HHS Public Access

Author manuscript

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2025 July 01.

Published in final edited form as:

Paediatr Perinat Epidemiol. 2024 July ; 38(5): 397–407. doi:10.1111/ppe.13082.

Malpresentation and autism spectrum disorder in the study to explore early development

Yitian Zhang[1,2], **Michelle T. Delahanty**[2], **Stephanie M. Engel**[2], **Stephen Marshall**[2], **T. Michael O'Shea**[3], **Tanya Garcia**[4], **Laura A. Schieve**[5], **Chyrise Bradley**[2], **Julie L. Daniels**[2]

[1]Epidemiology and Database Studies, Real World Solutions, IQVIA Inc, Durham, USA

[2]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, USA

[3]Department of Pediatrics, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, USA

[4]Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, USA

[5]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Abstract

Background: An infant's presentation at delivery may be an early indicator of developmental differences. Non-vertex presentation (malpresentation) complicates delivery and often leads to caesarean section, which has been associated with neurodevelopmental delays, including autism spectrum disorder (ASD). However, malpresentation could be an early sign of an existing developmental problem that is also an upstream factor from caesarean delivery. Little research has been done to investigate the association between malpresentation and ASD.

Objectives: We examine the association between malpresentation at delivery and ASD and whether this association differs by gestational age.

Methods: We used data from the Study to Explore Early Development (SEED), a multisite, case–control study of children with ASD compared to population controls. The foetal presentation was determined using medical records, birth records and maternal interviews. We defined malpresentation as a non-vertex presentation at delivery, then further categorised into breech and

Correspondence Julie L. Daniels, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. julie_daniels@unc.edu.

AUTHOR CONTRIBUTIONS

Yitian Zhang and Julie Daniels Conceived and designed the analysis; Chyrise Bradley, Julie Daniels and Laura Schieve designed study protocols and provided oversight for data collection; Yitian Zhang and Michelle Delahanty analysed the data; Tania Garcia, Stephanie Engel, Stephen Marshall, T Michael O'Shea and Julie Daniels provided guidance on the analytic approach. All authors contributed to the interpretation of the findings and writing of the manuscript.

SUPPORTING INFORMATION

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

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

other malpresentation. We used multivariable logistic regression to estimate the adjusted odds ratio (aOR) for the association between malpresentation and ASD.

Results: We included 4047 SEED participants, 1873 children with ASD and 2174 controls. At delivery, most infants presented vertex (n = 3760, 92.9%). Malpresentation was associated with higher odds of ASD (aOR 1.31, 95% confidence interval [CI] 1.02, 1.68) after adjustment for maternal age, poverty level, hypertensive disorder and smoking. The association was similar for breech and other types of malpresentation (aOR 1.28, 95% CI 0.97, 1.70 and aOR 1.40, 95% CI 0.87, 2.26, respectively) and did not differ markedly by gestational age.

Conclusions: Malpresentation at delivery was modestly associated with ASD. Early monitoring of the neurodevelopment of children born with malpresentation could identify children with ASD sooner and enhance opportunities to provide support to optimise developmental outcomes.

Keywords

autism spectrum disorder; breech; gestational age; malpresentation; pregnancy

1 | BACKGROUND

Autism spectrum disorder (ASD) is characterised by a range of persistent challenges in social communication and interaction across multiple contexts, as well as restricted, repetitive patterns of behaviour, interests or activities.[1] For 2023, the prevalence of ASD was estimated to be 28.0 per 1000 children in the United States.[2] Children with ASD can face great health challenges and may experience economic burdens when navigating societal structures.[3]

ASD is likely a result of complex gene–environment interactions impacting development during gestation and early life.[4,5] The fetal and neonatal periods are critical stages in brain development that are vulnerable to adverse events. Studies have found sub-optimal labour events, including caesarean delivery, to increase the likelihood of ASD[6,7]; however, findings are mixed.[8–10] Sub-optimal conditions at delivery are complicated and interconnected. The limited data and ability to adjust for confounding by indications of caesarean delivery limit the causal interpretation of caesarean delivery as causal. Upstream indications for caesarean delivery that have also been associated with ASD include labour dystocia,[11] abnormal fetal heart rate[12,13] and hypertensive disorders during the pregnancy period and foetal malpresentation at delivery.[13–16]

Malpresentation at delivery, or failure to turn, could result from foetal disorders,[17] insufficient intrauterine space,[18] abnormal maternal thyroid functions,[19] foetal growth restriction.[17] These conditions, specifically maternal thyroid dysfunction or foetal intrauterine growth restriction, have been associated with delayed child neurodevelopment.[20] Malpresentation could serve as an early marker of problems in foetal development that ultimately manifests in ASD during childhood, but the association between malpresentation and child neurodevelopment has not been well studied.

Most infants present in a vertex (head down) position at delivery.[21] Foetal malpresentation includes breech, shoulder, compound, face and brow presentations[22]; among these, breech

presentation is the most common.[23] The foetus changes position often in early gestation; the probability of a foetus turning into a vertex presentation increases as gestation progresses,[21] making malpresentation less common in term births.

Evidence regarding risks associated with malpresentation is mixed. Four studies[24–27] examined the association between foetal presentation and ASD, nearly all focusing on breech presentation specifically. Two record-based studies found malpresentation was moderately associated with an elevated risk of ASD but lacked confirmation of ASD.[25,27] Prior studies also had limited information to classify malpresentation.[25,26] Only one study accounted for the gestational age-dependency of malpresentation.[26]

We used detailed information on pregnancy, delivery and rigorous confirmation of ASD among children participating in the Study to Explore Early Development (SEED) to disentangle associations between malpresentation and ASD while considering potential differences in this association by gestational age.

2 | METHODS

2.1 | Study population

SEED is a case-control study aiming to identify risk factors for ASD and other developmental disabilities.[28] Children with potential ASD were ascertained through multiple clinical and special education programs that provide evaluation or support for children with ASD or related developmental conditions. Children enrolled as controls were identified by randomly sampling state vital records.

Children eligible for SEED during three phases of enrollment and data collection were required to have been: (1) born in the study catchment area during the periods of 2003–2006, 2008–2011, or 2014–2017; (2) between 30 and 68 months of age during study participation; (3) resident in multi-county catchment areas in California, Colorado, Georgia, Maryland, North Carolina, Pennsylvania, Missouri or Wisconsin at the time of participation and (4) lived with a knowledgeable caregiver (defined as parent or caregiver who was able to legally consent to the child's participation and birth record access and consistently cared for the child since he or she was 6 months of age or younger) who could communicate in English (or Spanish in California or Colorado). We restricted this analysis to singleton children (considering intra-uterine crowding prevents foetuses from turning to a vertex presentation in multiple gestations), children whose biological mothers were the caregivers completing the interview (>99% of participants),[28] and children who were classified into an ASD case group or population control group (POP) based on results of the developmental evaluation.[29]

Children with a wide range of birth and developmental challenges were recruited to SEED to screen for ASD among children with developmental disabilities and identify children with ASD who may not already have received a diagnosis. We restricted our analysis to those with confirmed ASD and those recruited as population controls from birth records because extensive heterogeneity among those with other developmental delays limits the ability to interpret findings.

2.2 | Case status

All children who participated in the study were initially screened for possible ASD using the social communication questionnaire (SCQ).[30] Children with a previous diagnosis 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)[31] and their caregivers completed the Autism Diagnostic Interview-Revised (ADI-R). The ADOS/ADI-R package is a validated and reliable measurement for ASD and is considered the gold standard for ASD diagnosis. Studies have reported that the instruments' sensitivity ranges from 86 to 100 per cent and specificity with other developmental disabilities from 73 to 100 per cent.[32] 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.[29] Untestable children or those who did not complete the ADOS or ADI-R were classified as possible ASD and excluded from this analysis.

Children randomly sampled from birth records who had no previous diagnosis of ASD and screened negative on the SCQ (SCQ score < 11) were classified as population controls (POP).

2.3 | Exposure

Information regarding a presentation at delivery was obtained from multiple sources: medical records for maternal labour and child's delivery, maternal interviews and birth records. We found strong agreement for breech presentation between maternal interviews and medical records (κ = 0.61, 95% CI 0.53, 0.69) and modest agreement for overall malpresentation between medical records and birth records (κ = 0.57, 95% CI 0.49, 0.66).[33] We defined malpresentation as a non-vertex presentation at delivery. Classification of malpresentation was determined using the following approach: malpresentation was reported in the medical record (when available); when the medical record was not available, malpresentation was reported during the maternal interview or birth record. The final classification of presentation at delivery was vertex or malpresentation. When available information indicated 'breech', breech presentation was further distinguished as a subset of malpresentation.

2.4 | Covariates

We used a directed acyclic graph (DAG) (Figure 1) to identify potential confounders based on a review of the literature.[14,34–36] For potential confounding, the minimally adjusted covariate set included maternal age at birth of a child, smoking during pregnancy, hypertensive disorders of pregnancy and household income. Maternal age at delivery was derived from birth records. Maternal smoking (ever/never during pregnancy) came from maternal interviews. Indications of hypertensive disorders included pre-existing chronic hypertension, pregnancy-induced hypertension, pre-eclampsia, eclampsia and HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets) derived from maternal interviews and medical records. The poverty index was derived by applying the federal thresholds to parent-reported income 12 months before the child's birth from the maternal interview. Income as a percentage of the federal poverty level (FLP) was categorised 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 differences in the association by gestational age because infants typically turn before term, thus, malpresentation at or after term may reflect aberrant development during pregnancy. Gestational age at delivery was based on a best clinical estimate from birth records and categorised into preterm (<37 weeks) or term (≥ 37 weeks).[37]

Though factors like parity, race, ethnicity and caesarean delivery were considered potential confounders in other studies, they were not included as covariates in this analysis. Parity was very weakly associated with malpresentation in our sample and not shown to be a risk factor for ASD in a recent meta-analysis.[7] Race and ethnicity are social constructs that are often used as a proxy for socioeconomic status and associated with access to healthcare; in our study, we had information on household income, which may better capture socioeconomic status and healthcare access.[38]

2.5 | Statistical analyses

We described the distribution and compared proportions of maternal and child characteristics and delivery details for both ASD and POP groups. We fit logistic regression models to estimate adjusted odds ratios (aOR) and the 95% Wald confidence intervals (CI) of ASD using the minimally sufficient adjustment covariate set. We chose the functional form of each covariate with the smallest Akaike information criterion (AIC).[39] Model diagnostic plots were also used to check the model performance.

To further distinguish the effect of breech from other malpresentation, we analysed 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 differ by pre-term. We did not adjust for caesarean delivery because it was likely the result of malpresentation (a descendent of malpresentation on the causal pathway).[40] All analyses were conducted in SAS version 9.4 software (SAS Institute, Inc., Cary, NC, USA).

2.6 | Sensitivity analysis

We conducted two sets of sensitivity analyses. To explore whether race and ethnicity would act as a potential confounder in addition to household income, we conducted a sensitivity analysis using race as a covariate. (Figure 1).

Moreover, because one SEED site with supplemental data found that maternal education was differently distributed in the participation of POP and ASD groups,[41] we conducted sensitivity analyses including maternal education as a covariate to evaluate the potential for maternal education to impact our results.

2.7 | Missing data

Minimal data were missing for individual variables: income relative FPL (3.9%), maternal smoking (1.1%), maternal hypertensive disorders (0.4%) and gestational age (0.3%). Because cumulative missing was 5.7%, 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 50 independent imputed datasets.

2.8 | Ethics approval

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.

3 | RESULTS

From the total SEED sample (n = 5308), we included 4056 participants in our analysis (Figure 2), 1879 with ASD and 2177 as population controls (POP). Most participants (88.9%) had two or more sources available to identify the child's presentation at delivery (Table 1); 287 children were classified with malpresentation at delivery, with 215 further classified as breech. Overall, 58.5% of mothers were 30–39 years old at delivery (Table 2). Most mothers (59.7%) were college graduates or higher, 61.3% were Non-Hispanic White and 18.0% were Non-Hispanic Black. Most families (52.9%) had an income above or equal to 400% of the federal poverty level (FPL).

Compared with POP, the biological mothers of children with ASD were more likely to be Non-Hispanic Black, have lower household income, have lower education and have a smaller proportion with low or healthy body mass index (BMI) (Table 2). The distribution of children with vertex or malpresentation did not vary markedly by participant demographic characteristics. For children delivered with malpresentation, mothers were more likely to have higher pre-pregnancy BMI (23.6% vs 18.8%) and maternal hypertension (23.3% vs 18.0%); the distribution of household income was similar to those with vertex presentation. Malpresentation at delivery occurred more frequently among children with ASD (8.1%) compared to POP (6.3%); children with ASD were also more regularly delivered preterm (12.5% vs 7.6%) and by caesarean (37.7% vs 29.2%) compared to POP children. Most children with malpresentation were delivered by caesarean delivery (82.9%), with 185 (86.0%) children presenting breech and 53 (73.6%) children with other malpresentation delivered by caesarean.

Overall, malpresentation at the time of delivery was associated with higher odds of ASD (aOR 1.31, 95% CI 1.02, 1.68) (Table 3). The association was similar when examining breech presentation (aOR 1.28, 95% CI 0.96, 1.70) separately from other malpresentation (aOR 1.40, 95% CI 0.87, 2.26).

When stratified by pre-term birth status, the association between malpresentation and ASD was similar among pre-term and term births, although imprecise for pre-term births due to the small sample size (Table 4). Among term births, the point estimate was higher for the association between other malpresentation and ASD than for breech and ASD.

We observed a stronger association between malpresentation and ASD among children born by vaginal delivery (aOR 1.30, 95% CI 0.72, 2.33) than by caesarean delivery (aOR 1.03, 95% CI 0.78, 1.38), though estimates are imprecise. (Table S1). Overall, results were not

altered by additional adjustment for maternal education (aOR 1.31, 95% CI 1.02, 1.68; Table S2) or maternal race/ethnicity (aOR 1.32, 95% CI 1.03, 1.70; Table S3).

4 | COMMENT

4.1 | Principal findings

Overall, we found that malpresentation at delivery was associated with a 31%-increased odds of ASD. While malpresentation was more common among pre-term infants, the association between malpresentation and ASD was similar among pre-term and term births.

4.2 | Strengths of the study

This study improves on previous investigations in several ways. SEED conducted standardised 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 and details on potential confounding factors. SEED's detailed data provided confidence in ASD classification and allowed control for critical covariates. Information on malpresentation was available from multiple sources. We prioritised information from the medical record based on prior validity studies,[42–44] but also found the agreement between sources in our study to be generally high. While medical records were most useful in distinguishing breach from other malpresentation, we expect the bias due to the misclassification of conditions related to labour and delivery to be small. Finally, our results were robust to the alternate adjustment sets (adding maternal education or race and ethnicity) and were not strongly biased by those factors.

4.3 | Limitations of the data

The ability to draw clear inferences from this investigation has some limitations. First, while we had a robust adjustment for confounding, the potential remains for residual confounding by unmeasured factors that might cause malpresentation and may also be associated with ASD, such as maternal thyroid dysfunctions or foetal disorders. Second, exposure classification relied on three available sources of data. Medical records were collected 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. However, the ability to combine multiple data sources increased our confidence in the characterisation of the presentation at delivery. We prioritised medical records and compared discrepancies that may result in misclassification of exposure. Only 6.2% had discordant classification on malpresentation. Moreover, bias coming from misclassification was non-differential and would bias the results to null. Finally, because malpresentation was relatively rare, the results stratifying on pre-term were very imprecise, and we did not have sufficient power to fully interrogate the potential for differences across gestational age or potential mediation by caesarean section.

4.4 | Interpretation

4.4.1 | The association between malpresentation and ASD—Our findings are consistent with the limited previous research on the association between malpresentation and ASD, which has mainly focused on breech presentation, rather than malpresentation more broadly defined.[24–26,45] Nested case–control studies from Utah and from Denmark reported associations between breech presentation and ASD (aOR 2.10, 95% CI 1.11, 3.98[26] and risk ratio = 1.63, 95% CI 1.18, 2.26),[25] respectively. A Canadian cohort study[45] and another Danish registry study[24] reported similar estimates of effect, but one without estimates of precision.[24] While several previously reported measures of association were of similar magnitude to our results, additional information on their precision such as 95% CI and methods to control for bias would allow support better comparison to our results.

For foetuses with malpresentation, due to the pressure exerted by the birth canal and surrounding structures, it is more likely for them to experience foetal bradycardia or asphyxia.[46,47] Moreover, malpresentation sometimes can happen with other obstetric complications, such as prolonged labour.[48] During prolonged labour, the injury could occur due to the excessive process of foetal head moulding, leading to head injury and several disorders on the foetal head.[49]

Upstream determinants of malpresentation could be associated with child neurodevelopment, such as maternal hormones or foetal disorders.[17,19] For example, maternal thyroid function has been shown to be associated with the risk of foetus not turning to vertex and child neurodevelopment,[19,50,51] but SEED did not have such information with sufficient detail to allow us to distinguish the potential influence of these underlying factors on malpresentation and ASD. Identifying the potential influence of these factors on the development of ASD might be helpful in future studies.

4.4.2 | Stratification by gestational age on the association between malpresentation and ASD—When stratified by gestational age, the association between malpresentation and ASD was primarily observed among term, rather than pre-term deliveries; but we had limited power to fully explore associations by gestational age category. Malpresentation is more common at younger gestational ages. While this study does not explore the underlying biology, we hypothesised that malpresentation among term infants may reflect delays in turning associated with early neurodevelopmental differences that later manifest as ASD. A study of vaginal breech delivery that used detailed data from the Finland Medical Birth Register and the Hospital Discharge Register reported no increase in risk of neurodevelopmental outcomes among extremely pre-term and very pre-term infants with breech presentation; however, among moderate to late pre-term births, breech was associated with an increased risk of ASD compared to children with vertex presentation.[52] However, because of the low prevalence of pre-term, breech presentation and ASD, the results of this and most studies have been very imprecise and should be interpreted with caution. Larger studies are needed to explore this important question.

4.4.3 | Malpresentation and caesarean delivery—Breech and other malpresentation are strong indications for cesarian delivery. Nearly, all children presenting

breech were delivered by caesarean, precluding further evaluation of differences in association by mode of delivery. However, there was variability in the mode of delivery for those with other types of malpresentation. The association between malpresentation and ASD was stronger for malpresenting children delivered vaginally than by caesarean. Prior research found vaginal delivery of non-vertex infants to be challenging and convey injury,[53] lower Apgar score at 1 and 5 minutes,[54] and higher risk of neonatal asphyxia.[47] The Term Breech Trial in 2000 demonstrated a reduced risk of perinatal and neonatal mortality, or serious morbidity, with planned caesarean delivery compared with vaginal delivery for breech presentation.[55] Following that trial, caesarean rates for breech presentation increased substantially. However, little published information is available for developmental risks associated with mode of delivery for malpresentation other than breech. Our observation of a slightly stronger association between malpresentation and ASD among children born by vaginal delivery than by caesarean delivery could support concerns about associated risks of brain injury and later development delay.[56,57] Whereas, we acknowledge that stratifying on mode of delivery, which temporally occurs after malpresentation at delivery, may bias the interpretation of associations between malpresentation and ASD. Furthermore, we lacked details about the timing of inter-related complications related to the mode of delivery, thus extra caution is necessary for a causal interpretation. Researchers should continue to study the developmental effects of vaginal delivery of malpresenting infants.

5 | CONCLUSIONS

Malpresentation at delivery was modestly associated with ASD in these data. While prior reports have focused on the association between caesarean and ASD, these data suggest that upstream factors of caesarean delivery, like malpresentation or its antecedents, could be contributing to that association with ASD. Further studies are necessary to understand the biological mechanisms through which this association operates.

Future well-powered studies should explore whether gestational age modifies these associations with ASD and whether malpresentation is a risk factor or more generally, an early sign of aberrant foetal development, perhaps resulting from other underlying endogenous and exogenous influences during pregnancy. Despite the need for additional research with more power to investigate whether the association is causal, our results should prompt new investigations to unravel complex inter-relationships among perinatal events and conditions involved in the aetiology of ASD during intrauterine development. Furthermore, several studies have shown the benefits of early diagnosis and pre-emptive intervention or support to optimise development at a later age.[58] Malpresentation has a prevalence of 3–4% in the general population; early monitoring of neurodevelopment among children born with malpresentation could identify children with ASD sooner and enhance opportunities to support their development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDG EMENTS

This article was supported by the following Cooperative Agreement Numbers from the Centers for Disease Control and Prevention: Cooperative Agreement Number U10DD000180, Colorado Department of Public Health; Cooperative Agreement Number U01000750, University of Colorado Denver; Cooperative Agreement Number U01DD001210, The Regents of the University of Colorado; Cooperative Agreement Number U10DD000181, Kaiser Foundation Research Institute (CA); Cooperative Agreement Number U01000748, Kaiser Foundation Research Institute (CA); Cooperative Agreement Number U10DD000182, University of Pennsylvania; Cooperative Agreement Number U01000752, University of Pennsylvania; Cooperative Agreement Number U10DD000183, Johns Hopkins University; Cooperative Agreement Number U01000746, Johns Hopkins University; Cooperative Agreement Number U01DD001214 and 1U01DD001209, Johns Hopkins University; Cooperative Agreement Number U10DD000184, University of North Carolina at Chapel Hill; Cooperative Agreement Number U01000749, University of North Carolina at Chapel Hill; Cooperative Agreement Number U01DD001205, University of North Carolina at Chapel Hill; Cooperative Agreement Number U10DD000498, Michigan State University; Cooperative Agreement Number U10DD000901, Michigan State University; Cooperative Agreement Number U01DD001216, Washington University and Cooperative Agreement Number U01DD001215, University of Wisconsin System. The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, US Department of Health and Human Services. We thank the Study to Explore Early Development Data Coordinating Center team at the Clinical and Translational Sciences Institute of Michigan State University for their support throughout this study.

Funding information

Centers for Disease Control and Prevention, Grant/Award Number: U10DD000180, U10DD000181, U10DD000182, U10DD000183, U10DD000184, U10DD000498, U01DD000746, U01DD000748, U01DD000749, U01DD000750, U01DD000752, U10DD00090, U01DD001205, U01DD001210, 1U01DD001209, U01DD001214, U01DD001215 and U01DD001216

DATA AVAILABILITY STATEMENT

SEED data should be confidential as it contains PHI and would not be publicly available.

REFERENCES

1. Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. Transl Pediatr. 2020;9:S55–S65. [PubMed: 32206584]
2. CDC. Autism Prevalence Higher, According to Data from 11 ADDM Communities. Center of Disease Control and Prevention; 2023 [updated March 23, 2023; cited 2023 August 3]. https://www.cdc.gov/media/releases/2023/p0323-autism.html
3. Gupte-Singh K, Singh RR, Lawson KA. Economic burden of attention-deficit/hyperactivity disorder among pediatric patients in the United States. Value Health. 2017;20:602–609. [PubMed: 28408002]
4. Hallmayer J, Cleveland S, Torres A, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry. 2011;68:1095–1102. [PubMed: 21727249]
5. Hegarty JP, Pegoraro LF, Lazzeroni LC, et al. Genetic and environmental influences on structural brain measures in twins with autism spectrum disorder. Mol Psychiatry. 2020;25:2556–2566. [PubMed: 30659287]
6. Yip BHK, Leonard H, Stock S, et al. Caesarean section and risk of autism across gestational age: a multi-national cohort study of 5 million births. Int J Epidemiol. 2016;46:429–439.
7. Wang C, Geng H, Liu W, Zhang G. Prenatal, perinatal, and postnatal factors associated with autism: a meta-analysis. Medicine. 2017;96:e6696. [PubMed: 28471964]
8. Molkenboer J, Roumen F, Smits L, Nijhuis J. Birth weight and neurodevelopmental outcome of children at 2 years of age after planned vaginal delivery for breech presentation at term. Am J Obstet Gynecol. 2006;194:624–629. [PubMed: 16522389]
9. Giuliani A, Schöll WM, Basver A, Tamussino KF. Mode of delivery and outcome of 699 term singleton breech deliveries at a single center. Am J Obstet Gynecol. 2002;187:1694–1698. [PubMed: 12501085]

10. Källén K, Serenius F, Westgren M, Maršál K, Group E. Impact of obstetric factors on outcome of extremely preterm births in Sweden: prospective population-based observational study (EXPRESS). Acta Obstet Gynecol Scand. 2015;94:1203–1214. [PubMed: 26249263]
11. Ravichandran L, Allen VM, Allen AC, Vincer M, Baskett TF, Woolcott CG. Incidence, intrapartum risk factors, and prognosis of neonatal hypoxic-ischemic encephalopathy among infants born at 35 weeks gestation or more. J Obstet Gynaecol Can. 2020;42:1489–1497. [PubMed: 33039315]
12. Nelson KB, Broman SH. Perinatal risk factors in children with serious motor and mental handicaps. Ann Neurol. 1977;2:371–377. [PubMed: 153120]
13. Begum T, Rahman A, Nababan H, et al. Indications and determinants of caesarean section delivery: evidence from a population-based study in Matlab, Bangladesh. PLoS One. 2017;12:e0188074.
14. Cordero C, Windham GC, Schieve LA, et al. Maternal diabetes and hypertensive disorders in association with autism spectrum disorder. Autism. Research. 2019;12:967–975. [PubMed: 30969030]
15. Maher GM, O'Keeffe GW, Dalman C, et al. Association between preeclampsia and autism spectrum disorder: a population-based study. J Child Psychol Psychiatry. 2020;61:131–139. [PubMed: 31531876]
16. You J, Shamsi BH, Hao M-c, Cao C-H, Yang W-Y. A study on the neurodevelopment outcomes of late preterm infants. BMC Neurol. 2019;19:1–6. [PubMed: 30606131]
17. Macharey G, Gissler M, Rahkonen L, et al. Breech presentation at term and associated obstetric risks factors—a nationwide population based cohort study. Arch Gynecol Obstet. 2017;295:833–838. [PubMed: 28176014]
18. Miller ME, Dunn PM, Smith DW. Uterine malformation and fetal deformation. J Pediatr. 1979;94:387–390. [PubMed: 423019]
19. Kooistra L, Kuppens S, Hasaart T, et al. High thyrotrophin levels at end term increase the risk of breech presentation. Clin Endocrinol (Oxf). 2010;73:661–665. [PubMed: 20718770]
20. Leung AM. Thyroid function in pregnancy. J Trace Elem Med Biol. 2012;26:137–140. [PubMed: 22658718]
21. Sekulić SR, Mikov A, Petrović ĐS. Probability of breech presentation and its significance. J Matern Fetal Neonatal Med. 2010;23:1160–1164. [PubMed: 20230320]
22. Sharshiner R, Silver RM. Management of fetal malpresentation. Clin Obstet Gynecol. 2015;58:246–255. [PubMed: 25811125]
23. Debero Mere T, Beyene Handiso T, Mekiso AB, Selamu Jifar M, Aliye Ibrahim S, Bilato DT. Prevalence and perinatal outcomes of singleton term breech delivery in Wolisso hospital, Oromia region, Southern Ethiopia: a cross-sectional study. Journal of environmental and public. Health. 2017;2017:1–8.
24. Eaton WW, Mortensen PB, Thomsen PH, Frydenberg M. Obstetric complications and risk for severe psychopathology in childhood. J Autism Dev Disord. 2001;31:279–285. [PubMed: 11518482]
25. Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2005;161:916–925. [PubMed: 15870155]
26. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics. 2009;123:1293–1300. [PubMed: 19403494]
27. Hamm MP, Cherry NM, Chan E, Martin JW, Burstyn I. Maternal exposure to perfluorinated acids and fetal growth. J Expo Sci Environ Epidemiol. 2010;20:589–597. [PubMed: 19865074]
28. Schendel DE, DiGuiseppi C, Croen LA, et al. The study to explore early development (SEED): a multisite epidemiologic study of autism by the centers for autism and developmental disabilities research and epidemiology (CADDRE) network. J Autism Dev Disord. 2012;42:2121–2140. [PubMed: 22350336]
29. Wiggins LD, Reynolds A, Rice CE, et al. Using standardized diagnostic instruments to classify children with autism in the study to explore early development. J Autism Dev Disord. 2015;45:1271–1280. [PubMed: 25348175]

30. Eaves LC, Wingert HD, Ho HH, Mickelson EC. Screening for autism spectrum disorders with the social communication questionnaire. J Dev Behav Pediatr. 2006;27:S95–S103. [PubMed: 16685191]
31. Lord C, Rutter M, Goode S, et al. Austism diagnostic observation schedule: a standardized observation of communicative and social behavior. J Autism Dev Disord. 1989;19:185–212. [PubMed: 2745388]
32. Reaven JA, Hepburn SL, Ross RG. Use of the ADOS and ADI-R in children with psychosis: importance of clinical judgment. Clin Child Psychol Psychiatry. 2008;13:81–94. [PubMed: 18411867]
33. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med. 2012;22:276–282.
34. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017;135:29–41. [PubMed: 27858958]
35. von Ehrenstein OS, Cui X, Yan Q, Aralis H, Ritz B. Maternal prenatal smoking and autism spectrum disorder in offspring: a California statewide cohort and sibling study. Am J Epidemiol. 2021;190:728–737. [PubMed: 32830844]
36. Durkin MS, Maenner MJ, Baio J, et al. Autism spectrum disorder among US children (2002–2010): socioeconomic, racial, and ethnic disparities. Am J Public Health. 2017;107:1818–1826. [PubMed: 28933930]
37. van der Burg JW, Sen S, Chomitz VR, Seidell JC, Leviton A, Dammann O. The role of systemic inflammation linking maternal BMI to neurodevelopment in children. Pediatr Res. 2016;79:3–12. [PubMed: 26375474]
38. Taylor K, Compton S, Kolenic GE, et al. Financial hardship among pregnant and postpartum women in the United States, 2013 to 2018. JAMA Netw Open. 2021;4:e2132103.
39. Sakamoto Y, Ishiguro M, Kitagawa G. Akaike information criterion statistics. Dordrecht, the Netherlands: D Reidel. 1986;81:26853.
40. Ananth CV, Schisterman EF. Confounding, causality, and confusion: the role of intermediate variables in interpreting observational studies in obstetrics. Am J Obstet Gynecol. 2017;217:167–175. [PubMed: 28427805]
41. Schieve LA, Harris S, Maenner MJ, Alexander A, Dowling NF. Assessment of demographic and perinatal predictors of non-response and impact of non-response on measures of association in a population-based case control study: findings from the Georgia study to explore early development. Emerg Themes Epidemiol. 2018;15:1–12. [PubMed: 29387137]
42. Northam S, Knapp TR. The reliability and validity of birth certificates. J Obstet Gynecol Neonatal Nurs. 2006;35:3–12.
43. Haghighat N, Hu M, Laurent O, Chung J, Nguyen P, Wu J. Comparison of birth certificates and hospital-based birth data on pregnancy complications in Los Angeles and Orange County, California. BMC Pregnancy Childbirth. 2016;16:1–10. [PubMed: 26728010]
44. Josberger RE, Wu M, Nichols EL. Birth certificate validity and the impact on primary cesarean section quality measure in New York state. J Community Health. 2019;44:222–229. [PubMed: 30324538]
45. Burstyn I, Sithole F, Zwaigenbaum L. Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. Chronic Dis Can. 2010;30:125–134. [PubMed: 20946713]
46. Pilliod RA, Caughey AB. Fetal malpresentation and malposition: diagnosis and management. Obstetrics and Gynecology Clinics. 2017;44:631–643. [PubMed: 29078945]
47. Berhan Y, Haileamlak A. The risks of planned vaginal breech delivery versus planned caesarean section for term breech birth: a meta-analysis including observational studies. BJOG. 2016;123:49–57. [PubMed: 26234485]
48. UK NGA. Management of breech presentation. 2021.
49. Moura R, Borges M, Vila Pouca MC, et al. A numerical study on fetal head molding during labor. Int J Numer Methods Biomed Eng. 2021;37:e3411.

50. Pop VJ, Brouwers EP, Wijnen H, Oei G, Essed GG, Vader HL. Low concentrations of maternal thyroxin during early gestation: a risk factor of breech presentation? BJOG. 2004;111:925–930. [PubMed: 15327606]

51. Andersen SL, Andersen S, Vestergaard P, Olsen J. Maternal thyroid function in early pregnancy and child neurodevelopmental disorders: a Danish nationwide case-cohort study. Thyroid. 2018;28:537–546. [PubMed: 29584590]

52. Toijonen A, Heinonen S, Gissler M, Seikku L, Macharey G. Impact of fetal presentation on neurodevelopmental outcome in a trial of preterm vaginal delivery: a nationwide, population-based record linkage study. Arch Gynecol Obstet. 2021;1–7:29–35.

53. Gunay T, Turgut A, Bor ED, Hocaoglu M. Comparison of maternal and fetal complications in pregnant women with breech presentation undergoing spontaneous or induced vaginal delivery, or cesarean delivery. Taiwan J Obstet Gynecol. 2020;59:392–397. [PubMed: 32416886]

54. Zewude SB, Ajebe TM, Gessesse SS, Wassie TH. Proportion and predictive factors of low apgar score at five minute among singleton term neonates delivered in Debre Tabor specialized hospital, northwest Ethiopia: a cross-sectional study. Int J Africa Nurs Sci. 2021;15:100322.

55. Rietberg CCT, Elferink-Stinkens PM, Visser GH. The effect of the term breech trial on medical intervention behaviour and neonatal outcome in The Netherlands: an analysis of 35,453 term breech infants. BJOG. 2005;112:205–209. [PubMed: 15663585]

56. Geirsson RT. 13 birth trauma and brain damage. Baillieres Clin Obstet Gynaecol. 1988;2:195–212. [PubMed: 3046800]

57. Alexopoulos K. The importance of breech delivery in the pathogenesis of brain damage. End results of a long-term follow-up. Obstet Gynecol Surv. 1973;28:720–721.

58. Whitehouse AJ, Varcin KJ, Pillar S, et al. Effect of preemptive intervention on developmental outcomes among infants showing early signs of autism: a randomized clinical trial of outcomes to diagnosis. JAMA Pediatr. 2021;175:e213298.

Synopsis

Study question

This study examined malpresentation, a common and important indication for caesarean delivery and its association with ASD.

What is already known

As caesarean delivery has been consistently shown to be moderately associated with ASD from different studies, this study explored the association between malpresentation, an indication for caesarean delivery and ASD.

What the study adds

By addressing limitations from previous studies, this study shed light on understanding the ASD etiological mechanisms and emphasised early monitoring of neurodevelopment among children born with malpresentation to enhance opportunities to support development among children with ASD.

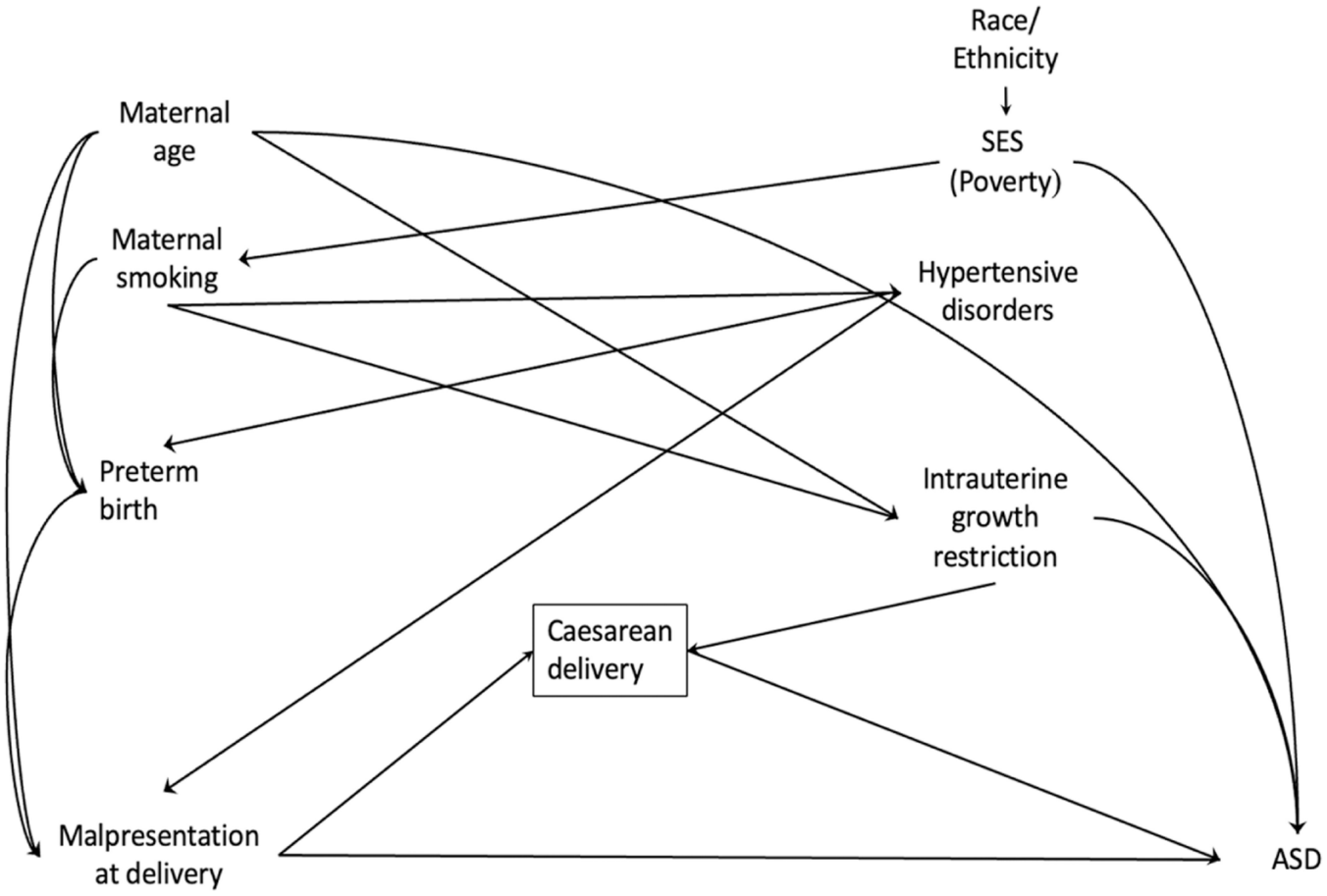

FIGURE 1.

Direct Acyclic Graph on malpresentation and autism spectrum disorder. ASD, Autism Spectrum Disorder; SES, Socioeconomic Status.

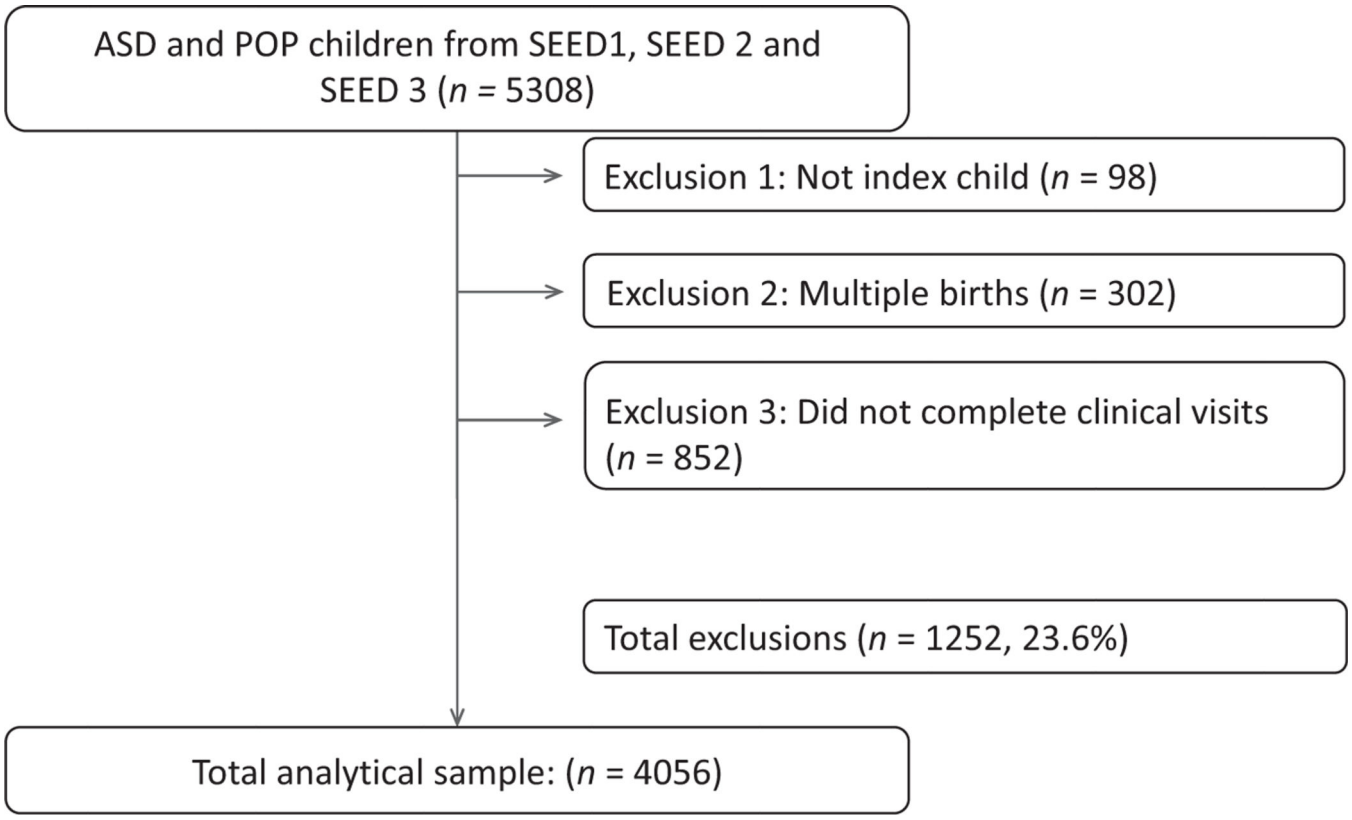

FIGURE 2.
Study flowchart. ASD, Autism Spectrum Disorder; POP, Population Controls; SEED, Study to Explore Early Development.

TABLE 1

Data sources to identify infant presentation at delivery *i*n the Study to Explore Early Development Phases 1–3, data collection years 2007–2020.

Data source available	***N***	**%**
Birth record, maternal interview, medical record	1587	39.1
Birth record and maternal interview	1363	33.6
Medical record and maternal interview	659	16.2
Birth record and medical record	7	0.2
Maternal interview only	403	9.9
Birth record only	21	0.5
Medical record only	10	0.2
Missing	9	0.2

TABLE 2

Maternal and child characteristics among infant presentation in the Study to Explore Early Development Phases 1–3, data collection years 2007–2020.

	ASD Cases		Population Controls		Vertex		Malpresentation		Total	
	N = 1873		*N* = 2174		*N* = 3760		*N* = 287		*N* = 4047[a]	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Maternal age (years)										
<29	754	40.3	724	33.3	1387	36.9	91	31.7	1478	36.5
30–39	1012	54.0	1356	58.8	2195	58.4	173	60.3	2368	58.5
≥40	107	5.7	94	6.6	178	4.7	23	8.0	201	5.0
Missing	0		0		0		0		0	
Maternal education										
≤High school	373	19.9	248	11.4	571	15.2	50	17.4	621	15.4
Some college	573	30.6	437	20.1	939	25.0	71	24.7	1010	25.0
≥College	926	49.5	1488	68.5	2248	59.8	166	57.8	2414	59.7
Missing	1		1		2		0		2	
Maternal race/ethnicity										
Non-Hispanic, White	971	51.9	1510	69.5	2303	61.3	178	62.0	2481	61.3
Non-Hispanic, Black	439	23.5	289	13.3	677	18.0	51	17.8	728	18.0
Non-Hispanic, Other	212	11.3	179	8.2	368	9.8	23	8.0	391	9.7
Hispanic	250	13.4	195	9.0	410	10.9	35	12.2	445	11.0
Missing	1		1		2		0		2	
Poverty[b]										
≤138%	399	22.3	275	13.1	625	17.3	49	17.4	674	17.3
139–250%	253	14.2	195	9.3	422	11.7	26	9.3	448	11.5
251–399%	337	18.9	377	17.9	665	18.4	49	17.4	714	18.3
≥400%	798	44.7	1260	59.8	1901	52.6	157	55.9	2058	52.9
Missing	86		67		147		6		153	
Pre-pregnancy body mass index (BMI)										
Low or Healthy	904	49.8	1333	62.5	2102	57.3	135	48.2	2237	56.7
Overweight	478	26.4	477	22.4	876	23.9	79	28.2	955	24.2
Obese	432	23.8	323	15.1	689	18.8	66	23.6	755	19.1

	ASD Cases		Population Controls		Vertex		Malpresentation		Total	
	N = 1873		*N* = 2174		*N* = 3760		*N* = 287		*N* = 4047[a]	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Missing	59		41		93		7		100	
Maternal smoking										
No	1629	87.8	2033	94.3	3399	91.2	263	92.0	3662	91.3
Yes	227	12.2	123	5.7	327	8.8	23	8.0	350	8.7
Missing	17		18		34		1		35	
Gestational age										
Preterm (<37 weeks)	234	12.5	165	7.6	336	9.0	63	22.0	399	9.9
Term (> = 37 weeks)	1631	87.5	2003	92.4	3411	91.0	223	78.0	3634	90.1
Missing	8		6		13		1		14	
Parity (including index child)										
1	879	49.1	961	45.7	1693	46.8	147	53.3	1840	47.2
2	583	32.5	749	35.6	1255	34.7	77	27.9	1332	34.2
3 or more	330	18.4	394	18.7	672	18.6	52	18.8	724	18.6
Missing	81		70		140		11		151	
Maternal hypertensive disorder										
No	1550	83.0	1907	87.9	3080	82.0	220	76.7	3300	81.6
Yes	317	17.0	263	12.1	677	18.0	67	23.3	744	18.4
Missing	2		1		3		0		3	
Delivery mode										
Vaginal	1166	62.3	1537	70.8	2655	70.6	48	16.8	2703	66.8
Caesarean delivery	707	37.7	635	29.2	1104	29.4	238	83.2	1342	33.2
Missing	0		2		1		1		2	
Child sex										
Male	1518	81.0	1142	52.5	2484	66.1	176	61.3	2660	65.7
Female	355	19.0	1032	47.5	1276	33.9	111	38.7	1387	34.3
Missing	0		0		0		0		0	
Birthweight (g)										
Mean (SD)	3270.9 (689.4)		3361.2 (583)		3342.7 (598.3)		3014.6 (957.7)		3319.4 (635.9)	
Median	3336.0		3402.0		3374.0		3245.0		3374.0	

	ASD Cases		Population Controls		Vertex		Malpresentation		Total	
	N = 1873		*N* = 2174		*N* = 3760		*N* = 287		*N* = 4047[a]	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Missing	12		9		19		2		21	

Abbreviations: ASD, Autism Spectrum Disorder; SD, Standard deviation.

[a] *N* = 4047, Missing = 9 for foetal presentation; however, the missing foetal presentation was imputed in the regression analysis.

[b] Poverty levels are the ratio of parent-reported household pre-tax income during the 12 months prior to the child's birth and the federal poverty threshold, then categorised poverty relative to the national threshold.

TABLE 3

Malpresentation at delivery and odds ratio for Autism Spectrum Disorder among 2–5 year-old children in the Study to Explore Early Development, data collection years 2007–2020.

Birth presentation	ASD *n* (%)	POP *n* (%)	Adjusted odds ratio (95% CI)[a]	CLR
Vertex	1722 (91.9)	2038 (93.7)	1.00 (Reference)	
Malpresentation	151 (8.1)	136 (6.3)	1.31 (1.02, 1.68)	1.65
Breech	112 (6.0)	103 (4.7)	1.28 (0.96, 1.70)	1.77
Other malpresentation	39 (2.1)	33 (1.5)	1.40 (0.87, 2.26)	2.60

Abbreviations: ASD, Autism Spectrum Disorder; CI, Confidence Interval; CLR, Confidence limit ratio; POP, Population Control.

[a]All models adjusted for maternal age, poverty level, maternal hypertensive disorder and maternal smoking.

TABLE 4

Malpresentation at delivery and odds ratio for Autism Spectrum Disorder among 2–5-year-old children, stratified by pre-term and term births in the Study to Explore Early Development, data collection years 2007–2020.

Birth presentation	ASD *n* (%)	POP *n* (%)	Adjusted odds ratio (95% CI)[a]	CLR
Term				
Vertex	1519 (93.1)	1892 (94.5)	1.00 (Reference)	
Malpresentation	112 (6.9)	111 (5.5)	1.29 (0.98, 1.70)	1.73
Breech	78 (4.8)	80 (4.0)	1.24 (0.89,1.71)	1.92
Other malpresentation	34 (2.1)	31 (1.6)	1.42 (0.86, 2.34)	2.72
Preterm				
Vertex	195 (83.3)	141 (85.5)	1.00 (Reference)	
Malpresentation	39 (16.7)	24 (14.5)	1.11 (0.62, 1.98)	3.19
Breech	34 (14.5)	22 (13.3)	1.09 (0.60, 1.99)	3.32
Other malpresentation	5 (2.1)	2 (1.2)	1.24 (0.22, 7.01)	31.86

Abbreviations: ASD, Autism Spectrum Disorder; CI, Confidence Interval; CLR, Confidence limit ratio; NA, Not applicable; NR, No OR estimate Reported due to a small number of cases; POP, Population Control.

[a]All models adjusted for maternal age, poverty level, maternal hypertensive disorder and maternal smoking.