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Prenatal Maternal Alcohol Exposure During the First Trimester of Pregnancy in Relation to Early Learning Ability, Behavioral Problems, and Autistic Traits in Preschool Children With or Without Autism Spectrum Disorder

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Abstract

Prenatal alcohol exposure has been linked to adverse neurodevelopmental outcomes. However, its effects on developmental outcomes in children with autism spectrum disorder (ASD) remain unclear. We examined associations between prenatal alcohol exposure during the first trimester (PAE-FT) and early learning ability, behavioral problems, and severity of autistic traits in preschool-aged children in a large multi-site case-control study, the Study to Explore Early Development. Children were classified as ASD ($n = 1237$) or population comparison without ASD (POP, $n = 1334$) after an in-person assessment covering cognitive abilities and detailed autistic traits. Mothers completed questionnaires on their child's behavior and autism-related traits, as well as their alcohol use during pregnancy. Of children in the ASD and POP groups, 18.5% and 20.2%, respectively, were exposed to PAE-FT. Exposure to 3 or more alcoholic drinks per week was associated with increased externalizing behaviors (i.e., attention deficits and aggressive behaviors) in children in both the ASD and POP groups, and with exacerbated social communication and interaction deficits in children with ASD only. First trimester exposure to 1–2 alcoholic drinks per week was associated with early learning delays for children in the ASD group, but not the POP group. As expected, our findings suggest that PAE-FT is associated with adverse behavioral development of children regardless of ASD status. However, PAE-FT may exacerbate autism-specific developmental problems and learning difficulties in children with ASD. Gathering a prenatal alcohol exposure history for children with and without ASD could contribute to a

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Conflicts of Interest

The authors declare no conflicts of interest.

better understanding of developmental trajectories, aiding informed decisions for interventions and support.

Keywords

alcohol; autism; behaviors; learning delays; neurodevelopment

1 | Introduction

Prenatal alcohol exposure (PAE) has been linked to many adverse neurodevelopmental outcomes, such as impaired motor skills, reduced cognitive function, and behavioral problems in children (Chu et al. 2022). Children with PAE are at risk for developing fetal alcohol spectrum disorders (FASDs), which involve a broad range of impairments in physical, behavioral, cognitive, mental, and adaptive functioning (Maya-Enero et al. 2021).

Autism spectrum disorder (ASD) is a heterogeneous developmental disorder characterized by deficits in social communication and interaction as well as the presence of restricted and repetitive behaviors, interests, and activities (American Psychiatric Association 2013; Lord et al. 2020). Children with ASD exhibit wide variability in the prevalence of intellectual disability or co-occurring behavioral, developmental, and medical conditions (Levy et al. 2010; Wiggins, Levy, et al. 2015; Wiggins et al. 2022; Tian et al. 2020). While there is no single underlying cause of ASD, available evidence indicates that both genetic and environmental risk factors play an important role in ASD etiologies (Miles 2011; Kim and Leventhal 2015; Lyall et al. 2017; Hertz-Picciotto et al. 2018). Genetic factors could influence an individual's predisposition to autism, while environmental factors might modify the phenotypic expression of this disorder through epigenetic alterations (Varadinova and Boyadjieva 2015). Some studies suggest that the embryonic period is a critical exposure window affecting the risk of developing ASD (Arndt et al. 2005; Packer 2016; Schieve, Tian, et al. 2018).

PAE has been investigated as a potential environmental risk factor for ASD, but its effect, if any, on ASD development remains unclear (Carpita et al. 2022; Luo et al. 2022). Individuals with ASD and FASDs share some characteristics, such as cognitive delays, behavioral problems, and social skill deficits (Stevens et al. 2013; Carpita et al. 2022). The clinical overlap of these conditions suggests possible shared etiologic mechanisms. However, a recent meta-analysis of observational studies suggested that currently available data do not support an independent association between PAE and ASD (Luo et al. 2022). These observational studies investigating the link between PAE and ASD typically assessed ASD outcomes using a binary measure, comparing those meeting the study's ASD criteria to a control group without ASD (Luo et al. 2022; Eliassen et al. 2010; Gallagher et al. 2018; Singer et al. 2017). Given the significant variability in ASD symptoms and severity, conducting a risk assessment solely based on a classification of ASD versus no ASD may obscure meaningful effects of PAE on the development of ASD in offspring. Furthermore, it remains unclear whether PAE has varying effects on neurodevelopmental outcomes, such as early learning ability, behavioral problems, and social engagement skills, in children with

ASD compared to those without ASD. Assessing the associations with neurodevelopmental outcomes could enhance our understanding of the heterogeneity of this disorder, potentially providing insights into its etiology, diagnosis, treatment, and prognosis (Georgiades et al. 2013).

The main objective of this analysis was to examine the association between PAE during the first trimester (PAE-FT) and various aspects of child development, including early learning ability, behavioral problems, and the severity of autistic traits in preschool children with and without ASD, using data from the Study to Explore Early Development (SEED), a large case–control study of risk factors for ASD in the United States. We sought to shed light on the relationship between PAE-FT and ASD, including core and co-occurring phenotypical symptoms and their severity. Additionally, we aimed to examine whether PAE-FT is differentially associated with these outcomes in children with ASD compared to those without ASD.

2 | Methods

2.1 | Participants and Data Collection

Study participants were caregivers and preschool children aged 2–5 years enrolled in SEED, phase 2, conducted between 2012 and 2016, and phase 3, conducted between 2017 and 2021. Data from SEED phase 1 was not included due to inconsistencies in alcohol data collection compared to phases 2 and 3. SEED is a multi-site case–control study of risk factors and behavioral phenotypes of ASD. Study methods have been published previously (Schendel et al. 2012). Briefly, SEED phases 2 and 3 recruited families of preschool children aged 2–5 years in defined regions of eight states (California [phase 2 only], Colorado, Georgia, Maryland, North Carolina, Pennsylvania [phase 2 only], Missouri [phase 3 only], and Wisconsin [phase 3 only]) in the United States. Children were identified through educational and health sources or random samples of birth certificate records within each study site's catchment area.

2.1.1 | Determination of Autism Spectrum Disorder Case Definition: Caregivers of all enrolled children were asked to complete the Social Communication Questionnaire (SCQ) (Rutter et al. 2003) to screen for possible ASD characteristics in the child and allow a trained clinician to evaluate the child's early learning ability during an in-person developmental evaluation. Caregivers of children with an SCQ score of ≥ 11 (indicating a risk of ASD), with a previous ASD diagnosis, or demonstrating ASD behaviors during the developmental evaluation were also asked to complete the Autism Diagnostic Interview Revised (ADI-R) (Lord et al. 1994) and have their child complete the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1999, 2012). Children meeting study criteria on the ADOS and ADI-R were classified as having ASD. Children in the population comparison group without ASD (POP) were those ascertained from birth certificate records who had an SCQ score < 11 or did not meet SEED ASD criteria. Details on the SEED final classification criteria were previously published (Wiggins, Reynolds, et al. 2015).

2.1.2 | Measurement of Early Learning Ability and Severity of Autistic Traits and Behavioral Problems: Early learning ability was measured via the Mullen Scales of

Early Learning (MSEL) (Mullen 1995). The MSEL is a standardized clinician-administered assessment of cognitive functioning in young children. The MSEL yields an early learning composite (ELC) standard score that is derived from four subscales: receptive language, expressive language, fine motor skills, and visual reception. The MSEL ELC has a mean of 100 and a standard deviation of 15 points, with higher scores reflecting more advanced skill development.

Severity of autistic traits was measured using the Social Responsiveness Scale (SRS), preschool and child versions (Constantino 2002; 2006 WPS Preschool Version). The SRS is a standardized caregiver questionnaire that measures autistic traits in general population samples. The SRS yields t-scores for social communication and interaction (SCI) deficits and restricted interests and repetitive behaviors (RRB). Higher SRS t-scores indicate more severe symptoms, with scores greater than or equal to 66 representing moderate or severe ASD risk.

Severity of behavioral problems was measured with the Child Behavior Checklist (CBCL) [Achenbach 2013]. The CBCL is a standardized caregiver questionnaire that measures internalizing behavior problems (i.e., emotional reactivity, somatic complaints, anxiety and depression, and social withdrawal) and externalizing behavior problems (i.e., attention deficits and aggressive behavior). The CBCL yields t-scores for internalizing and externalizing behavior problems. Higher CBCL t-scores indicate more frequent behavior problems, with scores greater than or equal to 60 suggesting borderline to clinically elevated problems in the child.

2.1.3 | Measurement of Prenatal Alcohol Exposure: PAE was assessed during a computer-assisted telephone interview with the child's mother. Mothers were asked about their alcohol use from the period of 3 months before pregnancy (preconception) until the end of pregnancy (by trimester of pregnancy). An alcoholic drink was defined as "one beer, one glass of wine, one mixed drink, or one shot of liquor." Those reporting any alcohol use also were asked about the average number of drinks per week in specific time periods. PAE was defined as "ever" exposure during the specific time of pregnancy (ever drinking versus no drinking), as well as the average quantity of alcoholic drinks consumed per week (categorized as: none, < 1 drink per week, 1–2 drinks per week, and ≥ 3 drinks per week) by trimester of pregnancy. Preliminary analyses indicated that most children with prenatal alcohol exposure were exposed during the first trimester of pregnancy (Table S1); therefore, remaining analyses focused on this exposure period, with a referent group of no alcohol consumption at any time during pregnancy and exclusion of mothers who drank only during second and/or third trimesters.

2.1.4 | Measurement of Other Covariates: Information on maternal and family characteristics considered in this analysis was collected from the telephone interview or a self-administered maternal medical history form included: birth order (first born, not first born); maternal age at birth (< 30, 30–34, ≥ 35 years), race/ethnicity (Non-Hispanic white, non-Hispanic black, Hispanic, other), education (high school or less, some college, college or higher), mother foreign born (yes, no), psychiatric conditions (yes, no), cannabis use during pregnancy (yes, no), and tobacco smoking (yes, no) during pregnancy; exposure to

household tobacco smoking during pregnancy (yes, no); and household income relative to the federal poverty threshold ($\leq 100\%$, $101\%–300\%$, $\geq 301\%$). The presence of at least one maternal psychiatric condition was defined as self-reporting that a healthcare provider ever diagnosed at least one of the following conditions: anxiety, bipolar, depressive, substance-related, feeding and eating, obsessive-compulsive, personality, schizophrenia spectrum, or a pervasive developmental disorder.

2.2 | Statistical Analysis

The timing of the consumption of alcohol during preconception and each trimester was reported, stratified by study group. Chi-squared tests were used to examine differences in categorical variables between study groups. Due to skewed distributions in some continuous measures, we presented medians instead of means. Mood's median tests were employed to evaluate median values between study groups for continuous measures.

Among children with PAE-FT exposure or no alcohol exposure, bivariate analyses were conducted to assess the association between PAE-FT and continuous early learning, behavioral, and autism symptom outcomes separately for children in the ASD and POP groups. Median values and their 95% confidence intervals across levels of PAE-FT were calculated within each study group, and Mood's median tests were used to assess differences across these levels.

In adjusted analyses, we examined the associations between PAE-FT and these outcomes using quantile regression, controlling for birth order, maternal age at birth, maternal race/ethnicity, maternal education, maternal natality (foreign-born, U.S. born), household income relative to the federal poverty threshold, maternal tobacco smoking during pregnancy, maternal exposure to household tobacco smoking during pregnancy, and self-report of at least one maternal psychiatric condition. These covariates were selected a priori that could be associated with PAE and the outcomes. Multicollinearity was assessed first using the variance inflation factor (VIF) before entering the models. Cannabis was considered but not included as a covariate since few mothers reported prenatal cannabis use, which led to imprecise estimates or model convergence issues. The reference group for quantile regression analyses was mothers who did not report any consumption of alcohol during pregnancy. For these analyses, quantile regression parameters estimated the change in median MSEL, SRS, or CBCL scores for a specific level of exposure in the average number of alcoholic drinks consumed by the mother per week in comparison to those without exposure while holding all other independent variables constant. To illustrate, using this method, an estimated MSEL coefficient of -3.00 can be interpreted as follows: the median early learning standard score of children with PAE-FT is 3.00 points lower than the median score of children with no prenatal alcohol exposure. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). All statistical tests were two-sided, and p -values < 0.05 were considered statistically significant.

3 | Results

Of 2714 children who were assigned a final study classification of ASD or POP, 2571 (94.7%) had data on maternal alcohol use, early learning ability, autistic traits, and

behavioral problems and were therefore included in the analysis. Of these, 1237 children were classified as ASD, and 1334 children were classified as comparisons without ASD (POP).

Maternal, child, and family characteristics of the study sample are provided in Table 1. Mothers of children in the ASD group vs. the POP group differed in maternal age at birth, race-ethnicity, education, and household income relative to the federal poverty threshold. Mothers of children with ASD were more likely to be foreign-born, to smoke or be exposed to household smoking during pregnancy, and to have a psychiatric condition. Children in the ASD group vs. the POP group were more likely to be firstborn and had lower median scores in early learning ability and higher median scores in autistic traits (both SCI and RRB) and behavioral problems (both internalizing and externalizing behaviors).

The timing of alcohol use by study group is presented in Table S1. Maternal alcohol use was more common during the first trimester than during the second and third trimesters in both study groups.

Maternal alcohol use was also more prevalent among children in the POP group compared to those in the ASD group during the preconception period and the second and third trimesters. However, the difference in the prevalence of alcohol exposure during the first trimester (20.2% vs. 18.5%, $p = 0.269$) was not statistically significant.

Among mothers of children with ASD, 80.7% reported no alcoholic drinks in the whole period of pregnancy; 10.5% reported an average of fewer than 1 alcoholic drink per week during the first trimester, 4.6% reported an average of 1–2 drinks per week during the first trimester, and 4.2% reported an average of 3 or more drinks per week during the first trimester (Table 2). Among mothers of children from the POP group, 77.8% reported no alcohol use in the whole period of pregnancy; 12.7% reported an average of fewer than 1 alcoholic drink per week during the first trimester, 6.2% reported an average of 1–2 drinks per week during the first trimester, and 3.4% reported an average of 3 or more drinks per week during the first trimester (Table 2). There were no differences in the distribution of alcohol quantity consumed per week between study groups ($p = 0.072$).

Unadjusted bivariate analyses showed that in both the ASD and the POP groups, when compared to children whose mothers did not consume alcohol during pregnancy, children whose mothers consumed 3 or more alcoholic drinks per week in the first trimester had more externalizing behavior problems (Table 2). Children in the POP group whose mothers consumed 3 or more alcoholic drinks per week had a lower median score in early learning ability, although the difference was not statistically significant. There were no statistically significant differences in median values across PAE-FT levels for any of the other outcome measures.

The maximum VIF was 1.6, indicating there was no severe collinearity problem between the explanatory variables. Adjusted quantile regression analyses demonstrated that in both the ASD and the POP groups, children whose mothers reported 3 or more alcoholic drinks per week during their first trimester had more externalizing behavior problems (Table 3). Specifically, the median CBCL externalizing behavior score of children whose mothers

consumed 3 or more drinks per week during their first trimester was 2.87 points higher for children with ASD and 5.89 points higher for children in the POP comparison group than children whose mothers abstained from alcohol throughout the entire pregnancy.

Moreover, among children in the ASD group, PAE-FT was associated with SCI deficits and early learning delays depending on the number of alcoholic drinks consumed per week. The median SRS SCI score of children in the ASD group whose mothers consumed 3 or more drinks per week during their first trimester was 5.13 points higher than that of children whose mothers abstained from alcohol throughout the entire pregnancy (Table 3). The median MSEL ELC score of children whose mothers consumed 1–2 drinks per week during their first trimester was 6.48 points lower than that of children whose mothers abstained from alcohol during pregnancy. PAE-FT was not associated with SCI deficits or early learning delays among children in the POP group.

4 | Discussion

We used a large community-based sample with standardized data collection to examine associations between PAE-FT and measures of early learning ability, as well as severity of behavior problems and autistic traits in children aged 2–5 years, with and without ASD. Results revealed that PAE-FT of 3 or more alcoholic drinks per week was associated with an increase in externalizing behaviors in both groups of children. This finding aligns with previous research on the relationship between FASDs and ASD in children (Carpita et al. 2022). It also aligns with previous studies involving children or adolescents from diverse populations (Khoury et al. 2018; Paley et al. 2005; Sood et al. 2001) and suggests that PAE-FT at this level can disrupt neurodevelopment in children with and without clinically significant manifestations of ASD. Healthcare providers can use this finding in support of educating women on the potential harms of PAE-FT to the developing fetus.

Our findings also revealed that PAE-FT, with an average consumption of 1–2 drinks per week, was associated with a decrease in early learning ability among children with ASD, but not those without ASD. However, we did not observe the same association for those who consumed 3 or more drinks per week. This finding could be due to a high level of variability in cognitive scores among children with ASD whose mothers consumed 3 or more drinks, as shown by the wide confidence interval for the median (ranging from 51 to 80, with a median of 58). Additionally, the number of children in this group was small. Nonetheless, children with ASD exposed to as few as one alcoholic drink per week during the first trimester could benefit from being monitored for early learning delays and provided educational support, if needed.

PAE-FT of 3 or more alcoholic drinks per week was associated with increased SCI impairment among children with ASD, but not among children without ASD. Genetic factors play critical roles in ASD, and researchers have identified hundreds of genes that contribute to the significant deficits in communication, social cognition, and behavior commonly observed in individuals with ASD (Qiu et al. 2022; Gonatopoulos-Pournatzis et al. 2020; Rylaarsdam and Guemez-Gamboa 2019). Alcohol-induced modifications in epigenetic processes have been considered to underlie the enduring effects of alcohol and

the passing down of autistic traits across generations (Varadinova and Boyadjieva 2015). Our findings, along with others, suggest that in addition to PAE neurodevelopmental effects, such exposure might interact with underlying genetic factors, possibly exacerbating SCI impairment in children with ASD. This finding has important implications for future research investigating the link between ASD and FASD and supporting pregnant mothers with genetic risk for ASD in their children.

Conversely, we found no significant associations of PAE-FT with early learning delays and SCI impairment among those without ASD in the population comparison group. A recent meta-analysis of six prospective cohorts (Jacobson et al. 2024) examining the effects of PAE on cognitive function found no evidence of PAE effects among the offspring of women who drank lightly (~1 drink per occasion) during pregnancy. This lack of effects at low exposure levels aligns with our findings of no association with early learning ability among children without ASD. However, the meta-analysis observed relatively strong effects in the offspring of mothers who consumed moderate (~2–3 drinks per occasion) or heavy (~3 or more drinks per occasion) amounts, which conflicts with our findings. Differences between the meta-analysis and our study may largely be attributed to confounding factors and differences in sample sizes. The meta-analysis included six cohorts with participants of unknown ASD status, whereas our study specifically examined children without ASD in the population comparison group. This allowed us to isolate the effects of PAE without the confounding influence of ASD-related risk factors, as the absence of genetic risk factors for ASD in the POP group may have reduced susceptibility to alcohol-induced genetic modifications. Additionally, by pooling data across six cohorts, the meta-analysis had larger numbers of participants in the moderate and heavy drinking categories, yielding greater statistical power. In contrast, our study had smaller sample sizes for individuals consuming an average of 1–2 drinks or 3+ drinks per week during the first trimester. These factors may also explain why we observed no association between PAE-FT and early learning ability in our non-ASD group, despite significant associations in the ASD group. Similarly, they may account for why an association between PAE-FT and SCI were observed in children with ASD but not in those without ASD.

The absence of an association between PAE-FT and the severity of RRB in children with or without ASD is congruent with findings from prior research, even though these earlier studies employed a binary measure (ASD versus non-ASD) as their outcome [Eliassen et al. 2010; Gallagher et al. 2018]. We also did not find an association between PAE-FT and internalizing behavior, as has been previously observed (Sood et al. 2001; Ichikawa et al. 2018). However, it is possible that the age of SEED participants limits the assessment of internalizing behaviors, like anxiety and depression, that are more likely to develop in school-aged children or adolescents (Liu et al. 2011).

This analysis could be limited by unmeasured confounding, exposure misclassification, and selection bias. First, although the SEED caregiver interview asked about many different health conditions and other health-related questions, we could not account for genetic, dietary, and other maternal and paternal characteristics that might potentially confound the associations. Second, we relied on retrospective reports of alcohol consumption collected 2–5 years after the birth of the child; reporting and recall errors may have

led to misclassification of the timing and/or amount of alcohol consumption. Because of uncertainty related to the timing of conception, it is possible that some women reporting only preconceptional alcohol use may have actually consumed alcohol during the first trimester of pregnancy but may have been considered unexposed in this analysis. This analysis also used broad categories for quantifying alcohol consumption due to the limited sample size of mothers consuming 3 or more alcoholic drinks per week, on average, which may not have captured the associations with higher levels of alcohol or with varying levels of consumption per episode of drinking. Finally, selection bias may be a concern. Analyses from one SEED site found non-response to be associated with younger maternal age at birth, lower maternal education, and non-white race (Schieve, Harris, et al. 2018). Further, other lifestyle and health-related behaviors of participants who agreed to participate in SEED's intensive research protocol may differ from those not represented in this study, which could—result in a sample that may not fully represent all children with PAE, with ASD, or without ASD, and might influence the generalizability of our findings.

This study has several strengths. First, we used data from a large case–control study that employed standardized instruments to evaluate and classify children with and without ASD. The data also included detailed information on alcohol use and covariates (Schendel et al. 2012). Second, we considered the heterogeneity of ASD and expanded previous analyses by examining continuous measures of early learning ability, behavior problems, and autistic traits in both children with and without ASD. This approach allowed for a more comprehensive evaluation of the relationship between PAE-FT and specific neurodevelopmental outcomes within each group, as well as identifying variations in associations between the two groups. Also, this study employed quantile regression to analyze the association between various levels of PAE-FT and continuous outcome measures. This method is more flexible in modeling non-normal distributions and is more robust against outliers compared to conventional linear regression. Additionally, alcohol exposure during the second or third trimester was excluded when assessing the associations between PAE-FT and the outcomes. By doing so, the comparison group consisted solely of mothers who abstained from alcohol throughout pregnancy, thus avoiding potential confounding effects of PAE during later stages of pregnancy.

In conclusion, we found that exposure to 3 or more alcoholic drinks per week during the first trimester of pregnancy was associated with increased externalizing behaviors in children with and without ASD. Exposure to 1–2 alcoholic drinks per week during the first trimester of pregnancy was associated with early learning delays in children with ASD, but not those without ASD. Additionally, first trimester prenatal exposure to 3 or more alcoholic drinks per week was associated with increased SCI deficits in children with ASD, but not those without ASD. These findings suggest that PAE-FT may adversely affect the behavioral development of children regardless of ASD status and may exacerbate autism-specific developmental problems and learning difficulties in children with ASD. These results are consistent with recommendations that women of reproductive age avoid alcohol entirely when pregnant, attempting to conceive, or could become pregnant (CDC 2016; ACOG 2011). Additionally, these data also point to the importance of obtaining a PAE history for all children (AAP 2024), including children with any neurodevelopmental disorder. This information can contribute to a better understanding of developmental trajectories, thereby

aiding in informed decisions regarding interventions and support tailored to each child's needs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

Research data are not shared.

References

- Achenbach T 2013. "Child Behavior Checklist." Burlington: Achenbach System of Empirically Based Assessment, Case Classification.
- American Academy of Pediatrics (AAP). 2024. "Screening for Prenatal Alcohol Exposure." <https://www.aap.org/en/patient-care/fetal-alcohol-spectrum-disorders/screening-assessment/screening-for-prenatal-alcohol-exposure/>.
- American Psychiatric Association. 2013. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association.
- Arndt TL, Stodgell CJ, and Rodier PM. 2005. "The Teratology of Autism." *International Journal of Developmental Neuroscience* 23, no. 2–3: 189–199. 10.1016/j.ijdevneu.2004.11.001. [PubMed: 15749245]
- Carpita B, Migli L, Chiarantini I, et al. 2022. "Autism Spectrum Disorder and Fetal Alcohol Spectrum Disorder: A Literature Review." *Brain Sciences* 12, no. 6: 792. 10.3390/brainsci12060792. [PubMed: 35741677]
- Centers for Disease Control and Prevention (CDC). 2016. "Vital Signs Alcohol and Pregnancy." <https://www.cdc.gov/vitalsigns/pdf/2016-02-vitalsigns.pdf>.
- Chu JTW, McCormack J, Marsh S, Wells A, Wilson H, and Bullen C. 2022. "Impact of Prenatal Alcohol Exposure on Neurodevelopmental Outcomes: A Systematic Review." *Health Psychology and Behavioral Medicine* 10, no. 1: 973–1002. 10.1080/21642850.2022.2129653. [PubMed: 36238426]
- Constantino JN 2002. The Social Responsiveness Scale. Western Psychological Services.
- Eliassen M, Tolstrup JS, Nybo Andersen AM, Gronbaek M, Olsen J, and Strandberg-Larsen K. 2010. "Prenatal Alcohol Exposure and Autistic Spectrum Disorders—A Population-Based Prospective Study of 80,552 Children and Their Mothers." *International Journal of Epidemiology* 39: 1074–1081. 10.1093/ije/dyq056. [PubMed: 20371506]
- Gallagher C, McCarthy FP, Ryan RM, and Khashan AS. 2018. "Maternal Alcohol Consumption During Pregnancy and the Risk of Autism Spectrum Disorders in Offspring: A Retrospective

- Analysis of the Millennium Cohort Study.” *Journal of Autism and Developmental Disorders* 48: 3773–3782. 10.1007/s10803-018-3626-6. [PubMed: 29948531]
- Georgiades S, Szatmari P, and Boyle M. 2013. “Importance of Studying Heterogeneity in Autism.” *Neuropsychiatry* 3: 123–125.
- Gonatopoulos-Pournatzis T, Niihori R, Salter EW, et al. 2020. “Autism-Misregulated eIF4G Microexons Control Synaptic Translation and Higher Order Cognitive Functions.” *Molecular Cell* 77, no. 6: 1176–1192. 10.1016/j.molcel.2020.01.006. [PubMed: 31999954]
- Hertz-Picciotto I, Schmidt RJ, and Krakowiak P. 2018. “Understanding Environmental Contributions to Autism: Causal Concepts and the State of Science.” *Autism Research* 11, no. 4: 554–586. 10.1002/aur.1938. [PubMed: 29573218]
- Ichikawa K, Fujiwara T, and Kawachi I. 2018. “Prenatal Alcohol Exposure and Child Psychosocial Behavior: A Sibling Fixed-Effects Analysis.” *Frontiers in Psychiatry* 9: 570. 10.3389/fpsyt.2018.00570. [PubMed: 30459661]
- Jacobson JL, Akkaya-Hocagil T, Jacobson SW, et al. 2024. “A Dose–Response Analysis of the Effects of Prenatal Alcohol Exposure on Cognitive Development.” *Alcoholism, Clinical and Experimental Research* 48: 623–639.
- Khoury JE, Jamieson B, and Milligan K. 2018. “Risk for Childhood Internalizing and Externalizing Behavior Problems in the Context of Prenatal Alcohol Exposure: A Meta-Analysis and Comprehensive Examination of Moderators.” *Alcoholism, Clinical and Experimental Research* 42: 1358–1377. 10.1111/acer.13805.
- Kim YS, and Leventhal BL. 2015. “Genetic Epidemiology and Insights Into Interactive Genetic and Environmental Effects in Autism Spectrum Disorders.” *Biological Psychiatry* 77: 66–74. [PubMed: 25483344]
- Levy SE, Giarelli E, Lee LC, et al. 2010. “Autism Spectrum Disorder and Co-Occurring Developmental, Psychiatric, and Medical Conditions Among Children in Multiple Populations of the United States.” *Journal of Developmental and Behavioral Pediatrics* 31, no. 4: 267–275. 10.1097/DBP.0b013e3181d5d03b. [PubMed: 20431403]
- Liu J, Chen X, and Lewis G. 2011. “Childhood Internalizing Behaviour: Analysis and Implications.” *Journal of Psychiatric and Mental Health Nursing* 18, no. 10: 884–894. 10.1111/j.1365-2850.2011.01743.x. [PubMed: 22070805]
- Lord C, Brugha TS, Charman T, et al. 2020. “Autism Spectrum Disorder.” *Nature Reviews. Disease Primers* 6, no. 1: 5. 10.1038/s41572-019-0138-4.
- Lord C, Rutter M, DiLavore P, and Risi S. 1999. *Autism Diagnostic Observation Schedule (ADOS)*. Western Psychological Services.
- Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, and Bishop SL. 2012. *Autism Diagnostic Observation Schedule, Second Edition; Part I: Modules 1–4*. Western Psychological Services.
- Lord C, Rutter M, and Le Couteur AL. 1994. “Autism Diagnostic Interview-Revised: A Revised Version of a Diagnostic Interview for Caregivers of Individuals With Possible Pervasive Developmental Disorders.” *Journal of Autism and Developmental Disorders* 24: 659–685. 10.1007/BF02172145. [PubMed: 7814313]
- Luo Z, Yang C, Cai T, et al. 2022. “Maternal Alcohol Consumption During Pregnancy and Autism Spectrum Disorder in Offspring: A Meta-Analysis.” *Review Journal of Autism Developmental Disorders* 11, no. 2: 265–274. 10.1007/s40489-022-00336-4.
- Lyall K, Croen L, Daniels J, et al. 2017. “The Changing Epidemiology of Autism Spectrum Disorders.” *Annual Review of Public Health* 38: 81–102. 10.1146/annurev-publhealth-031816-044318.
- Maya-Enero S, Ramis-Fernández SM, Astals-Vizcaino M, and García-Algar Ó. 2021. “Neurocognitive and Behavioral Profile of Fetal Alcohol Spectrum Disorder.” *Anales de Pediatría* 95, no. 3: 208. 10.1016/j.anpede.2020.12.012.
- Miles JH. 2011. “Autism Spectrum Disorders—A Genetics Review.” *Genetics in Medicine* 13: 278–294. [PubMed: 21358411]
- Mullen E. 1995. *Mullen Scales of Early Learning*. Pearson.
- Packer A. 2016. “Neocortical Neurogenesis and the Etiology of Autism Spectrum Disorder.” *Neuroscience and Biobehavioral Reviews* 64: 185–195. [PubMed: 26949225]

- Paley B, O'Connor MJ, Kogan N, and Findlay R. 2005. "Prenatal Alcohol Exposure, Child Externalizing Behavior, and Maternal Stress." *Parenting: Science and Practice* 5, no. 1: 29–56. 10.1207/s15327922par0501_2.
- Qiu S, Qiu Y, Li Y, and Cong X. 2022. "Genetics of Autism Spectrum Disorder: An Umbrella Review of Systematic Reviews and Meta-Analyses." *Translational Psychiatry* 12, no. 1: 249. 10.1038/s41398-022-02009-6. [PubMed: 35705542]
- Rutter M, Bailey A, and Lord C. 2003. SCQ: Social Communication Questionnaire. Western Psychological Services.
- Rylaarsdam L, and Guemez-Gamboa A. 2019. "Genetic Causes and Modifiers of Autism Spectrum Disorder." *Frontiers in Cellular Neuroscience* 13: 385. 10.3389/fncel.2019.00385. [PubMed: 31481879]
- Schendel D, DiGiuseppi C, Croen L, et al. 2012. "The Study to Explore Early Development (SEED): A Multi-Site Epidemiologic Study of Autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) Network." *Journal of Autism and Developmental Disorders* 42: 2121–2140. [PubMed: 22350336]
- Schieve LA, Harris S, Maenner MJ, Alexander A, and Dowling NF. 2018. "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." *Emerging Themes in Epidemiology* 15, no. 1: 12. 10.1186/s12982-018-0081-y. [PubMed: 30147744]
- Schieve LA, Tian LH, Drews-Botsch C, et al. 2018. "Autism Spectrum Disorder and Birth Spacing: Findings From the Study to Explore Early Development (SEED)." *Autism Research* 11, no. 1: 81–94. 10.1002/aur.1887. [PubMed: 29164825]
- Singer AB, Aylsworth AS, Cordero C, et al. 2017. "Prenatal Alcohol Exposure in Relation to Autism Spectrum Disorder: Findings From the Study to Explore Early Development (SEED)." *Paediatric and Perinatal Epidemiology* 31: 573–582. 10.1111/ppe.12404. [PubMed: 28881390]
- Sood B, Delaney-Black V, Covington C, et al. 2001. "Prenatal Alcohol Exposure and Childhood Behavior at Age 6 to 7 Years: I. Dose-Response Effect." *Pediatrics* 108, no. 2: E34. 10.1542/peds.108.2.e34. [PubMed: 11483844]
- Stevens SA, Nash K, Koren G, and Rovet J. 2013. "Autism Characteristics in Children With Fetal Alcohol Spectrum Disorders." *Child Neuropsychology* 19: 579–587. [PubMed: 23030694]
- The American College of Obstetrician and Gynecologists (ACOG). 2011. "Committee Opinion No. 496: At-Risk Drinking and Alcohol Dependence: Obstetric and Gynecologic Implications." *Obstetrics and Gynecology* 118, no. 2 Pt 1: 383–388. 10.1097/AOG.0b013e31822c9906. [PubMed: 21775870]
- Tian LH, Wiggins LD, Schieve LA, et al. 2020. "Mapping the Relationship Between Dysmorphology and Cognitive, Behavioral, and Developmental Outcomes in Children With Autism Spectrum Disorder." *Autism Research* 13, no. 7: 1227–1238. 10.1002/aur.2314. [PubMed: 32567802]
- Varadinova M, and Boyadjieva N. 2015. "Epigenetic Mechanisms: A Possible Link Between Autism Spectrum Disorders and Fetal Alcohol Spectrum Disorders." *Pharmacological Research* 102: 71–80. 10.1016/j.phrs.2015.09.011. [PubMed: 26408203]
- Wiggins LD, Levy SE, Daniels J, et al. 2015. "Autism Spectrum Disorder Symptoms Among Children Enrolled in the Study to Explore Early Development (SEED)." *Journal of Autism and Developmental Disorders* 45, no. 10: 3183–3194. 10.1007/s10803-015-2476-8. [PubMed: 26048040]
- Wiggins LD, Reynolds A, Rice CE, et al. 2015. "Using Standardized Diagnostic Instruments to Classify Children With Autism in the Study to Explore Early Development." *Journal of Autism and Developmental Disorders* 45, no. 5: 1271–1280. 10.1007/s10803-014-2287-3. [PubMed: 25348175]
- Wiggins LD, Tian LH, Rubenstein E, et al. 2022. "Features That Best Define the Heterogeneity and Homogeneity of Autism in Preschool-Age Children: A Multisite Case-Control Analysis Replicated Across Two Independent Samples." *Autism Research* 15, no. 3: 539–550. 10.1002/aur.2663. [PubMed: 34967132]

Summary

- We looked at whether mothers consuming alcohol in early pregnancy was associated with learning, social, and behavioral delays in children aged 2–5 with and without autism spectrum disorder (ASD).
- We found that children with and without ASD exposed to 3 or more alcoholic drinks per week in the first trimester had more behavioral problems. Importantly, first trimester alcohol exposure was associated with more pronounced learning delays and social problems for children with ASD compared with those without ASD.

TABLE 1 |
Maternal, child, and family characteristics of preschool-aged children with and without autism spectrum disorder, Study to Explore Early Development.

Characteristic	Children with ASD (N = 1237) n (%)	Population comparison without ASD (N = 1334) n (%)	p, Children with ASD versus population comparison without ASD
Child birth order			
First born	569 (50.3)	574 (45.4)	0.017
Not first born	562 (49.7)	690 (54.6)	
Maternal age at birth (years)			
< 30	498 (40.3)	453 (34.0)	0.002
30–34	409 (33.1)	516 (38.7)	
≥ 35	330 (26.7)	364 (27.3)	
Maternal race-ethnicity			
Non-Hispanic white	621 (50.2)	930 (69.7)	< 0.001
Non-Hispanic black	327 (26.4)	185 (13.9)	
Hispanic	168 (13.6)	114 (8.6)	
Other	121 (9.8)	105 (7.9)	
Maternal education			
High school or less	227 (18.4)	141 (10.6)	< 0.001
Some college	390 (31.5)	243 (18.2)	
College or higher	620 (50.1)	950 (71.2)	
Mother foreign born			
Yes	240 (19.4)	171 (12.8)	< 0.001
No	997 (80.6)	1163 (87.2)	
Household income relative to federal poverty threshold			
≤ 100%	116 (9.8)	81 (6.2)	< 0.001
101%-300%	337 (28.4)	240 (18.5)	
≥ 301%	734 (61.8)	978 (75.3)	
Maternal cannabis use during pregnancy			
Yes	38 (3.1)	39 (2.9)	0.828
No	1199 (96.9)	1294 (97.1)	
Maternal smoking during pregnancy			

Characteristic	Children with ASD (N = 1237) n (%)		Population comparison without ASD (N = 1334) n (%)	p, Children with ASD versus population comparison without ASD
Yes	147 (11.9)		73 (5.5)	< 0.001
No	1090 (88.1)		1261 (94.5)	
Maternal exposure to household smoking during pregnancy				
Yes	107 (8.7)		62 (4.7)	< 0.001
No	1123 (91.3)		1269 (95.3)	
^a At least one maternal psychiatric condition				
Yes	485 (39.3)		355 (26.7)	< 0.001
No	750 (60.7)		977 (73.4)	

	Median (95% CI)	Median (95% CI)	p, Children with ASD versus population comparison without ASD
Early learning ability (MSEL composite standard scores)	57 (55, 59)	104 (102, 105)	< 0.001
Severity of internalizing behaviors (CBCL internalizing behaviors t-scores)	63 (63, 64)	43 (41, 43)	< 0.001
Severity of externalizing behaviors (CBCL externalizing behaviors t-scores)	59 (59, 60)	43 (42, 43)	< 0.001
Social communication and interaction deficits (SRS social communication and interaction [SCI] t-scores)	71 (71, 72)	44 (44, 44)	< 0.001
Severity of restricted interests and repetitive behaviors (SRS restricted interests and repetitive behavior[RRB] t-scores)	71 (71, 73)	44 (44, 44)	< 0.001

Note: p-value, derived from chi-square tests for categorical variables and from median tests for continuous variables.

Abbreviations: ASD, autism spectrum disorder group; CBCL, child behavior checklist; CI, confidence interval; MSEL, Mullen scales of early learning; n, total number of subjects.

^a Presence of at least one maternal psychiatric condition was defined as self-report that a healthcare provider ever diagnosed at least one of the following conditions: an anxiety, bipolar, depressive, substance related, feeding and eating, obsessive-compulsive, personality, schizophrenia spectrum, or pervasive developmental disorder.

TABLE 2 |
Bivariate analysis of the associations of maternal drinking during the first trimester with early learning ability, behavioral problems, and severity of autistic traits by case status, Study to Explore Early Development.

Average drinks per week	No drinking during pregnancy	< 1	1–2	3 or more	p
Children with ASD (N= 1186)					
n (%)	957 (80.7)	125 (10.5)	54 (4.6)	50 (4.2)	
Median (95% CI)					
Early learning ability (MSEL composite standard scores)	57 (55, 59)	58 (53, 63)	53 (49, 59)	58 (51, 80)	0.379
Severity of internalizing behaviors (CBCL internalizing behaviors t-scores)	63 (62, 64)	63 (60, 65)	63 (59, 66)	65 (63, 66)	0.451
Severity of externalizing behaviors (CBCL externalizing behaviors t-scores)	59 (58, 60)	60 (58, 62)	59 (55, 63)	64 (62, 67)	0.023
Social communication and interaction deficits (SRS social communication and interaction [SCI] t-scores)	71 (70, 72)	73 (70, 76)	71 (68, 75)	76 (70, 78)	0.380
Severity of restricted interests and repetitive behaviors (SRS restricted interests and repetitive behavior [RRB] t-scores)	71 (70, 73)	72 (70, 74)	71 (68, 73)	76 (73, 84)	0.129
Population comparison without ASD (N = 1216)					
n (%)	946 (77.8)	154 (12.7)	75 (6.2)	41 (3.4)	
Median (95% CI)					
Early learning ability (MSEL composite standard scores)	103 (101, 105)	105 (100, 109)	106 (104, 109)	99 (97, 110)	0.070
Severity of internalizing behaviors (CBCL internalizing behaviors t-scores)	41 (41, 43)	43 (41, 45)	41 (37, 45)	45 (41, 49)	0.527
Severity of externalizing behaviors (CBCL externalizing behaviors t-scores)	42 (42, 43)	44 (42, 47)	43 (42, 46)	50 (46, 51)	0.001
Social communication and interaction deficits (SRS social communication and interaction [SCI] t-scores)	44 (44, 45)	44 (43, 45)	43 (42, 46)	43 (41, 46)	0.878
Severity of restricted interests and repetitive behaviors (SRS restricted interests and repetitive behavior [RRB] t-scores)	44 (44, 44)	44 (44, 45)	44 (44, 46)	46 (44, 48)	0.433

Note: The sample for this analysis comprises children born to mothers who used alcohol during the first trimester (irrespective of use during other periods) and children born to mothers who abstained from alcohol throughout pregnancy. *p*-value, derived from median tests for testing the equality of medians across levels of PAE-FT within each study group; In addition, a chi-square test yielded a *p*-value of 0.072, comparing the distribution of alcohol consumption (average drinks per week) between children with ASD and children without ASD.

Abbreviations: ASD, autism spectrum disorder; CBCL, child behavior checklist; CI, confidence interval; MSEL, Mullen scales of early learning; *n*, total number of subjects sampled.

TABLE 3 |

Adjusted associations of maternal drinking during the first trimester with early learning ability, behavioral problems, and severity of autistic traits by case status, Study to Explore Early Development.

Average number of drinks per week	Children with ASD (N = 1186)			Population comparison without ASD (N = 1216)		
	Adjusted coefficient (95% CI) < 1	Adjusted coefficient (95% CI) 1–2	Adjusted coefficient (95% CI) 3 or more	Adjusted coefficient (95% CI) < 1	Adjusted coefficient (95% CI) 1–2	Adjusted coefficient (95% CI) 3 or more
Early learning ability (MSEL composite standard scores)	−0.45 (−4.66, 3.77)	−6.48 (−10.98, −1.97) **	−0.74 (−11.65, 10.17)	0.62 (−2.85, 4.09)	2.29 (−1.15, 5.73)	2.02 (−4.85, 8.89)
Severity of internalizing behaviors (CBCL internalizing behaviors <i>t</i> -scores)	−0.00 (−2.48, 2.48)	1.48 (−0.83, 3.79)	1.63 (−1.99, 5.25)	−0.17 (−2.67, 2.64)	0.00 (−3.45, 3.45)	2.45 (−2.04, 6.93)
Severity of externalizing behaviors (CBCL externalizing behaviors <i>t</i> -scores)	0.47 (−1.76, 2.70)	0.90 (−3.01, 4.81)	2.87 (0.29, 5.44) *	2.12 (−0.49, 4.73)	0.71 (−1.97, 3.39)	5.89 (2.10, 9.68) **
Social communication and interaction deficits (SRS social communication and interaction [SCI] <i>t</i> -scores)	1.78 (−1.50, 5.04)	1.06 (−1.90, 4.00)	5.13 (0.06, 10.19) *	−0.33 (−1.63, 0.96)	0.33 (−1.45, 2.11)	0.67 (−2.47, 3.80)
Severity of restricted interests and repetitive behaviors (SRS restricted interests and repetitive behavior [RBB] <i>t</i> -scores)	0.60 (−2.37, 3.57)	−1.50 (−6.25, 3.25)	1.60 (−3.13, 6.33)	−0.51 (−1.33, 0.31)	−0.00 (−1.07, 1.07)	0.86 (−1.78, 3.50)

Note: The sample for this analysis comprises children born to mothers who used alcohol during the first trimester (irrespective of use during other periods) and children born to mothers who abstained from alcohol throughout pregnancy (reference group). Adjusted coefficients, derived from quantile regression models at the quantile level 0.5 of outcome variables, the estimated coefficient of −6.48 can be interpreted as the median of MSEL composite standard scores of children born to mothers reporting 1–2 drinks per week during the first trimester is 6.48 lower than the median score of children born to mothers reporting no alcohol use at any time during pregnancy; all other coefficients in the table can be similarly interpreted; all analyses adjusted for birth order, maternal age at birth, maternal race/ethnicity, maternal education, mother foreign born, household income relative to federal poverty threshold, maternal smoking during pregnancy, maternal exposure to household smoking during pregnancy, and at least one maternal psychiatric condition (defined as self-report that a healthcare provider ever diagnosed at least one of the following conditions: an anxiety, bipolar, depressive, substance related, feeding and eating, obsessive-compulsive, personality, schizophrenia spectrum, or pervasive developmental disorder); *p*-value, derived from quantile regression models to test the hypothesis that the coefficient is 0.

Abbreviations: ASD, autism spectrum disorder group; CBCL, child behavior checklist; CI, confidence interval; MSEL, Mullen scales of early learning.

* 0.01 ≤ *p* < 0.05.

** 0.001 ≤ *p* < 0.01.