both term and preterm) in Western Australia between January 1984 and December 1999. After adjusting for

birth year and sociodemographic factors, they found no association between breech presentation and intellectual disability.

In contrast, a Danish study[33] enrolled 4,298 males born between 1973 and 1976 and reported an association between breech presentation and cognitive function, based on the Boerge Prien IQ test. The study also stratified on mode of delivery. In another study of 456,947 children[34], the researchers measured education attainment and linked three Scotland-wide administrative databases (annul school census, examinations database, and maternal database) at the individual level. The study was restricted to singleton children, born at term, attending Scottish schools between 2006 and 2011. They reported a lower examination attainment among children born by a vaginal breech delivery compared to those born by either planned cesarean section for breech presentation or vaginal cephalic delivery. The difference of the study results compared to our study may result from the different measurements of cognitive function, our inclusion of malpresentation other than breech, and comparisons to different reference groups (not stratified by cesarean).

Moreover, previous studies[33, 34, 93, 94] varied in their inclusion of different gestational ages at delivery, which could contribute to inconsistency in results across studies. Only one study[94] included both term and preterm births; the studies by Mackay et al.[34] and by Sorenson et al.[33] only focused on term births, and the study by Azria et al.[93] was restricted to children with a gestational age of 27 to 32 weeks, and reported no association while adjusting for gestational age. The prevalence of malpresentation was different across gestational age, due to the continuous change in fetal position in the uterus during pregnancy.[22] Before the 25th week, the fetal presentation changes frequently and malpresentation at this time does not affect the probability of malpresentation at delivery at a later gestational age. From 25 to 35 gestational

week, the incidence of vertex presentation increases, and the probability of malpresentation is inversely associated with gestational age. After the 36th week, the probability of vertex and malpresentation changes in favor of vertex presentation. It is important to consider the potential for the association to be modified by gestational age, because malpresentation early in gestation may not be associated with poor cognitive function. While we tried to explore this question, due to the low prevalence of preterm and malpresentation, the results were very imprecise. Therefore, larger studies are needed to explore this important question.

A variety of assessments are used to measure cognitive function in young children, making it difficult to compare results across studies[96]. In the general population, IQ is relatively stable across the lifespan, and school-aged IQs is a good predictor of adult cognitive function[147, 148]. However, psychometric intelligence tests are usually administered to older children[149]. In our study, children were young (30-68 months of age); the MSEL is a well-validated assessment tool for this age group[96]. Studies also have shown that MSEL composite scores at age 2 were predictive of IQ at age 6[150]. Still many prior studies focused on developmental measures among older children, which can provide a more stable assessment of IQ.

Among children with ASD, there is wide variability in verbal and cognitive abilities. Limited social interaction and communication skills further interfere with the accurate assessment of a young child with ASD's cognitive abilities.[58] Normal tests IQ are frequently invalid for the assessment of children with very low IQ, as the development and standardization samples rarely include substantial representation of this segment of the population.[99] The MSEL has been widely used to measure cognitive function among children with developmental delays because of its potential to capture uneven development in different cognitive abilities[151]. Many studies of children with ASD use the MSLE as its primary measure of cognition.[100] In our study,

the MSEL score was much lower in children with ASD, compared to POP children, which was consistent with prior literature[13].

All the previous studies focused on breech presentation. After the Term Breech Trial[128], most with breech presentation were delivered by cesarean. Cesarean delivery is a descendent of malpresentation and could be on the causal pathway from malpresentation to cognitive function. As illustrated in our DAG, stratifying on cesarean delivery could introduce collider stratification bias.[124] As such, though the previous two studies[33, 34] had the power to stratify on mode of delivery, the results be confounded by over adjusting for the descendent of exposure, or a potential intermediate[124].

D.2 Strengths and limitations

This study improves on previous investigations in several ways. SEED conducted standardized high-quality evaluation of neurodevelopment using validated assessment tools for young children and collected detailed information on obstetric conditions.[35] The MSEL has good internal, test-retest, and interrater reliabilities.[98] The MSEL provides a standardized assessment of the child's cognitive function allowing more generalized comparison than academic metrics. Information on malpresentation was available from multiple sources, including medical records.[106, 139, 140] As we found moderate agreement between sources on malpresentation, we expect any potential bias due to misclassification of malpresentation to be small. Though sources like medical records may not be complete for all children, we were able to fill in missing data from additional sources and use multiple imputation to address potential selection bias introduced by missingness. While we had robust adjustment for confounding, the potential remains for uncontrolled confounding by variables that were not collected in the study,

especially maternal thyroid dysfunction, which could be associated with child malpresentation[29], although results from prior studies remain unclear[152, 153].

E. Conclusions

Malpresentation at delivery was not associated with cognitive function, either among children sampled from the general population or children with ASD in this sample. However, the potential association between malpresentation and cognitive function among children from general sample who were born preterm warrants further research. We had no evidence that malpresentation is associated with or be a sign of concern regarding children's early cognitive function, and may not increase the possibility of cognitive delay in early age in most births. Future well-powered studies are warranted to explore whether gestational age or pre-pregnancy BMI modifies these association.

Supplemental tables

Supplemental Table 5.1 Malpresentation and below average cognitive function in SEED population, additionally adjusting for by maternal education.

MSEL scores			
POP			
Scores	Mean difference	Standard error	95% CI
MSEL composite	0.00	1.28	(-2.50, 2.52)
Visual reception	-0.42	0.88	(-2.14, 1.30)
Fine motor	-0.20	0.90	(-1.93, 1.52)
Receptive language	-0.44	0.87	(-2.15, 1.28)
Expressive language	0.65	0.85	(-1.02, 2.32)

Below average cognitive function	OR	Confidence interval	CLR
POP			
vertex	1.00	-	
malpresentation	0.83	0.43, 1.60	3.70
ASD			
vertex	1.00	-	
malpresentation	0.94	0.61, 1.45	2.37

All models adjusted for maternal age, poverty level, maternal education, maternal hypertensive disorder, and maternal smoking (Linear regression additionally adjusted for child sex)

CHAPTER 6. CESAREAN DELIVERY AND ASD

In Chapter 4, we examined the association between malpresentation and ASD and found that malpresentation was moderately associated with ASD. As previously mentioned, we were originally interested in malpresentation because it is the upstream of cesarean delivery, which has been found to be consistently and moderately associated with ASD in previous studies[17, 18]. However, most studies did not consider the potential confounding by the indication of malpresentation, which would likely bias their results. In previous chapters, we did not investigate the association between cesarean delivery and ASD as it was not the association of interest. However, the association between cesarean delivery and ASD in the SEED population remains of interest because of concerns raised in the literature. In particular, we would like to explore if cesarean delivery is associated with ASD after adjusting for potential indication, to reduce the bias by confounding by indication. As such, we further explored the association between cesarean delivery and ASD in our study population.

A. Methods

A.1 Identify mode of delivery

Mode of delivery was available in maternal interviews, medical records, and birth records. Among those children with both data sources available, we found almost perfect agreement for delivery method (κ=0.99 95% CI 0.99, 1.00 between maternal interview and medical record; κ=0.94 95% CI 0.93, 0.96 between birth record and medical record). We

prioritized the medical records to identify deliveries by cesarean delivery, then used information from birth records and maternal interviews to fill in missingness (n=684, 23.3%).

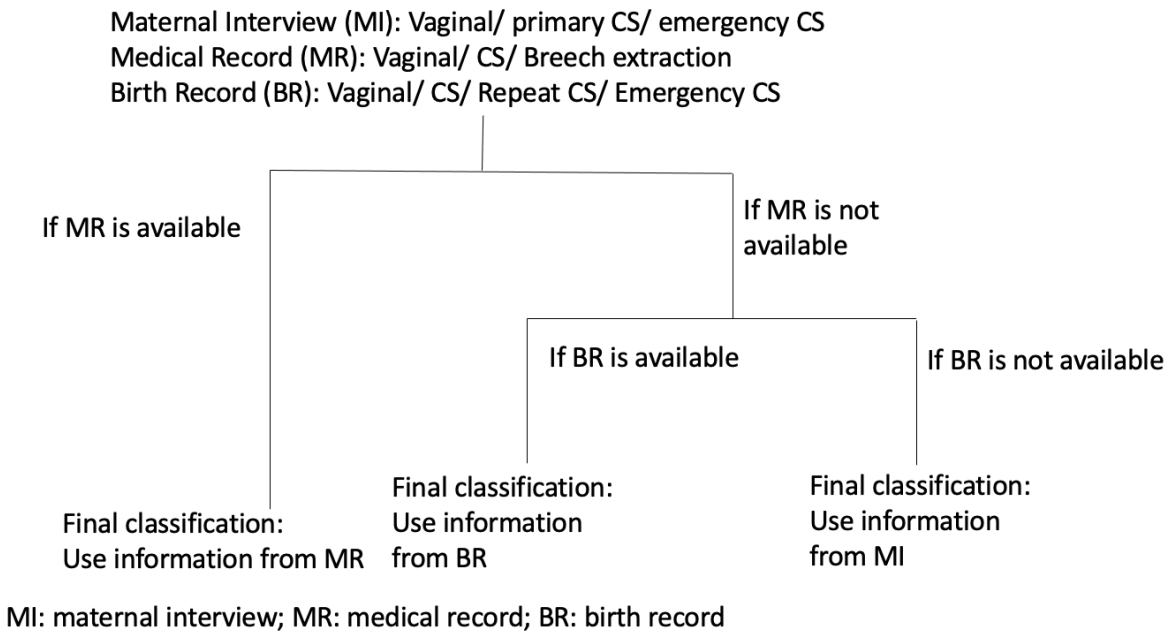


Figure 6.1 Final classification of mode of delivery

We fit logistic regression models to model the probability of ASD by the mode of delivery, estimating the adjusted odds ratios (ORa) and 95% Wald confidence intervals (CI). In examining the association between cesarean delivery and ASD, we further controlled for child malpresentation in order to control for confounding by indication.

Table 6.1 Cesarean delivery and odds ratio of ASD within subgroups of gestational age and pre-pregnancy BMI in ASD and POP children in the US, 2003-2011

			Adjusted model 1			Adjusted model 2		
	ASD	POP	OR	Confidence interval	CLR	OR	Confidence interval	CLR
Vaginal	856 (62.4)	1101 (69.9)	1.00	-		1.00	-	
CS	515 (37.6)	473 (30.0)	1.40	1.20, 1.65	1.38	1.36	1.15, 1.61	1.39
Gestational age								
Term								
Vaginal	769 (64.0)	1034 (71.3)	1.00	-		1.00	-	
CS	433 (36.0)	417 (28.7)	1.43	1.21, 1.70	1.40	1.40	1.17, 1.66	1.42
Preterm								
Vaginal	82 (51.0)	63 (53.4)	1.00	-		1.00	-	
CS	79 (49.0)	55 (46.6)	1.03	0.62, 1.71	2.77	0.94	0.54, 1.62	2.98
Pre-pregnancy BMI								
Low or healthy BMI								
Vaginal	478 (68.1)	741 (75.5)	1.00	-		1.00	-	
CS	224 (31.9)	241 (24.5)	1.47	1.18, 1.83	1.55	1.43	1.14, 1.79	1.58
Overweight or obese								
Vaginal	340 (55.3)	331 (59.6)	1.00	-		1.00	-	
CS	275 (44.7)	224 (40.4)	1.23	0.96, 1.57	1.63	1.19	0.93, 1.52	1.65

Adjust model 1: adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking

Adjust model 2: adjusted for maternal age, poverty level, maternal hypertensive disorder, maternal smoking, and malpresentation

Table 6.2 Cesarean delivery and odds ratio of ASD, among vertex presentation, within subgroups of gestational age and pre-pregnancy BMI in ASD and POP children in the US, 2003-2011

	ASD	POP	OR	Confidence interval	CLR
Vaginal	805 (66.5)	1065 (74.0)	1.00	-	
CS	406 (33.5)	375 (26.0)	1.46	1.22, 1.73	1.38
Gestational age					
Term					
Vaginal	722 (67.4)	999 (74.9)	1.00	-	
CS	350 (32.7)	335 (25.1)	1.50	1.25, 1.80	1.44
Preterm					
Vaginal	78 (59.5)	62 (60.8)	1.00	-	
CS	53 (40.5)	40 (39.2)	0.99	0.56, 1.74	3.10
Pre-pregnancy BMI					
Low or healthy BMI					
Vaginal	453 (73.1)	715 (78.8)	1.00	-	
CS	175 (27.9)	192 (21.2)	1.47	1.15, 1.87	1.62
Overweight or obese					
Vaginal	317 (58.9)	323 (64.6)	1.00	-	
CS	221 (41.1)	177 (35.4)	1.32	1.02, 1.72	1.69

All adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking

Table 6.3 Cesarean delivery and odds ratio of ASD, among malpresentation, within subgroups of gestational age and pre-pregnancy BMI in ASD and POP children in the US, 2003-2011

	ASD	POP	OR	Confidence interval	CLR
Vaginal	49 (31.8)	34 (30.0)	1.00	-	
CS	105 (68.2)	97 (74.1)	0.67	0.39, 1.16	2.97
Gestational age					
Term					
Vaginal	46 (36.8)	33 (29.0)	1.00	-	
CS	79 (63.2)	81 (71.1)	0.65	0.37, 1.15	3.13
Preterm					
Vaginal	3 (10.3)	1 (6.3)	1.00	-	
CS	26 (89.7)	15 (93.8)	NEP	NA	NA
Pre-pregnancy BMI					
Low or healthy BMI					
Vaginal	25 (33.8)	26 (34.7)	1.00	-	
CS	49 (66.2)	49 (65.3)	1.10	0.54, 2.22	4.11
Overweight or obese					
Vaginal	23 (29.9)	8 (14.6)	1.00	-	
CS	54 (70.1)	47 (85.5)	0.29	0.11, 0.78	7.06

All adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking
NEP: no OR estimate presented due to small number of cases
NA: Not applicable
CLR: Confidence limit ratio

To explore if cesarean delivery was associated with ASD in our study population, we compared children delivered by cesarean delivery to those delivered vaginally (see Table 6.1). We found a moderate association between cesarean delivery and ASD with an ORa of 1.40 (95% CI: 1.20, 1.65). The association was similar among infants born at term (ORa=1.43, 95% CI: 1.21, 1.70), but imprecise among preterm births. Among different BMI groups, the association for cesarean delivery and ASD was stronger among the low and healthy BMI mothers (ORa: 1.47, 95% CI: 1.18, 1.83). Since we previously found an association between malpresentation

and ASD, and malpresentation is a strong indication for cesarean delivery, we further controlled for malpresentation (as confounding by indication) to explore the association between cesarean delivery and ASD. As Table 6.1 demonstrated, the association was similar yet attenuated for all subgroups. When stratifying on child presentation at delivery, a stronger association between cesarean delivery and ASD was observed among children with a vertex presentation at delivery than those with malpresentation.

B. Cesarean delivery indication and obstetric complications

Nearly all children with breech presentation were delivered by cesarean delivery. We also identified obstetric complications that are indications for cesarean delivery in order to reduce bias by indication when evaluating the association between cesarean delivery and ASD.

B.1 Identification of indications for cesarean delivery

We used information from medical records and maternal interviews to collect information on obstetric complications as possible indications for cesarean delivery. Using literature[120, 154] and subject matter knowledge, we categorized the following complications as maternal and delivery related cesarean delivery indications/ complications: active phase arrest, prolonged latent stage, arrest of descent, deep transverse arrest, failure to progress, cholestasis of pregnancy or intrahepatic cholestasis, slow slope active phase, failed trial of labor, vasa previa, uterine rupture, and active genital herpes. Fetal conditions and complications related to cesarean delivery included low Biophysical Profile or non-reassuring fetal testing, macrosomia, fetal distress or intolerance of labor, intra-uterine growth retardation.

B.2 Categorization of exposure

To combine the information from obstetric complications, we then categorized the conditions that could be indications for cesarean delivery into the following categories: Both

having maternal and fetal conditions; Maternal or delivery conditions; Fetal conditions; Previous cesarean delivery without other complications; No indication; Other indications. We further combined all conditions as obstetric complications due to the low prevalence in each condition.

Therefore, we combined fetal presentation, mode of delivery, and complications to categorize exposure into the following 8 groups: Vaginal + no complications noted (reference group); Vaginal + other malpresentation + no complications noted; Vaginal + complications; cesarean delivery + vertex+ complications (maternal, fetal, other); cesarean delivery + vertex+ previous cesarean delivery with no other complications; cesarean delivery + vertex+ no complications; cesarean delivery + breech; cesarean delivery + other malpresentations.

C. Results

To explore if cesarean delivery is associated with ASD after controlling for infants' presentation and other complications, we compared infants with cesarean delivery, to vaginal delivery, among infants with vertex presentation and experienced no complications. The adjusted OR among infants for cesarean delivery was 1.56 (95% CI: 1.19, 2.05), compared to infants with a vertex presentation who had no complications. The OR was similar among infants born at term (OR=1.64, 95%CI: 1.23, 2.19) and was very imprecise for preterm births. Among different BMI groups, the association for cesarean delivery was similar across groups with different pre-pregnancy BMI.

Table 6.4 Cesarean delivery and odds ratio of ASD among vertex presentation, within subgroups of gestational age and pre-pregnancy BMI in ASD and POP children in the US, 2003-2011

	ASD	POP	OR	Confidence interval	CLR
Vaginal+ vertex+ no complication	583 (42.5)	827 (52.5)	1.00	-	
CS+ vertex+ no complication	155 (11.3)	144 (9.2)	1.56	1.19, 2.05	1.71
Gestational age					
Term					
Vaginal+ vertex+ no comp	526 (43.9)	780 (53.9)	1.00	-	
CS+ vertex+ no comp	131 (10.9)	123 (8.5)	1.64	1.23, 2.19	1.78
Preterm					
Vaginal+ vertex+ no comp	54 (33.8)	43 (36.4)	1.00	-	
CS+ vertex+ no comp	23 (14.4)	21 (17.8)	0.88	0.40, 1.94	4.90
Pre-pregnancy BMI					
Low or healthy BMI					
Vaginal+ vertex+ no comp	335 (47.7)	564 (57.4)	1.00	-	
CS+ vertex+ no comp	62 (8.8)	64 (6.5)	1.59	1.08, 2.36	2.18
Overweight or obese					
Vaginal+ vertex+ no comp	224 (36.4)	245 (44.1)	1.00	-	
CS+ vertex+ no comp	88 (14.3)	76 (13.7)	1.43	0.97, 2.10	2.17

Adjusted for maternal age, poverty level, maternal hypertensive disorder, and maternal smoking

D. Discussion

We found a moderate association between cesarean delivery and ASD that remained after controlling for malpresentation, an indication for cesarean delivery. These study results were consistent with most previous studies which also adjusted for fetal presentation[155-157], and two studies[155, 157] additionally adjusted for potential cesarean delivery indications like hypertension or

large for gestational age. However, some prior research[78-80] reported no association between cesarean and ASD after adjusting for fetal presentation, but these were focused on breech presentation.[78-80] Another study[31] also found that when restricted to vertex presentation, the association between primary cesarean delivery and ASD was eliminated. That study was a surveillance study among US children at 8 years' old, but it did not control for key confounders like maternal smoking or hypertensive disorder; therefore, was susceptible to residual confounding and may have biased results.

As the cesarean delivery has many indications including malpresentation,[69, 70] by comparing the overall ORa for cesarean delivery and ASD to the ORa after controlling for malpresentation, we may able to tell how much malpresentation, as an indication, attributed to the association observed between cesarean delivery and ASD. However, our study had its own limitation as we were unable to fully examine indication by breech because most breech presentation was delivered by vaginal delivery. We also lacked full details on indications for cesarean delivery. Despite that, our study results suggested that the association between cesarean delivery and ASD could partially be a result of other indications by cesarean delivery, like labor dystocia or maternal conditions.

Labor dystocia usually refers to abnormal labor progression during the latent (up to 4-6 cm dilation) or active phases (from 4-6 cm until full dilation) of the first stage of labor, or during the second stage (from complete cervical dilation until delivery of the baby).[158] Prolonged labor may increase the risk for maternal and neonatal infection, fetal distress (always diagnosed by abnormal fetal heart rate)[159], neonatal hypoxia, uterine rupture, and postpartum hemorrhage.[160] Although some population-based evidence has suggested that labor dystocia is not directly associated with child neurodevelopmental delay or ASD[154, 161], others have found that fetal

distress[18, 120, 162], a possible result for labor dystocia and another indication for cesarean delivery, and abnormal labor progression[163] are risk factors for child neurodevelopment disorders.[18, 120, 160, 162]

Maternal health conditions such as hypertension and diabetes may also be a risk factors for both cesarean delivery and ASD. High blood pressure can make it hard for blood to reach the placenta, which provides nutrients and oxygen to the fetus. Reduced blood flow can slow the growth of the fetus and place the mother at greater risk of preterm labor and preeclampsia.[164] Hypertension during pregnancy (either pre-existing or pregnancy-induced) and preeclampsia has been associated with ASD.[19, 20] A meta-analysis also found gestational diabetes was associated with an increased risk.[165] As such, further studies focusing on indications for cesarean delivery are warranted.

Besides cesarean delivery indications, such as malpresentation or labor dystocia, animal studies suggest that altered neonatal gut microbiome, induced by cesarean delivery, may also contribute to the association between cesarean delivery and ASD. Studies suggested that the resident microbiota can exert considerable influence over host behavior, and the infant and child microbiota is susceptible to a range of environmental influences, including birth mode (vaginal vs. cesarean delivery)[166, 167]. Cesarean delivery was reported to alter the infant's gut microbiota due to an inadequate microbial colonization[157], which could further lead to neurodevelopment disorders because of gut-brain axis[168].

Therefore, future studies are necessary to further identify whether the association between cesarean delivery and ASD is causal, and the biological mechanism behind the association.

CHAPTER 7. DISCUSSION

A. Summary

The prevalence of ASD was 23.0 per 1,000 children in the US in 2018, reflecting a continuous rise in documented prevalence over the past two decades.[4] Children with ASD experience challenges with social interaction and communication skills, ability to maintain attention, and sensory issues.[58] More than 70% of individuals with ASD have concurrent medical, developmental, or psychiatric conditions.[46] As for cognitive impairment, a recent study on child/adolescent population showed a high prevalence of intellectual disability of 18.30/1000 (95%CI 15.17–21.43)[5], and intellectual disability accounts for a substantial proportion of disability-adjusted life-years for the patients[169]. ASD and cognitive impairment can impair personal, social, academic, or occupational functioning throughout lifetime.[6] Such disorders can cause substantial burdens for impacted individuals and their families.[7, 8] While attention towards understanding the prevalence and needs of individuals with ASD and cognitive impairment has increased, the etiology is very complicated and remains unclear.

Brain development begins in early pregnancy,[12] and can be affected by prenatal and perinatal factors. Previous studies found that complications of pregnancy, including small gestational age at delivery[13, 14], mode of delivery[15, 16, 17, 18], and complications of high blood pressure[19, 20], have been associated with cognitive development and ASD. Despite evidence[170, 171] showing that cesarean delivery is moderately associated with ASD and cognitive function impairment, few studies have focused on identifying the effect of upstream factors for cesarean

delivery, especially malpresentation, an important indication for cesarean delivery. This study examines malpresentation, a common and important indication for cesarean delivery, and its association between ASD and cognitive function.

We leveraged data from the Study to Explore Early Development, a US multisite case-control study with multiple-source ascertainment of children with ASD, and children sampled from the general population, to identify etiological risk factors for ASD.[35] SEED collected data retrospectively on delivery and labor from medical records, maternal telephone interviews, and birth records. In SEED, ASD cases were ascertained through the ADI-R and ADOS gold standard measurement, and cognitive function was measured by Mullen Scale of Early Learning, a validated measurement for cognitive function, especially for children with ASD.

This work had two specific aims: 1) to examine the association between malpresentation at delivery and ASD in the offspring, with sub-aims to examine whether the association was modified by gestational age or pre-pregnancy BMI, and 2) to examine the association between malpresentation and cognitive function, among ASD and children sampled from general population (POP children) separately. While some studies have shown a positive association between breech, the most common malpresentation, and ASD or cognitive function, others have shown no association, and their role in the development of ASD or cognitive impairment is still unknown. Moreover, as the prevalence of malpresentation is inversely associated with increased gestational age, few studies addressed the variation of malpresentation over the pregnancy. We addressed limitations from previous studies and tried to identify possible etiological mechanisms for ASD and cognitive function for further study.

B. Malpresentation and ASD

For the first aim, we investigated the association between malpresentation at delivery and ASD. We identified malpresentation (including breech presentation and other malpresentation) using medical records, maternal caregiver interviews, and birth records. For important factors that might modify the association, gestational age was identified by birth records, and pre-pregnancy BMI was identified by maternal interview.

Our analysis showed that malpresentation was moderately associated with ASD, especially among children born with a malpresentation other than breech presentation. However, due to low prevalence of malpresentation, we lacked power to conclude that the association was modified by gestational age or pre-pregnancy BMI. As such, our study results may need to be interpreted with extra caution, especially for the results from subgroup analysis.

The process during labor is very complex. More than often, conditions happening during labor and delivery are always intertwined, making it is hard to define the temporal order of clinical events and tease out the effect of each single obstetric complication. As such, we proposed several possible biological mechanisms to explain how malpresentation at delivery may affect fetal neurodevelopment.

A plausible explanation is malpresentation itself could result in neurodevelopmental delay, due to the potential damage malpresentation causes during delivery. In other studies, malpresentation delivered vaginally, especially breech presentation, has been associated with a lower Apgar score at 1 and 5 minutes[129], brain injury[141], neonatal intensive care unit (NICU) admission[172], and neonatal asphyxia[142]. In our study, even though most breech presentation was delivered by cesarean delivery, half of the other mispresenting infants were delivered vaginally.

These studies suggested that there might be potential injury and fetal distress for an infant with malpresentation if they go through a vaginal delivery.

Injury could happen during the process of labor and delivery. The labor leading to delivery is divided into three stages. The first stage of labor is the longest stage of labor and can be divided into two sub-stages. At first, uterine contracts progressively and rhythmically and causes the cervix to dilate. The first sub-stage is known as the latent phase, which can last for several hours and starts from the cervical size of 0 cm to dilation of the cervix to 6 cm. The second sub-stage is known as the active phase, which includes the time from the end of the latent phase to the complete dilation of the cervix[173]. The second stage of labor includes the time from complete cervical dilation, which is the end of the first stage to delivery of the fetus[174]. The final stage includes the time after the child is born to the delivery of the placenta[175]. During the second stage, the fetus begins to descend and it is also the time for clinicians to identify the fetal presentation at delivery.[176]

For fetuses with malpresentation, due to the pressure exerted by the birth canal and surrounding structures, it is more likely for them to experience fetal bradycardia or asphyxia.[130, 177] Moreover, malpresentation sometimes can happen with other obstetric complications, such as prolonged labor[178], which occurs in 5% of the deliveries and more than half of obstetric emergencies[179]. During a prolonged labor, injury could occur due to the excessive process of fetal head molding, leading to head injury and several disorders on the fetal head.[180]

For some fetuses that go through the first stage of labor but experience some complications during the second stage of labor, it is also possible for them to have adverse birth outcomes. If certain complications are observed during a vaginal delivery, an emergency cesarean delivery will be performed. Studies have suggested that emergency cesarean delivery,

especially those performed at the second stage of labor, is associated with an increased risk for a lower Apgar score and NICU admission[181, 182]. Those studies additionally suggested that brain injury is likely to occur at the second stage of labor, when a fetus begins to descend through the birth canal. As such, the probability for an adverse neurodevelopmental outcome, whether short-term or long term, could be higher for fetuses with malpresentation. However, we did not have detailed data to investigate this level of detail in our study.

Another potential mechanism is that there are some upstream factors of malpresentation that could be associated with ASD. As discussed previously, failure to turn to a vertex presentation could be a sign of several sub-optimal conditions. For example, maternal thyroid dysfunction, either hyperthyroidism or hypothyroidism, is shown to be associated with fetal malpresentation. Studies[28, 29, 183, 184] have suggested that women with higher TSH level near the end of term or a lower T4 concentration at early gestation were at risk for fetal breech presentation at term. Both hyperthyroidism and hypothyroidism[152] have been shown to be associated with child neurodevelopment in some studies[143, 144], while others have reported no association between maternal thyroid dysfunction and child neurodevelopment[185, 186]. We did not have sufficient data to explore this mechanism in SEED, but cannot dismiss the possibility that the relation between malpresentation and poor neurodevelopment might be thyroid-related.

Most of previous studies on malpresentation and ASD focused on breech presentation, which is now mostly managed by cesarean delivery, to reduce potential risk by vaginal delivery. In our study, we were able to use medical records as the primary source to identify fetal presentation and to distinguish breech from other malpresentation. Our data showed that prevalence of mode of delivery for other malpresentation varied more, but less is known for other malpresentations from prior studies. For both potential mechanisms, it is difficult to predict

which one is more likely to happen as our study was not able to tease out events and complications happening during pregnancy, or have the information on important upstream factors of malpresentation. However, those mechanisms are biologically plausible and merit attention for future studies.

We did not have convincing evidence that gestational age or pre-pregnancy BMI modify the association between malpresentation and ASD. For gestational age, as we discussed, failure to turn at a certain gestational age might be a sign of aberrant fetal development. Therefore, we hypothesized that we might observe a stronger association between malpresentation and ASD among term births; but the sample size limited our ability to investigate changes in risk over gestational age and led to imprecise study results from preterm births. Comparing BMI stratum-specific estimates was also limited by sample size, and we did not observe differences in the association among mothers with pre-pregnancy BMI in the low/normal BMI or overweight/ obese categories due to imprecise confidence intervals. Previous studies have reported gestational age or pre-pregnancy BMI might be associated with the development of ASD[131-134]. Our results suggest that future studies with better power are necessary to confidently conclude whether the association between malpresentation and ASD could be modified by gestational age or pre-pregnancy BMI.

In conclusion, we observed modest observations between malpresentation and ASD. We hypothesize that this may be due to injury happening through vaginal delivery or be an indication that upstream factors related to failure to turn at proper gestational age and neurodevelopment, which deserves further investigation.

Public health implications

Our study provides additional support that malpresentation may be associated with ASD. This association may be present because of damage during vaginal delivery, such as brain damage or fetal asphyxia, or factors that prevent a fetus from turning at a proper gestational age. Further studies are necessary to understand the biological mechanisms through which this association operates. Nowadays, breech presentation is nearly always delivered by cesarean delivery. Our study suggests that it is important to manage malpresentation other than breech. With currently available evidence, early monitoring of children's development can be implemented to better identify children with ASD and initiate early intervention. Several studies[187, 188] have shown the benefits of early diagnosis and preemptive intervention on preventing progressive symptom development in later age, and these results may help identify children at risk for developmental disorders earlier.

C. Malpresentation and cognitive function

We also examined the association between malpresentation and child cognitive function. Child cognitive function was measured by MSEL, and the 4 subscales were administered: fine motor, visual reception, receptive language, and expressive language. In addition, an MSEL composite score was also calculated as a standard score. The main outcome of cognitive function was identified as both a binary outcome (below average cognitive function/ average and above cognitive function) in both ASD and the children sampled from general population (POP), and as a linear MSEL score for the general sample children (POP children) only.

We did not find an association between malpresentation and below average cognitive function among children sampled from the general population. In POP children, we also measured the association between malpresentation and linear MSEL composite score.

Malpresentation was also not associated with changes in MSEL composite score. In subgroup analysis, we did not find pre-pregnancy BMI modify the association, likely due to the lack of power in each stratum. We also found a potential stronger association between malpresentation and MSEL composite score in children with preterm births; however, the results were sufficiently imprecise for us to draw a conclusion. In children with ASD, there was also no evidence that malpresentation was associated with below average cognitive function.

Due to imprecise estimates, we were not able to dismiss the potential of the underlying association for malpresentation and cognitive function. Our results were consistent with some previous studies[93, 94], but not with others[33, 34]. Differences in these results may be in large part due to different measurements of cognitive function, or methodological flaws of stratifying on factors that are not confounders such as mode of delivery. In future, well-powered studies may be necessary to help us better understand the association, and the potential modification by gestational age or pre-pregnancy BMI.

Public health implications

Our study indicates that malpresentation at delivery may not be associated with cognitive function, either children sampled in general population or children with ASD. During 2014-2016[42], the prevalence of children ever diagnosed with intellectual disability was 0.73% among children aged 3-7 years. During the past decade, there was a significant increase in the documented prevalence of intellectual disability in the general population with typical development[56, 57] as well as children with ASD[2, 3, 47, 189]. The observed trend may be due to the improvements in maternal and child health care, national screening programs, and increased community awareness to developmental delays, leading to the identification of more children[57]. However, the increased prevalence has also introduced concerns with cognitive impairment in

children, and efforts were taken to understand the etiology of neurodevelopmental delay, and to conduct early prevention. Our study results suggested that malpresentation at delivery, as an obstetric sub-optimal condition, may not be associated with children's cognitive function, or be a sign of concern. Therefore, our study could be helpful to relieve the concerns that malpresentation at delivery contributes to cognitive delay in early age.

D. Strengths & limitations

The case-control study design of SEED has many advantages and disadvantages, as it allows us to evaluate the association between the exposure and a rare outcome in an efficient manner, such as the case of ASD in this analysis. Several strengths and limitations of the study methods are reviewed here.

Information bias

SEED offers multiple sources for information on labor and delivery information. These included maternal phone interviews, abstracted medical records, and birth records. To classify malpresentation or mode of delivery, the information was available in all the sources. While having different sources of data for one exposure may be beneficial, there may be discrepancies across data sources, as the information may be categorized differently or might be missing. We evaluated agreement among sources, but may still face with some exposure misclassification within each data source.

The maternal interview was conducted at the time of enrollment and contained questions regarding the mother's pregnancy and the labor and delivery period. The child was required to be 30 to 68 months at enrollment and the information was susceptible to recall bias. While data from medical records may be more valid as they were retrieved from hospitals, information

abstracted from the medical records may be incomplete, based on what was recorded and what was provided to the study. Birth records were presumably to be filled within 10 days of child's birth and were less susceptible to recall bias, but they collected less information compared to medical records[190]. Each source also used different categories to report malpresentation.

As such, we defined malpresentation prioritizing medical records, and used information from birth records and maternal interviews to fill the missingness. However, we could not rule out the possibility that the poor recall from maternal interviews can lead to exposure misclassification that impacts study results. It is possible that this misclassification is differential by outcome status resulting in recall bias, where mothers of affected children may be more likely to search their memories and remember earlier events[191].

External cephalic version is a procedure to turn malpresentation fetus after 32 weeks of gestation to a vertex presentation[81]. Those who succeeded in ECV would likely be documented as vertex, introducing potential misclassification, specifically when considering the mechanism related to malpresentation as a marker of altered fetal neurodevelopment. However, we used medical records and only identified 4 mothers who succeeded in ECV procedure (and were shown as a vertex presentation in final classification). Moreover, in a large population study, the rate of successful ECV was also very low.[192] Therefore, we expect the bias by ECV procedure to be minimal, though it is unclear how completely such practices were recorded.

To evaluate the agreement between data sources for malpresentation, we calculated Cohen's kappa (κ) with 95% CI. The strength of agreement was interpreted as: <0 none, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 as substantial, 0.81–1 nearly perfect[193]. The results showed substantial agreement for malpresentation between maternal interview and medical records, and moderate yet similar agreement between birth records and medical records.

In two SEED sites, if a child did not have malpresentation, it was coded as "Missing" on the birth records, therefore missing data in those two sites could be a mix of "No" and "Missing". In other sites, the missing was pretty low (N=67, 3.52%). We tried to recode the "Missing" in those two sites to "No" and found similar agreement, suggesting a limited potential for exposure misclassification. It is possible that any disagreement could have been due to potential exposure misclassification, as it is likely non-differential regarding the outcome, it can bias our results toward the null.

Residual confounding

Our data limited our ability to interpret the role of malpresentation, as it could be a simple position for fetus at delivery, or could be a sign of complex neurodevelopmental differences. Factors that prevent a fetus from turning to a vertex presentation could also be associated with child neurodevelopment. For example, maternal thyroid dysfunction, was shown to be associated with both malpresentation at term and neurodevelopmental delays in previous studies. However, even though SEED collected for related information such as treatment for thyroid diseases or thyroid diseases during pregnancy, it was very incomplete and was subject to recall bias. Therefore, we did not include it into our study analysis. However, as the association between maternal thyroid dysfunction and neurodevelopmental delays was not clear and inclusive, we expect the bias by residual confounding to be small.

Sample size

The case-control study design increases statistical power to detect associations with a rare outcome. In our study, we were able to detect associations with malpresentation and ASD with fairly precise confidence intervals. While we had sufficient sample size for main effects for aim 1, we suffered with lack of power for subgroup analysis between malpresentation and ASD, and

main effects for aim 2, where we examined the association between malpresentation and cognitive function, in ASD and POP children separately. Future studies should be conducted in larger sample sizes to confirm associations between malpresentation and cognitive function, and explore the association between malpresentation and ASD or cognitive function in different gestational age or pre-pregnancy BMI groups.

Strengths

SEED is designed to identify etiologic factors contributing to ASD. It is a multi-site study and is the largest study focusing on ASD in the U.S. population, with sites in different regions of the U.S., two of which recruited Spanish-speaking participants. The case-control study design of SEED is ideal for investigating rare outcomes such as ASD and below average cognitive function. SEED also provides extensive data on prenatal and labor and delivery information, making it is possible for us to minimize the possibility of residual confounding.

One of the biggest advantages of SEED is the in-person assessment conducted to confirm ASD using the ADOS and ADI-R, the gold standard instruments for ASD diagnosis. Such approach reduces outcome misclassification compared to other studies that use school records, ICD codes, or administrative datasets to classify a child. MSEL is also a valid tool to assess child's cognitive function in-person at an early age, especially for children with ASD. Hence, the possibility of outcome misclassification or inaccurate measurement is expected to be low. Measuring cognitive function has always been a major challenge for younger children[96]. In the general population, school-aged IQs is a good predictor pf adult cognitive function[147, 148]. However, psychometric intelligence is usually administered to older children[149]. In our study, children were young (30 to 68 months of age). Therefore, MSEL is a well-validated assessment tool for this age group as well[96].

Malpresentation was defined using multiple sources. Though it could lead to exposure misclassification, but it also reduced the possibility of having false negatives. In addition, we found good agreement between data sources to confirm their validity. Moreover, all covariates in this study were identified by SEED investigators using multiple sources and deliberated approach, making it is very unlikely to have confounding introduced by misclassification in the covariate set.

E. Reflections

Our study found an interesting result that malpresentation could be associated with ASD, but was unlikely to be associated with a significant decrement in cognitive function. It could be due to behaviors or sensory abilities, which manifest more in ASD, are more susceptible to some upstream factors of malpresentation, compared to cognitive function. However, that was our speculation and evidence on this was very limited. A check on child other behavioral characteristics using the Child Behavior Checklist in SEED might be helpful to further test this hypothesis.

Estimate of the WHO showed that 15% of expected births suffering from obstetric complications[194]. The consequences of birth and acute maternal complications include death and different conditions of neurodevelopmental disabilities. Previous studies have found that cesarean delivery is moderately associated with ASD or cognitive function, and this study aimed to explore whether one indication of cesarean delivery, malpresentation, was associated with ASD or cognitive function. However, during the process of labor, lots of events could happen, making it is very challenging to tease out the effect of each factor. Our study encountered several methodological challenges to understand the specific impact of any one event.

The first challenge I faced was how to measure the effect of malpresentation while taking out the effect of cesarean delivery. At first, this study focused on breech presentation only, which made it even harder to estimate the association of breech presentation solely, as more than 90% of the children with breech presentation were delivered by cesarean delivery. When we combined breech presentation with other malpresentation, the prevalence of cesarean delivery in this group was still much higher compared to vaginal delivery. Therefore, we tried to stratify on mode of delivery to control for the potential impact of cesarean delivery. In the proposal development stage, the exposure was categorized into 'malpresentation + cesarean delivery', 'vertex + cesarean delivery', and 'vertex + vaginal delivery'.

When I tried to compare 'malpresentation + cesarean delivery' to 'vertex + cesarean delivery', I also realized the potential other indications for cesarean delivery could also confound the association. However, cesarean delivery indications were not well-captured in SEED data. As such, for the second challenge, I took an extra step by identifying potential cesarean delivery indications in our study, using literature review and consultation with obstetricians. I was able to identify some obstetric complications that could potentially be indications. Finally, we ended up with very refined exposure groups, by combining mode of delivery, presentation, and potential cesarean delivery indications.

I went far before I was remined that the approach could be methodologically flawed. During my interim meeting, my committee raised the question that, in the DAG, cesarean delivery could be a collider and could mediate the association of interest, thus it will introduce bias if I stratify on mode of delivery. Moreover, we had a very extensive adjustment set, which may be a problem considering we had limited power. After a careful discussion, we decided to not stratify on cesarean delivery, as cesarean delivery is a descendent of malpresentation and

could be a mediator, and adjusting for cesarean delivery may end in over adjusting and lead to biased results. We also decided to re-define the adjustment set, based on literature review and a re-visit on DAG, to focus on important confounders only, to help us to have a both valid and precise estimates.

Such detour was actually rewarding, even though some of the work was not included in the main papers. I developed extensive knowledge on the process of delivery, and how each condition could interact with each other. I was also able to get familiar with SEED data collection progress for each instrument, and the potential advantages and disadvantages of each source. Moreover, since the information on fetal presentation and mode of delivery was available in multiple sources and had discrepancies, I used what I learned from the data collection process and came up with a solution on how to consolidate discrepancies on fetal presentation, mode of delivery, and cesarean delivery indication classification. Moreover, we conducted several additional studies which may warrant for an additional paper. The whole process also reminded me on how important it was to always take a step back. During my dissertation development, it was always important to have progress; however, it is equally crucial to always remember to see the big picture. I hope that I can progress while remembering to look at the bigger picture while I navigate my career in the field of epidemiology.

F. Future directions

In specific aim 1, results from this study showed an association between malpresentation and ASD. As discussed, the potential brain damage happening during delivery, or the potential factors that lead to malpresentation, could contribute to the association. Further studies are needed to determine whether these associations are causal, or if malpresentation is a proxy for some other upstream factors of malpresentation. As the prevalence of malpresentation changes as

gestational age increases, I was also interested in how the association was modified by gestational age, as a sub-aim. However, the number of malpresentation and preterm birth was very low, limiting our ability to interpret the results. One main area for future study will be to explore if gestational age will modify the association between malpresentation and ASD, with sufficient power. For pre-pregnancy BMI, we expect the association to be modified by both low BMI category and overweight or obese group. It is also important for a well-powered study to investigate the role of pre-pregnancy BMI on the causal pathway, and how BMI interacts with gestational age.

In specific aim 2, the power decreased very quickly, as we separated ASD and POP children. Therefore, though results suggested no association between malpresentation and cognitive function, the possibility of failing to detect an underlying association could not be ruled out. Future studies should be conducted in a larger sample to confirm the results. We also observed a strong but imprecise association between malpresentation and linear MSEL composite score among children born preterm. It would be interesting to see whether the association persists in a larger study, and whether other factors associated with preterm contribute to the association.

Data from SEED phase 3 are available now; however they were not incorporated in this study because medical records, our primary source for malpresentation, were no longer collected in SEED 3. Future SEED studies could develop a method to identify malpresentation in all 3 SEED phases, increasing the study power while maintaining the accuracy of exposure classification. A bigger sample size in SEED may also help us explore the subgroup analysis by gestational age and BMI.

G. Conclusions

Our study results serve as evidence that malpresentation may be associated with ASD. The observations merit future study to explore the biological mechanism for the association. In children with ASD or children sampled from the general population, we further discovered that malpresentation was not associated with cognitive function in each group. However, as we cannot dismiss the possibility of not being able to detect the underlying association between malpresentation and cognitive function, it is also important for future studies to confirm our results with well-powered sample size. Despite the need for additional research, early monitoring of neurodevelopment among children born with malpresentation could identify children with ASD sooner and enhance opportunities for early intervention.

It is very important to continue and explore further to identify specific risk factors and etiology for ASD and cognitive function, especially for events happening during delivery. Though a lot of the conditions during labor and delivery are very acute and cannot be preemptively prevented, identifying those factors can help us start early monitoring and early intervention for children with developmental concerns.

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