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Prenatal ultrasound use and risk of autism spectrum disorder: Findings from the case-control Study to Explore Early Development

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Abstract

Background: Studies evaluating the association between prenatal ultrasounds and autism spectrum disorder (ASD) have largely produced negative results. Concern remains due to the rising identification of children with ASD and ultrasound use.

Objective: To evaluate the association between prenatal ultrasound use and ASD.

Methods: We used data from the Study to Explore Early Development, a multisite case-control study of preschool-aged children with ASD implemented during 2007–2012. We recruited cases from children receiving developmental disability services and randomly selected population controls from birth records. ASD case status was based on in-person standardised assessments. We stratified analyses by pre-existing maternal medical conditions and pregnancy complications associated with increased ultrasound use (ultrasound indications) and used logistic regression to

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AUTHOR CONTRIBUTIONS

AAA, LAC, LAS, GCW and SKS contributed to the conception and design of the work. DC, LJE, KP, LAC, NFD, LAS, SCT, GCW, WMC and SKS contributed to the analytic plan for the analysis, which was completed by DC, LHT and KJO. DC and KP were responsible for drafting the manuscript. LJE, KJO, AAA, LAC, NFD, LAS, LHT, SCT, GCW, WMC and SKS reviewed and provided critical comments for revision. All the authors approve and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors have indicated they have no potential conflicts of interest to disclose. The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

SUPPORTING INFORMATION

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

model case status by increasing ultrasound counts. For pregnancies with medical record data on ultrasound timing, we conducted supplementary tests to model associations by trimester of exposure.

Results: Among 1524 singleton pregnancies, ultrasound indications were more common for ASD cases than controls; respectively, for each group, no indications were reported for 45.1% and 54.2% of pregnancies, while ≥2 indications were reported for 26.1% and 18.4% of pregnancies. The percentage of pregnancies with multiple ultrasounds varied by case status and the presence of ultrasound indications. However, stratified regression models showed no association between increasing ultrasound counts and case status, either for pregnancies without (aOR 1.01, 95% CI 0.92, 1.11) or with ultrasound indications (aOR 1.01, 95% CI 0.95, 1.08). Trimester-specific analyses using medical record data showed no association in any individual trimester.

Conclusions: We found no evidence that prenatal ultrasound use increases ASD risk. Study strengths included gold-standard assessments for ASD case classification, comparison of cases with controls, and a stratified sample to account for conditions associated both with increased prenatal ultrasound use and ASD.

Keywords

autism; developmental disorder; epidemiology; pregnancy complications; prenatal ultrasound

1 | BACKGROUND

The proportion of children diagnosed with autism spectrum disorder (ASD) has risen over the last two decades,[1,2] prompting evaluation of potential contributing factors. While evidence supports a genetic component to ASD aetiology,[3–7] environmental factors may also contribute to ASD risk, potentially interacting with genetic susceptibility.[8]

Ultrasound in pregnancy is an essential tool to assess gestational age, monitor fetal growth and development, and detect fetal malformations.[9,10] While the routine use of prenatal ultrasound roughly doubled between 1995 and 1997 and 2005-2006,[11] the American College of Obstetricians and Gynecologists (ACOG) recommends ultrasound should be performed only in the presence of a valid medical indication and using the lowest possible exposure settings for purposes such as confirmation of intrauterine pregnancy and fetal cardiac activity, estimation of gestational age and evaluation of fetal anatomy.[9] Indications for additional ultrasounds include evaluation of fetal growth and well-being, follow-up of obstetric complications, and evaluation of fetal anomalies.[9]

Because thermal and non-thermal exposures from prenatal ultrasound could theoretically affect neurologic development,[12,13] and rodent studies have reported associations between ultrasound and neurologic function or behaviour,[14–17] ultrasound has been examined as an exposure of interest in human development.[18] However, existing research has largely reported no association between prenatal ultrasound use and various measures of adverse perinatal and neurologic outcomes.[18] Studies specifically examining the potential association between prenatal ultrasound use and ASD also have reported largely negative results,[10,19–22] but have been limited by the use of administrative data without information

on the rigour of clinical assessment for ASD,[10,19] small samples sizes and the absence of a control group[20] or not accounting for maternal medical or pregnancy conditions associated both with increased prenatal ultrasound use and ASD.[10,19–21]

The objective of this analysis was to examine whether there is an association between prenatal ultrasound use and ASD using data from the Study to Explore Early Development (SEED), one of the largest studies of risk factors for ASD in the United States. SEED includes gold-standard in-person developmental assessments to determine ASD case status, data on the number of prenatal ultrasounds administered, and extensive and detailed data on maternal and pregnancy exposures, health status and other factors potentially related to ASD.

2 | METHODS

2.1 | Case-control selection

Subjects for this analysis were participants in the first phase of SEED (SEED1). SEED1 is a case–control study of risk factors, behavioural phenotypes, and co-occurring health conditions related to ASD. SEED1 was conducted during 2007–2012 at six study sites within California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania. A detailed description of the SEED eligibility criteria, ascertainment methods, enrollment methods, and data collection protocol has been previously published.[23]

Eligible children were born from September 2003 to August 2006, were aged 2–5 years at the time of enrollment, resided in one of the six catchment areas at birth and at first contact with study staff, and lived with a knowledgeable caregiver who could communicate in English (or in California and Colorado, English or Spanish). Study participants were identified in two ways: (1) children in the population control (POP) group were identified from a random sample of state vital birth records and (2) children with potential ASD or other developmental disabilities (DDs) were identified from multiple educational sources and health providers who diagnose and serve children with DDs.

Of the participants in SEED1, 3769 received a final study group classification (Figure 1). For this analysis, we excluded children in the DD group, given its inclusion of heterogeneous conditions, and children with a possible ASD classification. Of 1930 children in the ASD (n = 707) or POP (n = 1223) group, 1280 had data on ultrasound counts reported by the biological mother from the interview data, as well as data on maternal medical and pregnancy conditions associated with heightened ultrasound monitoring; of the remaining 1930 participants with an ASD or POP classification, we excluded 319 without data on prenatal ultrasounds from interview data and then created multiply imputed data sets (described below) to obtain counts of maternal medical conditions and pregnancy complications for 331 participants with missing data, for a sample of 1611 participants (ASD = 663, POP = 948). An additional 87 pregnancies with multiple foetuses were excluded from our main analyses due to small numbers, for a final analytic sample of 1524 singleton pregnancies (ASD = 614, POP = 910).

2.2 | Exposures

Data were collected on family medical history, maternal reproductive health and obstetrical history, and child development using a variety of data collection methods - telephone interviews, self-administered forms, in-person child development assessments, and abstraction of maternal and child medical records. Limited data were obtained from birth certificates.

2.2.1 | Ultrasounds—Data from the caregiver interview and medical record abstractions were used to examine prenatal ultrasound exposure. When interviewed, respondents (biological mothers only) were asked how many ultrasounds they received and whether any problems or abnormalities were identified. While not asked to report the indication for each ultrasound, respondents were asked to select problems identified during pregnancy from a list (problems of fetal growth, placenta, biophysical profile; decreased fetal movement; amniotic fluid volume; a fetal malformation or defect; other). Respondents also were asked in which trimester the first ultrasound abnormality was noted but not the first trimester of ultrasound administration.

Prenatal medical record abstractions included the date of the ultrasound(s), gestational age estimates, and the reason for each ultrasound (confirm dates; obtain biophysical profile; check amniotic fluid volume, fetal growth or decreased movement; concerns with the placenta; rule out or monitor malformations; other).

2.2.2 | Maternal medical and pregnancy conditions—We used maternal medical and pregnancy conditions that were potential indications for heightened ultrasound monitoring to stratify analyses, given their association with ASD as well as with increased ultrasound use. Based on a review of the literature and consensus discussion of an expert panel, including an obstetrician/gynaecologist and paediatrician, a comprehensive list of maternal medical and pregnancy conditions most likely to be associated with both heightened ultrasound monitoring (ultrasound indications) and with ASD risk was identified. This list included prior prenatal ultrasound abnormality; birth defects; breech presentation; intrauterine growth retardation; infertility; prenatal valproic acid use; maternal pre-pregnancy body mass index ≥30; multiple foetuses and several maternal medical conditions (diabetes [preconceptional and gestational], hypertension [preconceptional; pregnancy-induced; pre-eclampsia; eclampsia; hemolysis, elevated liver enzymes, low platelet count syndrome], Addison disease, cystic fibrosis, Graves disease, Hashimoto thyroiditis, haemophilia, myasthenia gravis, neurofibromatosis, systemic lupus erythematosus, Sjogren syndrome, Sydenham chorea, and von Willebrand disease). For each participant, the presence of these ultrasound indications was determined using data from the caregiver interview and other self-reported forms (maternal medical history form, autoimmune disease questionnaire), birth certificate records, and medical record abstractions when available. For each participant, the number of indications was grouped into 0, 1, and ≥2 conditions.

2.3 | Covariates

Maternal characteristics associated both with ASD risk and ultrasound use included age (<35, ≥35 years), education (some high school or high school grad, some college/college grad, postgraduate), smoking during pregnancy (yes, no), and race/ethnicity (non-Hispanic White, non-Hispanic Black/Hispanic/other). Child sex (male, female) and study site (California, Colorado, Georgia, Maryland, North Carolina, Pennsylvania) also were included. Child sex was obtained from birth certificates while all other covariates were ascertained from interview data.

2.4 | Outcome

Study procedures for ASD case classification have been described previously.[24] Briefly, the Social Communication Questionnaire (SCQ)[25] was administered to all study participants at enrollment to screen for ASD. Children with a pre-existing ASD diagnosis or identified to have ASD risk based on the SCQ (all children with a score ≥11, including those initially recruited from birth records for the POP group) received caregiver consent to complete a more comprehensive developmental evaluation, including the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) at 3–7years.[26,27] Children who met the study criteria for ASD based on the ADOS and ADI-R were classified in the ASD group irrespective of the severity of their autism.

2.5 | Statistical analysis

To assess the distribution of covariates, the presence of ultrasound indications (0, 1, ≥2), and the number of ultrasounds, we examined percentages by case status for the full analytic sample of singleton pregnancies with data on ultrasound indications and ultrasound counts from interview data (n = 1524). We conducted supplemental analyses to describe the sample that included pregnancies with multiple foetuses (n = 1611), and to provide a detailed distribution of ultrasound indications by type of maternal medical or pregnancy condition and case status using the original unimputed values (n = 1280).

To test for an association between ASD case status and increasing numbers of prenatal ultrasounds, we stratified analyses into pregnancies without any prenatal ultrasound indications (n = 754), and pregnancies with ≥1 ultrasound indication reported (n = 770). We first assessed the distribution of the number of prenatal ultrasounds (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or ≥10). We then used logistic regression models to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CIs), accounting for maternal age, education, race/ethnicity, and smoking; child sex and study site.

We also conducted a secondary analysis using ultrasound counts from medical record data to test for the association between ASD case status and prenatal ultrasound use by trimester of exposure. This analysis included 568 participants who had no ultrasound indications and had ultrasound count data from both the caregiver interview and medical records (ASD = 209; POP = 359). During the implementation of SEED, a core set of providers was contacted for medical records (i.e., prenatal, neonatal and paediatric providers). These medical records provided information on ultrasound timing, although some SEED participants were potentially lacking medical records from relevant speciality providers, particularly those

outside of general prenatal care, and reliability testing resulted in an intra-class correlation coefficient of 0.39 (95% CI 0.34, 0.44) for the concordance of ultrasounds from the two data sources. Nonetheless, given findings on the importance of the timing of exposure for ASD risk,[28] use of available medical records allowed for analyses by trimester of exposure.

All the analyses were conducted using SAS Version 9.4.

2.6 | Missing data

To account for the missingness of maternal medical conditions and pregnancy complications, we used multiple imputations with fully conditional specification methods (logistic regression for all categorical variables and predictive mean matching method for continuous variables) to create 50 imputed datasets. In addition to 331 participants with unknown maternal medical conditions and pregnancy complications, there were small numbers of participants with missing data for the covariates included in our regression models (<1%). Our imputation model assumed values were missing at random and included case status, maternal medical conditions and pregnancy complications, ultrasound counts, maternal age at interview, maternal race/ethnicity, maternal education at interview, maternal smoking during pregnancy, child sex, and study site. Each imputed data set was analysed and the results from each of the 50 imputed data sets were combined and summarised using Rubin's rule.[29]

2.7 | Sensitivity analyses

Given the association of maternal medical conditions and pregnancy complications both with increased ultrasound monitoring and with ASD, we stratified our analyses into pregnancies with and without these factors and included both samples in our main analysis. Because of the small number of pregnancies with multiple foetuses, we limited these pregnancies to the description of our sample population. Finally, although many pregnancies lacked ultrasound count data from medical record abstractions, we included an analysis using the subset of pregnancies with this information to allow for an assessment by trimester of exposure. For this analysis, we ensured the comparability of our sample population by drawing from the sample population used in our main analysis with ultrasound exposure data from the maternal interview.

2.8 | Ethics approval

The SEED protocol was approved by the Institutional Review Board at CDC and each study site. All caregivers provided verbal informed consent at study enrollment and written informed consent during an in-person evaluation of their child.

3 | RESULTS

A higher percentage of children in the ASD versus the POP group were male and born preterm. A higher percentage of mothers of children in the ASD versus the POP group smoked during pregnancy, while a lower percentage had advanced education and were non-Hispanic White (Table 1). The same patterns were observed in supplemental analyses

including pregnancies with multiple foetuses, with the additional finding that pregnancies with multiple foetuses were more common in the ASD versus the POP group (Table S1).

Ultrasound indications were more common among mothers of children in the ASD versus the POP group. Among ASD (n = 614) and POP (n = 910) mothers with singleton pregnancies, 45.1% and 54.2%, respectively, reported no indications for increased prenatal ultrasound use, while 26.1% and 18.4% reported ≥2 indications (Table 2). Examination of specific types of indications for heightened ultrasound monitoring showed that the percentage was higher among mothers in the ASD versus the POP group for most every type of indication (Table S2).

In analyses stratified into pregnancies with and without indications for increased ultrasound monitoring, the percentage of pregnancies with multiple ultrasounds varied by case status and by the presence of ultrasound indications (Table 3). Among pregnancies with no indications, ≤1 ultrasound was reported for 9.8% and 13.8% of pregnancies in the ASD and the POP group, respectively, while ≤10 ultrasounds were reported for just 1.1% and 2.0% of pregnancies. By contrast, among pregnancies with indications, ≥1 ultrasound was reported in just 5.1% and 5.5% of pregnancies, in the ASD and POP group, respectively, while ≥10 ultrasounds were reported for 11.5% and 8.8% of pregnancies. Further, adjusted odds ratios showed no association between increasing ultrasound counts and ASD case status (Table 3; no ultrasound indications: aOR 1.01, 95% CI 0.92, 1.11; ≥1 ultrasound indications: aOR 1.01 95% CI 0.95, 1.08).

Among the subpopulation with data on ultrasound counts from both the caregiver interview and prenatal medical records (ASD, n = 209; POP, n = 359), adjusted logistic regression models showed no association between medical record ultrasound counts and ASD case status (aOR 0.98, 95% CI 0.86, 1.11). Similarly, trimester-specific analyses showed no association between increasing ultrasound counts and ASD case status in any individual trimester (Table 4).

4 | COMMENT

4.1 | Principal findings

We found no association between prenatal ultrasound exposure and ASD risk in this study. While maternal medical and pregnancy conditions associated with heightened ultrasound monitoring (ultrasound indications) were more common among ASD cases than population controls, the number of ultrasounds did not differ for ASD cases and population controls when pregnancies were stratified for analysis into those that did and did not have ultrasound indications. Stratified multivariable regression models also showed no association between increasing numbers of ultrasounds and ASD case status. Trimester-specific analysis using medical record data for pregnancies with no ultrasound indications further showed no association between case status and increasing ultrasound counts in any individual trimester.

4.2 | Strengths of the study

In many ways, this study strengthens findings from previous research demonstrating no association between ultrasound use and ASD.[10,19–22] Previous studies have been limited by

the use of administrative data without information on the rigour of clinical assessment for ASD, small sample sizes and failing to account for factors associated both with ASD and heightened ultrasound monitoring. By contrast, SEED conducted comprehensive in-person assessments using the gold standard ADOS and ADI-R assessments to classify children with ASD. It also included a control group and collected detailed information on maternal and child health characteristics and demographic variables. Using this information, we were able to stratify our analyses for pregnancies that did and did not have documented indications for increased ultrasound monitoring, and then further controlled for sociodemographic variables that were potential confounders.

4.3 | Limitations of the data

This study also has limitations. The use of maternal retrospective reports of ultrasound exposure is subject to recall bias. Prenatal medical records were available for a subset of women, but records may have been incomplete, particularly for speciality providers caring for women with complex pregnancies. Another limitation is that ultrasound protocols and exposures are relevant to the study period (2003–2006). While ACOG has discouraged the use of ultrasound for nonmedical purposes dating back to the study period,[30] protocols may have changed over time in terms of intensity,[31] types of ultrasound, frequency of transducers or duration of exposure, or acoustic intensity.[32] Finally, many women initially identified as potentially eligible for SEED could not be contacted, resulting in differential case and control selection. However, data from one SEED site with data on all potential study participants originally sampled indicate that differential participation likely had minimal impact on association with several perinatal factors (preterm delivery, Caesarean delivery, and induction/stimulation of labour).[33]

4.4 | Interpretation

The ability to account for maternal and child demographics and health characteristics, including pre-existing maternal medical conditions and pregnancy complications, is an important aspect of our analysis since many are risk factors for ASD that have also been associated with heightened ultrasound monitoring. In a 2017 meta-analysis that included 17 studies with >37,000 children with ASD and >12,000 controls, the authors identified the following risk factors for ASD: advanced maternal age, gestational hypertension, pre-eclampsia, gestational diabetes, antepartum haemorrhage, breech presentation, and fetal distress.[34]

While our current analysis fills an important gap, it is consistent with previous human studies that have largely found negative results when assessing the potential association between prenatal ultrasound use and the risk of ASD. The most comparable case–control study to our current analysis found no overall association between ultrasounds and ASD risk, although this study did find an increased risk for ASD among female children from pregnancies with an increasing number of ultrasounds in the second trimester.[19] However, while this study excluded multiple foetuses and used medical record data, limitations included the lack of control for medical indications for ultrasound use and the use of diagnostic codes from clinical databases for ascertainment of ASD case status. A more recent case–control study using medical records included the number of ultrasounds and

timing of exposure, along with a number of measures of intensity.[20] This study found no difference by case status in the number of scans. Compared to controls with typical development, the ASD group had a greater mean depth of ultrasound exposure, but there were no other differences by case status in measures of ultrasound intensity.

Two randomised trials also reported negative results. The first compared pregnancies with a single prenatal ultrasound at 18 weeks to pregnancies with an ultrasound examination and Doppler flow study at 18, 24, 28, 34 and 38 weeks.[21] Parents were asked to report diagnoses of ASD at five follow-up times between 5 and 17 years, and their children completed the Autism Spectrum Quotient (AQ)[35] at 19 and 20 years. No differences were found between prenatal ultrasound groups, although the study was not large enough to detect significant effects for diagnosed ASD and no information was provided on maternal medical or pregnancy indications for ultrasound. The second randomised trial found similar rates of ASD (1.2%) with prenatal ultrasound performed for nuchal translucency assessment at either 12 or 18 weeks,[10] although this study made no adjustment for maternal medical or pregnancy conditions.

A final study using data from the Simons Simplex Collection of individuals with ASD reported that first-trimester ultrasound exposure combined with the presence of copy number variants (CNVs) in the child was associated with increased repetitive behaviour and decreased non-verbal intelligence quotient among male children with ASD.[22] Importantly, this study used propensity scores to adjust for factors that increased the likelihood of receiving a first-trimester ultrasound, including maternal and pregnancy characteristics. Nonetheless, because the acoustic output of ultrasound increased by an order of magnitude comparing the years 1984–1991 to 1992–2010,[31] further studies with strengths similar to those in the current analysis are needed to examine the effect of ultrasound intensity.[20] Additionally, given genetic research showing different effects of CNV variant,[22] follow-up in larger studies with prospectively collected measures of antenatal ultrasound exposure, gold-standard ASD phenotypic data and genetic data are warranted.

5 | CONCLUSIONS

Findings from this analysis suggest no increased risk of ASD with the use of prenatal ultrasound. Our results re-affirm findings from previous studies of no association between prenatal ultrasound use and ASD for pregnancies with and without medical indications for increased prenatal ultrasound monitoring. Unlike previous studies, the current analysis was unique in that it used gold-standard assessments for ASD case classification, compared cases with controls and accounted for pre-existing medical conditions and pregnancy complications associated both with heightened prenatal ultrasound monitoring and ASD risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Deidentified individual participant data will not be made publicly available. Because sensitive and identifiable information was collected through the SEED, this study was granted a Certificate of Confidentiality, and participants were assured during the consent process that their identifiable information would not be shared.

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Synopsis

Study question

Is there an association between prenatal ultrasound use and autism spectrum disorder (ASD)?

What's already known

Studies evaluating the association between prenatal ultrasound use and ASD have largely produced negative results. Concern remains due to the rising identification of children with ASD and the common use of prenatal ultrasound.

What this study adds

Unlike previous studies, the current analysis was unique in that it used gold-standard assessments for ASD case classification, compared cases with controls, and accounted for pre-existing medical conditions and pregnancy complications associated both with heightened prenatal ultrasound monitoring and ASD. Our results reaffirm findings from previous studies of no association between prenatal ultrasound use and ASD for pregnancies with and without medical indications for increased prenatal ultrasound monitoring.

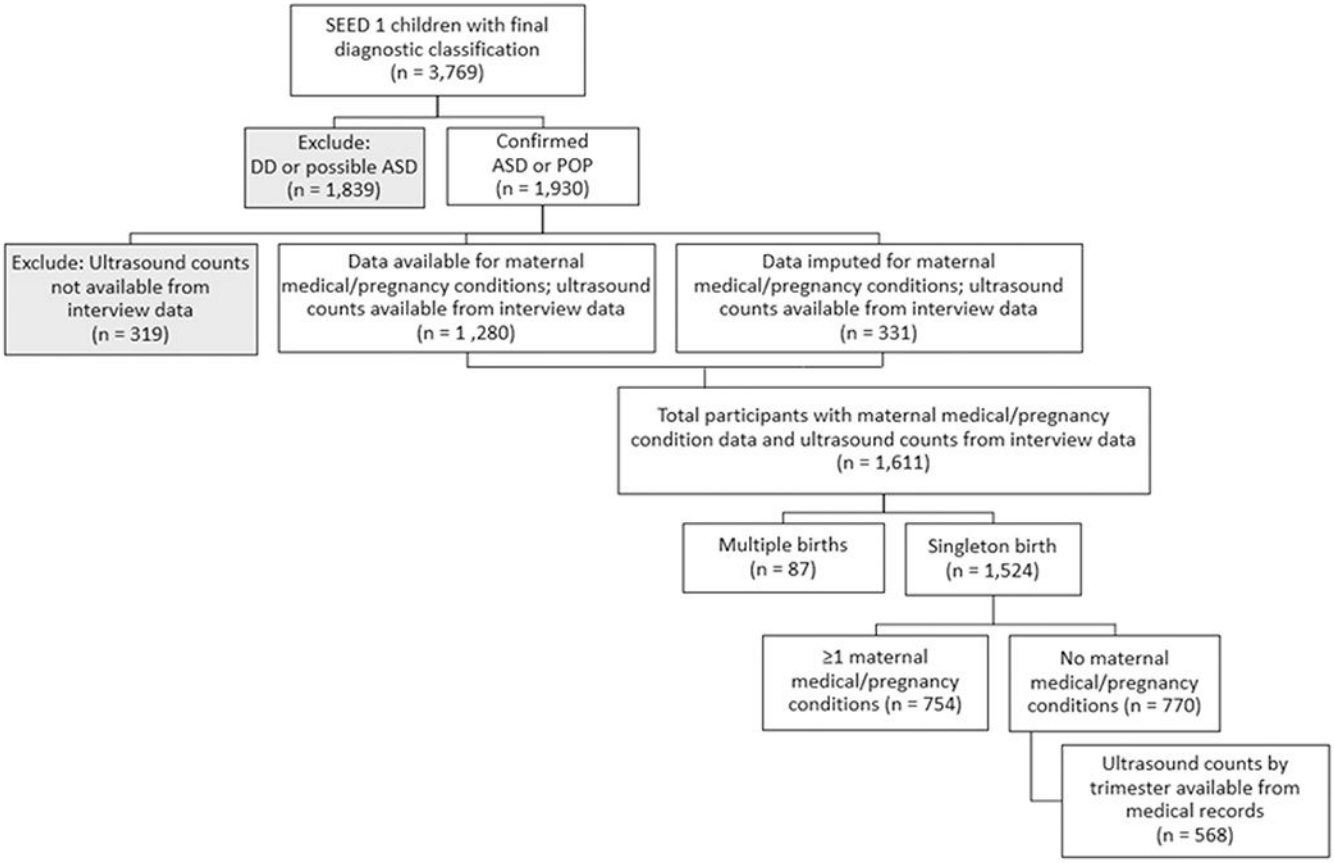

FIGURE 1.

Participant flow diagram, Study to Explore Early Development Phase 1 (SEED 1). ASD, autism spectrum disorder case group; DD, other developmental disability control group; POP, population control group.

TABLE 1

Sociodemographic and perinatal characteristics among autism spectrum disorder cases and population controls for singleton pregnancies with ultrasound data from the caregiver interview (n = 1524).

Characteristics[a]	Autism cases (n = 614) % of pregnancies	Population controls (n = 910) % of pregnancies
Maternal age at interview (years)		
<35	72.6	71.4
≥35	27.4	28.6
Maternal education at interview		
Some high school or high school grad	15.8	10.1
Some college/college grad	63.4	60.0
Postgraduate	20.8	29.9
Maternal race/ethnicity		
Non-Hispanic White	55.9	70.4
Non-Hispanic Black	19.7	12.4
Non-Hispanic Other	12.1	8.8
Hispanic	12.3	8.4
Maternal smoking during pregnancy		
No	86.9	91.1
Yes	13.1	8.9
Child sex		
Male	82.2	53.3
Female	17.8	46.7
Gestational age at birth (weeks)		
<32	3.1	0.8
32–36	16.6	13.3
≥37	79.6	85.5
Missing	0.7	0.4

[a]Maternal age, education, and race/ethnicity; and child sex are reported based on multiply imputed data; for each variable, <1% of participants were missing data for these variables from the original data set.

TABLE 2

Number of potential indications for heightened prenatal ultrasound monitoring among singleton pregnancies with ultrasound data from the caregiver interview (n = 1524).

	Autism cases (n = 614)	Population controls (n = 910)
Number potential indications for ultrasound[a]	**% of pregnancies**	**% of pregnancies**
No indications	45.1	54.2
1 indication	28.8	27.5
≥2 indications	26.1	18.4

[a] Data are reported based on multiply imputed data.

TABLE 3

Distribution of ultrasound counts and adjusted odds for autism spectrum disorder with increasing ultrasounds counts, among singleton pregnancies with ultrasound count data from caregiver interview (n = 1524).

Singleton pregnancies with no maternal medical or pregnancy conditions that were potential indications for ultrasound (n = 770)			**Singleton pregnancies with ≥1 maternal medical or pregnancy conditions that were potential indications for ultrasound (n = 754)**	
Ultrasound measure[a]	**Autism cases (n = 277)**	**Population controls (n = 493)**	**Autism cases (n = 337)**	**Population controls (n = 417)**
Ultrasound counts	**% of pregnancies**	**% of pregnancies**	**% of pregnancies**	**% of pregnancies**
0	0.4	0.4	0.3	0.3
1	9.4	13.4	4.8	5.2
2	28.2	30.4	18.7	18.0
3	30.7	27.4	25.4	25.4
4	14.4	12.6	16.3	16.3
5	9.7	5.7	12.4	8.4
6	2.9	4.7	4.6	9.5
7	1.4	1.4	1.4	4.1
8	1.4	1.4	2.4	3.0
9	0.4	0.6	2.2	1.1
≥10	1.1	2.0	11.5	8.8
Odds of ASD with increasing ultrasound count from 0 to ≥10	**aOR** [b]	**95% CI**	**aOR** [b]	**95% CI**
	1.01	0.92, 1.11	1.01	0.95, 1.08

Abbreviations: ASD, autism spectrum disorder; aOR, adjusted odds ratio; CI, confidence interval.

[a] Data are reported based on multiply imputed data.

[b] Adjusted for maternal age, education, race/ethnicity and smoking; child sex and study site, using multiply imputed datasets; for each variable, <1% of participants were missing data for these variables from the original data set.

TABLE 4

Distribution of ultrasound counts by trimester of exposure and adjusted odds for autism spectrum disorder, among singleton pregnancies with no indications reported for increased ultrasound monitoring and ultrasound counts from medical record data (n = 568).

1st trimester		
	Autism cases (n = 209)	**Population controls (n = 359)**
Number of ultrasounds[a]	**% of pregnancies**	**% of pregnancies**
0	46.4	40.4
1	43.1	46.5
≥2	10.5	13.1
Odds of ASD with increasing ultrasound count from 0 to ≥10	**aOR** [b]	**95% CI**
	0.81	0.63, 1.05
2nd trimester		
Number of ultrasounds[a]	**% of pregnancies**	**% of pregnancies**
0	11.5	11.7
1	61.2	62.7
≥2	27.3	25.6
Odds of ASD with increasing ultrasound count from 0 to ≥10	**aOR** [b]	**95% CI**
	1.02	0.82, 1.28
3rd trimester		
Number of ultrasounds[a]	**% of pregnancies**	**% of pregnancies**
0	57.9	61.6
1	30.1	25.6
≥2	12.0	12.8
Odds of ASD with increasing ultrasound count from 0 to ≥10	**aOR** [b]	**95% CI**
	1.02	0.86, 1.21

Abbreviations: ASD, autism spectrum disorder; aOR, adjusted odds ratio; CI, confidence interval.

[a] Data are reported based on multiply imputed data.

[b] Adjusted for maternal age, education, race/ethnicity and smoking; child sex and study site, using multiply imputed datasets; for each variable, <1% of participants were missing data for these variables from the original data set.