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# Association of Prenatal Alcohol Exposure With Psychological, Behavioral, and Neurodevelopmental Outcomes in Children From the Adolescent Brain Cognitive Development Study

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## Abstract

**Objective:** Data on the neurodevelopmental and associated behavioral effects of light to moderate in utero alcohol exposure are limited. This retrospective investigation tested for associations between reported maternal prenatal alcohol use and psychological, behavioral, and neurodevelopmental outcomes in substance-naive youths.

**Methods:** Participants were 9,719 youths (ages 9.0 to 10.9 years) from the Adolescent Brain Cognitive Development Study. Based on parental reports, 2,518 (25.9%) had been exposed to alcohol in utero. Generalized additive mixed models and multilevel cross-sectional and longitudinal mediation models were used to test whether prenatal alcohol exposure was associated with psychological, behavioral, and cognitive outcomes, and whether differences in brain structure and resting-state functional connectivity partially explained these associations at baseline and 1-year follow-up, after controlling for possible confounding factors.

**Results:** Prenatal alcohol exposure of any severity was associated with greater psychopathology, attention deficits, and impulsiveness, with some effects showing a dose-dependent response. Children with prenatal alcohol exposure, compared with those without, displayed greater cerebral and regional volume and greater regional surface area. Resting-state functional connectivity was largely unaltered in children with in utero exposure. Some of the psychological and behavioral

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Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive. A listing of participating sites and a complete listing of study investigators may be found at https://abcdstudy.org/consortium_members.

The ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This article reflects the views of the authors and may not reflect the opinions or views of NIH or of the ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from https://dx.doi.org/10.15154/1504431.

Dr. Teesson is director of Climate Schools, which distributes evidence-based education resources to education organizations. The other authors report no financial relationships with commercial interests.

outcomes at baseline and at the 1-year follow-up were partially explained by differences in brain structure among youths who had been exposed to alcohol in utero.

**Conclusions:** Any alcohol use during pregnancy is associated with subtle yet significant psychological and behavioral effects in children. Women should continue to be advised to abstain from alcohol consumption from conception throughout pregnancy.

Alcohol use during pregnancy has been related to poorer offspring postnatal health and cognitive and behavioral outcomes from birth through adulthood (1). The global prevalence rate of any alcohol use in pregnancy is approximately 10% (2). Factors such as dose and exposure patterns, as well as accompanying environmental factors, likely contribute to the significant variability in the range and magnitude of adverse pregnancy outcomes associated with prenatal alcohol exposure.

One of the most disabling potential outcomes of drinking during pregnancy is fetal alcohol syndrome, which has an estimated global prevalence in the general population of 14.6 per 10,000 people (2). Fetal alcohol syndrome is associated with brain anomalies, postnatal growth restriction, and facial dysmorphology, as well as psychological, behavioral, and cognitive deficits (3). Fetal alcohol spectrum disorder is a more inclusive umbrella term used to describe individuals within the overarching category of prenatal alcohol exposure, including fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder, fetal alcohol effects, and alcohol-related birth defects. Estimates suggest that one of every 13 women who consumed alcohol during pregnancy delivered a child with fetal alcohol spectrum disorder, equivalent to 76.9 per 10,000 children in the general population (4). Children with fetal alcohol spectrum disorder exhibit poorer behavior and emotions, lower intelligence, cognitive deficits, and neurodevelopmental delays (5, 6). Neuroimaging studies show that youths with fetal alcohol spectrum disorder, who were exposed to heavy alcohol use in utero (i.e.,>.7 drinks/week), exhibit smaller cerebral surface area and aberrant cortical thickness (both thinner and thicker cortices have been reported) and generally show widespread reductions in brain volume throughout cortical and subcortical regions when compared with unexposed youths (7–11), although other studies have reported increased gray matter in the parietal and temporal lobes (12). Youths with fetal alcohol spectrum disorder also exhibit reduced resting-state functional connectivity in the default, salience, dorsal and ventral attention, and executive control networks (13).

Although there is an established literature on the adverse outcomes associated with heavy alcohol use in pregnancy, evidence of the effects of lighter alcohol use (i.e., <,7 drinks/week) on offspring psychological, behavioral, and neurodevelopmental outcomes is sparse and inconsistent, perhaps because of sample size and inadequate adjustment for potential confounding factors in some studies (14). To fill these knowledge gaps, the present study utilized clinical interview, youth and parent self-report, cognitive tasks, and structural and resting-state functional MRI data from 9,719 community-based children ages 9–10 years in the Adolescent Brain Cognitive Development (ABCD) Study. We aimed to address four research questions critical for families, clinicians, and policy makers. First, do psychological, behavioral, and neurodevelopmental (i.e., brain structure, brain function, and

cognition) outcomes differ between youths prenatally exposed to alcohol and unexposed youths during preadolescence, before youths have initiated alcohol and other substance use? Second, is there a dose-dependent relationship between levels of alcohol exposure and outcomes of interest? Third, what are the common alcohol exposure patterns in the ABCD community sample, and are these patterns associated with adverse outcomes? And fourth, do structural and functional brain differences mediate the association between prenatal alcohol exposure and neurobehavioral outcomes? An examination of this large, diverse community sample of children in the United States, where patterns of exposure are more typical of the general population, is urgently needed.

## METHODS

### Study Population

This study used data from the ABCD Study annual release2.0.1, which consists of 11,875 participants born between 2005 and 2008. A detailed account of the recruitment strategy has been previously published (15). A probability sample was recruited through schools and selected based on sex, race/ethnicity, socioeconomic status, and urbanicity. Children with fetal alcohol spectrum disorder were not explicitly excluded from study participation. All parents provided written informed consent, and all children provided assent to the research protocol approved by a central institutional review board. Of the 11,875 participants enrolled, 2,156 were removed from the present analyses because of incomplete data (N=1,733) and/or because brain scans did not pass the ABCD Study's quality control (N=1,381) (16). Therefore, up to 9,719 participants were included in the analyses (Figure 1).

### Prenatal Alcohol Exposure

Prenatal alcohol exposure was measured using the modified Developmental History Questionnaire (17, 18) through parents' retrospective report of maternal alcohol use before and after knowledge of pregnancy (no or yes), the maximum number of drinks consumed on a single occasion, and the average number of drinks consumed per week during pregnancy. From this information, a dichotomous prenatal alcohol exposure variable was derived (exposure indicates any use at any time during pregnancy), an estimate of the total number of drinks consumed during pregnancy was calculated, and youths were categorized into common alcohol exposure patterns based on established prenatal alcohol use classification (19). Further details and relevant questions from the ABCD protocol are provided in the online supplement.

### Psychological and Behavioral Variables

Psychopathology was examined in children using the eight empirically based syndrome scales and higher-order factors of the parent-reported Child Behavior Checklist (CBCL) (20). Lifetime mental disorder diagnoses (i.e., past and/or present) were determined using parent-reported responses on the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS), based on DSM-5 criteria (21). Impulsivity was assessed using the 20-item Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form (22). Motivation was examined using the four subscales of the behavioral avoidance and behavioral inhibition scales (23).

The single-item Cash Choice Task was utilized as a measure of delayed gratification, motivation, and impulsivity (24). All data were available for baseline assessment (N=9,719), and 1-year follow-up data were available for all psychopathology syndrome scales and higher-order factors as measured by the CBCL and for the externalizing disorders as measured by the K-SADS (N=4,169).

## Cognitive Variables

The NIH Toolbox (25) fluid intelligence battery was utilized, and this includes the Picture Sequence Memory, Dimensional Change Card Sort, Flanker Inhibitory Control and Attention, List Sorting Working Memory, and Pattern Comparison Processing Speed tasks. All scores were age-corrected standard scores. The Rey Auditory Verbal Learning Test was utilized to measure verbal learning (trials I–V) and immediate (trial VI) and delayed (trial VII) memory (26).

## Covariates

We adjusted for fixed and random effects. Fixed covariates were chosen based on prior evidence of an association with the outcomes or because of statistically significant group differences in the present sample (Table 1). Birth-related covariates included weight and whether the child was born prematurely (yes, no, unknown). Genetic covariates included sex at birth (female, male) and race/ethnicity (White, Black, Hispanic, Asian, other). Youth age at time of assessment and school grade performance (grades A to F) were also included. Maternal covariates included maternal age at birth, a history of maternal depression (yes, no, unknown), and other substance use during pregnancy, with tobacco, cannabis, cocaine, and heroin use (yes, no, unknown) each included as separate variables. The highest level of parental education was used as an indicator of socioeconomic status (less than high school diploma, high school diploma or General Equivalency Diploma, some college, bachelor's degree, postgraduate degree). Random effects included nesting youths within families to account for sibling effects and nesting youths within MRI scanner site.

## Imaging Procedure

Imaging acquisition and scanning parameters are described elsewhere (16). Briefly, all scans were uploaded to a shared server that is maintained by the Data Analysis, Informatics, and Resource Center of the ABCD Study. Brain data were collected on 3-T scanners, including the Siemens MAGNETOM Prisma, the GE Discovery MR750, and the Philips Achieva. The $T_1$ images were corrected for gradient nonlinearity distortions using scanner-specific, nonlinear transformations. Cortical reconstruction and volumetric segmentation were performed by the Data Analysis, Informatics, and Resource Center using FreeSurfer, version 5.3.0. The Desikan-Killiany brain registration atlas was used in the present analyses to examine cortical thickness, surface area, and volume of 68 cortical regions, as well as volume in 40 subcortical segmentations. Participants also completed four 5-minute resting-state blood-oxygen-level-dependent scans, with their eyes open and fixated on a crosshair. Resting-state images were acquired in the axial plane using an echo-planar imaging sequence. Using a functional atlas, cortical surface regions were grouped into 12 predefined large-scale networks (27): auditory, cingulo-opercular, cingulo-parietal, default-mode, dorsal-attention, fronto-parietal, retrosplenial-temporal, salience, sensorimotor-hand,

sensorimotor-mouth, ventral-attention, and visual networks. Resting-state functional connectivity strength indices were then calculated using the Fisher r-to-z transformation of the average correlation values between pairs of regions within each large-scale network (N=12), between these 12 networks (N=66), and between the networks and 19 subcortical regions (N=228). The Data Analysis, Informatics, and Resource Center used a combination of automated and manual methods to review the data sets for quality control before sharing data via the National Institute of Mental Health Data Archive.

## Statistical Analysis

A series of generalized additive mixed models and multilevel mediation analyses were performed using R, version 3.5.3 (the "mgcv" package), and Mplus, version 8.4, respectively. Participants with missing or inadequate imaging quality data were excluded from analyses. In all analyses with imaging measures, the false discovery rate was used to correct for multiple comparisons, and the adjusted p values are reported (28).

**Associations with prenatal alcohol exposure.—**First, prenatal alcohol exposure was examined as a dichotomous variable (unexposed or exposed). Generalized additive mixed models exploring associations with psychological, behavioral, neural, and cognitive outcomes were run adjusting only for random effects and then were repeated after entering all covariates as fixed effects (see the Covariates subsection above). Structural and functional neural indices found to be significantly associated with prenatal alcohol exposure when adjusting for fixed and random effects were identified as regions of interest for the remaining analyses. Follow-up analyses included intracranial volume as an additional covariate in statistically significant volumetric models. Considering the large number of functional indices explored and the strict multiple comparisons adjustment applied, uncorrected results were also reported for connectivity within and between a narrower selection of major networks previously associated with fetal alcohol spectrum disorder (13). To examine dose-dependent relationships, spline models with 1.5% winsorization to convert outliers were conducted to flexibly fit associations between the estimated total number of drinks consumed during pregnancy and outcomes of interest, adjusting for fixed and random effects. Next, the prevalence of alcohol exposure patterns was estimated, and the effect of these patterns of drinking in pregnancy on the outcomes of interest was examined using generalized additive mixed models. The week of maternal pregnancy awareness was added as an additional covariate. Follow-up analyses examined whether there were differential effects associated with varying gradations of alcohol use throughout pregnancy.

Sensitivity analyses were conducted, where the dichotomous prenatal alcohol exposure groups were demographically matched on all covariates after excluding rarer cases on which groups were mismatched, including youths with other in utero substance use exposure and positive reports of maternal depression (using the R package "MatchIt"). The aforementioned association analyses were then repeated with this more homogeneous subsample (N=2,542; see Tables S10–S12 in the online supplement).

**Mediation analysis.—**Cross-sectional multilevel mediation analyses were conducted to determine whether significant associations between prenatal alcohol exposure and

psychological, behavioral, and cognitive outcomes were partially explained by differences in brain structure or function, when adjusting for fixed and random effects. Here, significant mediation effects are strictly a measure of association, which does not prove causality.

For psychological measures where 1-year follow-up data were available, longitudinal multilevel mediation analyses were conducted (N=4,169). The follow-up psychological data were entered into models alongside baseline parental reports of prenatal alcohol exposure and imaging measures to explore prospective associations between prenatal alcohol exposure, brain structure and function, and psychological outcomes, when accounting for fixed and random effects.

## RESULTS

### Study Sample

Of the 9,719 youths included in these analyses (52.1% male), 2,518 (25.9%) had parent-reported in utero alcohol exposure. Demographic characteristics are provided in Table 1, and psychological, behavioral, and cognitive characteristics of youths are provided in Table S1 in the online supplement. The winsorized estimated total number of drinks consumed during pregnancy ranged from 0 to 90, and among those who consumed alcohol, the mean number of drinks was 26.9 (SD=24.5). A significantly larger proportion of youths prenatally exposed to alcohol, compared with unexposed youths, were exposed to tobacco (N=628; 24.9%), cannabis (N=325;12.9%), cocaine (N=44; 1.7%), and heroin (N=8; 0.3%).

### Associations With Prenatal Alcohol Exposure

**Dichotomous prenatal alcohol exposure associations.—**Results of unadjusted models and effect sizes are provided in Tables S2–S5 in the online supplement. In covariate-adjusted models, youths prenatally exposed to alcohol exhibited significantly greater psychopathology, impulsivity, and cognitive functioning compared with unexposed youths (Figure 2). Exposed youths were more likely to have a lifetime diagnosis of separation anxiety disorder (adjusted odds ratio=1.21, 95% CI=1.11–1.31) and oppositional defiant disorder (adjusted odds ratio=1.17, 95% CI=1.09–1.26) relative to unexposed youths.

Exposed youths also exhibited greater total cerebral volume and greater regional cortical volume and surface area throughout the temporal, occipital, and parietal lobes, relative to unexposed youths. Regional cortical volume differences in the left inferior temporal lobe passed false-discovery-rate correction when intracranial volume was included as an additional covariate (see Table S6 in the online supplement). No significant differences between exposed and unexposed youths were observed for cortical thickness. Compared with unexposed youths, exposed youths exhibited hypoconnectivity between the auditory network and the right ventral diencephalon, and hyperconnectivity between the sensorimotor hand and salience networks (see Table S4 in the online supplement). Connectivity within and between the other networks and subcortical indices was not significantly associated with prenatal alcohol exposure (see Table S5 in the online supplement for uncorrected results of networks previously associated with fetal alcohol spectrum disorder). Considering that no significant associations were observed within or between established networks previously

associated with fetal alcohol spectrum disorder, no further results of functional analyses are presented here (additional results are provided in the online supplement, including a summary of significant associations between covariates and outcomes in Table S7).

**Dose-dependent associations.—**In covariate-adjusted models, linear and nonlinear associations were observed between the estimated total number of drinks consumed during pregnancy and total psychological problems, internalizing psychopathology and somatic complaints, attention deficits, sensation-seeking behavior, and performance on the Flanker Task, which measured attention and inhibitory control (Figure 3; see also Table S8 in the online supplement). The total number of drinks was linearly associated with greater cerebral volume (Figure 3). Both linear and nonlinear associations were observed between the total number of drinks and regional volume throughout the temporal, occipital, and parietal lobes (see Figure S1 in the online supplement). Dose-dependent responses were not observed for any other outcome of interest.

**Exposure pattern associations.—**Six patterns of parent-reported alcohol use in pregnancy were identified (Figure 1). Because of sample size, exposure pattern analyses were limited to abstinent mothers, light reducers, light, stable users, and heavier reducers, accounting for 98.1% of the sample. On average, light reducer mothers consumed 2.3 drinks/week for the first 7 weeks (SD=5.6) of pregnancy (mean total drinks, 15.8, SD=14.7). Light stable-drinking mothers consumed approximately 1.1 drinks/week throughout pregnancy (mean total drinks, 44.0, SD=25.8), while heavier reducer mothers consumed approximately 5.3 drinks/week for the first 7 weeks (SD=5.1) of pregnancy (mean total drinks, 36.2, SD=25.5). Participant characteristics for each group are provided in Table S9 in the online supplement.

Covariate-adjusted models showed that, compared with unexposed youths, all exposure groups exhibited greater psychopathology and behavioral problems, varying mental disorders (i.e., separation anxiety disorder, oppositional defiant disorder, specific phobia, and/or attention deficit hyperactivity disorder [ADHD]), and greater cognitive functioning. Children of heavier reducers also reported greater withdrawn or depressed behavior, attention deficits, rule breaking behavior, and aggression compared with children of light reducers. Significant associations are presented in Figure 4.

Youths with exposure to any pattern of drinking exhibited greater total cerebral volume relative to unexposed youths in covariate-adjusted models. Regional brain volume and surface area disparities were also observed for all prenatal alcohol exposure groups compared with unexposed youths, although no significant differences were observed between prenatal alcohol exposure groups.

When gradations of use were explored separately for heavier reducers (i.e., heavier to light compared with heavier to abstinence), similar results were found for both groups. Results of all psychological, behavioral, cognitive, and neural indices analyses are provided in Table S10 in the online supplement.

**Sensitivity analysis.—**When youths were demographically matched, results remained generally consistent (see Tables S11–S16 in the online supplement). Of note, the majority of previously observed cognitive benefits for youths prenatally exposed to alcohol were no longer found. When examined dichotomously, no cognitive domains were significantly different between groups. A nonlinear association remained for total drinks and Flanker Task performance. Some structural brain indices were no longer significantly different between groups or were no longer dose dependent.

### Mediation Analysis

Structural brain indices were negatively associated with psychological and behavioral outcomes and partially mediated all significant associations between prenatal alcohol exposure and neurobehavioral outcomes in covariate-adjusted cross-sectional models (see Tables S17–S31 in the online supplement). Inconsistent mediation was observed, where at least one of the mediated effects occurred in a different direction to the direct effect (29); for example, prenatal alcohol exposure was significantly associated with greater brain volume and surface area and with greater psychopathology and behavioral problems, while greater brain volume and surface area were negatively associated with psychopathology and behavioral problems. Conversely, for Flanker Task attention and inhibitory control performance, consistent positive associations were observed. Longitudinal mediation models replicated associations between prenatal alcohol exposure, varying baseline structural brain indices, and follow-up psychopathology and externalizing disorders (see Tables S32–S42 in the online supplement).

## DISCUSSION

### Alcohol Exposure Findings

To our knowledge, this is the largest examination of prenatal alcohol exposure and psychological, behavioral, and neurodevelopmental outcomes in preadolescence. The estimated total number of drinks consumed during pregnancy ranged from 0 to 90 following outlier conversion. This alcohol dose is relatively low, and the parent-reported exposure patterns prevalent in the ABCD cohort are more typical and reflective of the general population than those investigated in previous studies of fetal alcohol spectrum disorder (2).

Prenatal alcohol exposure of any severity was associated with greater psychopathology, impulsivity, and likelihood of being diagnosed with separation anxiety and oppositional defiant disorder, with some observed dose-related associations. Heavier exposure was also associated with greater withdrawn or depressed behavior, attention deficits, rule breaking, aggression, and a greater likelihood of being diagnosed with ADHD. Early, light exposure, compared with no exposure, was associated with better attention and inhibitory skills. Exposed youths also exhibited greater cerebral volume, in a dose-dependent manner, and greater volume and surface area, but not cortical thickness, throughout regions of the parietal, temporal, and occipital lobes, after accounting for potentially confounding factors. Resting-state functional connectivity was largely unaltered in these youths. Aberrant brain structure partially mediated associations between prenatal alcohol exposure and psychological, behavioral, and cognitive outcomes at baseline and at the 1-year follow-up.

These reported associations passed a stringent demographic-matching protocol. Unmodifiable factors greatly contributed to the large effect sizes in the adjusted models. Of the modifiable factors, prenatal alcohol exposure was a critical determinant of brain structure, and some neurobehavioral outcomes, accounting for >50% of the explained variance by modifiable factors. The findings were in a largely substance-naive cohort of youths (99.999%), allowing for investigation of the effects of prenatal alcohol exposure on the developing brain and behavior in the absence of youths' own substance use, which is known to affect neurodevelopment (30).

## Comparison With Other Studies

Our findings replicate previous clinical studies indicating that children exposed to alcohol in utero have higher rates of mental disorders and present with behavioral anomalies, including impulsiveness and attention deficits (14). Results from our dose-dependent and exposure pattern analyses support the notion that the severity of psychopathology and behavioral problems depends on alcohol dose and timing of exposure. The present results are also consistent with previous reports using the ABCD cohort of associations between psychopathology, brain structure, and resting-state functional connectivity (31, 32). Consistent with previous meta-analyses, a small, beneficial association between prenatal alcohol exposure and cognitive ability was observed (33, 34). However, when participants were demographically matched, the vast majority of associations were no longer significant. This association may be the result of residual confounding from socioeconomic status and other demographic variables, as previously hypothesized (33, 34). Other confounding variables not captured in this analysis may be contributing to the positive association between early, light exposure and attention and inhibition.

The long-term neurostructural and functional effects of light maternal drinking, where offspring who do not necessarily present with fetal alcohol spectrum disorder, have not been well studied. Consistent with our findings, one study has reported larger regional volume among youths prenatally exposed to alcohol relative to unexposed youths (35). However, in contrast to our results, a common finding, when investigated both categorically and continuously, has been less volume and surface area among youths with fetal alcohol spectrum disorder and those with heavier prenatal alcohol exposure compared with unexposed youths (7, 36). Furthermore, a previous study of youths with fetal alcohol spectrum disorder reported hypoconnectivity between numerous large-scale neurocognitive networks (13), yet in the present study, no significant alterations in resting-state functional connectivity were observed within or between these networks (see Table S5 the online supplement).

The disparate findings may be explained by the large discrepancies in clinical severity of prenatal alcohol exposure between the ABCD sample and previous cohorts. The impact of heavier prenatal alcohol exposure may have a differential effect on preadolescent brain structure and function. Interestingly, some regions of the occipital, temporal, and parietal lobes exhibited an inverted-U association between alcohol dose and volume or surface area (see Figure S1 in the online supplement). It is possible, therefore, that we would have observed reduced volume and surface area among youths exposed to heavier doses (i.e., >90

drinks consumed during pregnancy). Furthermore, potentially confounding factors in previous studies of children with heavier prenatal alcohol exposure or fetal alcohol spectrum disorder may contribute to the discrepant findings, such as greater co-occurring substance exposure, early-life stress, and quality of parental care. Importantly, our findings suggest that youths exposed to even light alcohol doses in utero exhibit widespread differences in brain structure, when compared with unexposed youths.

Finally, our results are consistent with previous studies of children with fetal alcohol spectrum disorder that have linked behavioral, psychological, and cognitive outcomes to changes in brain structure (10). However, our study is the first to test and identify inconsistent mediation between these variables (29). Similar to previous conclusions drawn on the effects of prenatal alcohol exposure (37), our results suggest that there is no safe threshold for alcohol consumption during pregnancy.

## Interpretation and Potential Biological Mechanisms Underlying Neurobehavioral Outcomes

Alcohol is a known teratogen in utero, and it is thought to affect regions of the developing fetal brain via neural proliferation and migration errors, hypoxia, and cell death (38). The teratogenic effects likely differ as a result of dose, frequency, and timing of exposure and may vary across brain regions. Our findings demonstrate that there are complex effects of prenatal alcohol exposure on offspring development. Here, we provide four potential interpretations of mechanisms underlying associations between prenatal alcohol exposure, differences in brain structure, and neurobehavioral consequences.

First, our results may reflect a compensatory response of some brain regions attempting to counter the effects of other, poorer functioning regions affected by low alcohol doses (39). Our inconsistent mediation findings provide some support for this interpretation, where greater brain volume and surface area were associated with better neurobehavioral outcomes, yet youths who were exposed to alcohol in utero exhibited greater volume and surface area but more neurobehavioral problems at baseline and follow-up. Despite a potential compensatory response of the brain to counter the effects of relatively low doses of alcohol, these youths continue to show subtle, yet poorer, psychological and behavioral outcomes through early life.

Second, our findings may also suggest that relatively light prenatal alcohol exposure may result in slightly atypical neurodevelopment. Such exposure may slow or alter the overall process of gray matter maturation, where greater absolute volume and surface area in exposed youths represent delayed or incomplete cortical pruning compared with this process in unexposed, prepubertal youths (40). Consistent with this hypothesis, we observed this trend largely in regions where gray matter loss in unexposed children progresses linearly from childhood through adolescence (41). Typically among this age group, the left hemisphere matures earlier than the right (i.e., left hemisphere gray matter loss prior to right hemisphere gray matter loss; 41, 42). Greater volume and surface area among exposed youths in left posterior cortices known to develop most rapidly between childhood and adolescence provide further support of delayed development. Examining the developmental trajectories of this cohort when multiple waves of imaging data are available will provide further insight into whether atypical development is occurring among exposed youths.

Third, the inconsistent mediation findings may also be partly capturing the effects of the inverted-U associations between total alcohol dose and regional brain volume and surface area. Youths exposed to greater alcohol doses (i.e., approximately 90 drinks consumed during pregnancy) exhibited greater psychopathology and behavioral problems between ages 9 and 10 than youths exposed to lighter doses (i.e., approximately 40 drinks), and these more heavily exposed youths exhibited lower volume and surface area in regions of the parietal and temporal lobes than youths exposed to lighter doses.

Lastly, there may be other critical changes resulting from prenatal alcohol exposure that mediate associations with brain structure differences and psychological and behavioral outcomes. For example, ethanol provokes a wide range of epigenetic modifications, including altered DNA and histone methylation, which persist from birth through childhood (43). Animal studies suggest that prenatal alcohol exposure affects DNA methylation through antagonistic effects on methyl donors, such as folate, and via long-lasting changes in gene expression (43). Preliminary evidence from studies of children with fetal alcohol spectrum disorder show genome-wide differences in DNA methylation (44). Further research is required to examine epigenetic markers and their role in adverse outcomes among exposed youths; DNA methylation or other epigenetic markers could potentially provide objective indicators of prenatal alcohol exposure.

Limitations of our study include potential maternal underreporting of alcohol use during pregnancy, imprecise retrospective data on the timing, amount, and frequency of alcohol exposure, and absence of data on trimester-specific alcohol exposure. The effects of underreporting by mothers who indicated alcohol use during pregnancy may have inflated the observed associations, while underreporting by mothers who indicated no alcohol use when they did in fact consume alcohol would have attenuated the associations toward the null. Future studies may benefit from interviewing an independent reporter of prenatal maternal alcohol use. Furthermore, data were not available on mothers who regularly consumed less than a full unit of alcohol. Therefore, youths exposed to this pattern of drinking would have been included in the unexposed group, potentially diluting outcome effects. Despite the large sample size, there were relatively few cases of youths exposed to stable light drinking throughout pregnancy, and too few cases of stable heavier drinking or increased consumption throughout pregnancy, to examine the impact on offspring. There is a larger body of existing evidence based on the consequences of heavier alcohol exposure (7). The small sample size of youths exposed to light, stable drinking throughout pregnancy resulted in wider variance in outcome measures and may underestimate the true impact. Other notable explanatory variables of early life that may influence the observed associations between prenatal alcohol exposure and neurobehavioral outcomes include childhood adversity and quality of parental care. These variables may contribute to mediating effects of neurodevelopment and possible epigenetic modifications (45). The baseline ABCD Study protocol did not capture these variables, although future waves will. Longitudinal analyses of this cohort should consider these variables as possible confounding factors. In addition, we did not examine the effect of preconception paternal alcohol exposure on preadolescent brain structure, and this should be explored in future studies.

In conclusion, relatively light levels of prenatal alcohol exposure were associated with small yet significantly greater psychological and behavioral problems, including internalizing and externalizing psychopathology, attention deficits, and impulsiveness. These outcomes were linked to differences in cerebral and regional brain volume and regional surface area among exposed youths ages 9 to 10 years. Examination of dose-dependent relationships and light alcohol exposure patterns during pregnancy shows that children with even the lowest levels of exposure demonstrate poorer psychological and behavioral outcomes as they enter adolescence. Associations preceded offspring alcohol use and were robust to the inclusion of potential confounding factors and during stringent demographic matching procedures, increasing the plausibility of the findings. Women should continue to be advised to abstain from alcohol consumption from conception throughout pregnancy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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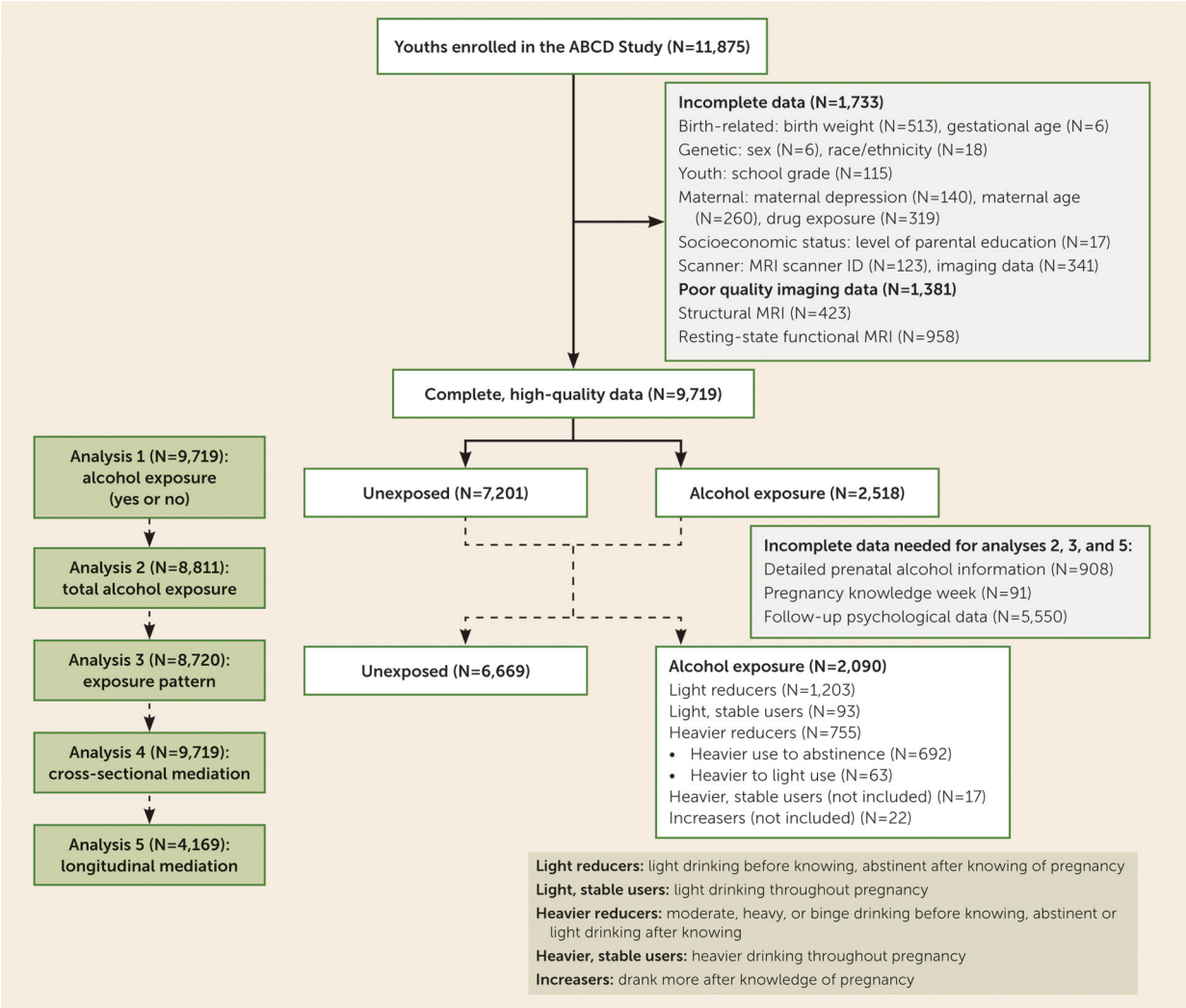


**FIGURE 1.**

Selection of the Adolescent Brain Cognitive Development (ABCD) cohort for each series of analyses in a study of the association of prenatal alcohol exposure with psychological, behavioral, and neurodevelopmental outcomes in children

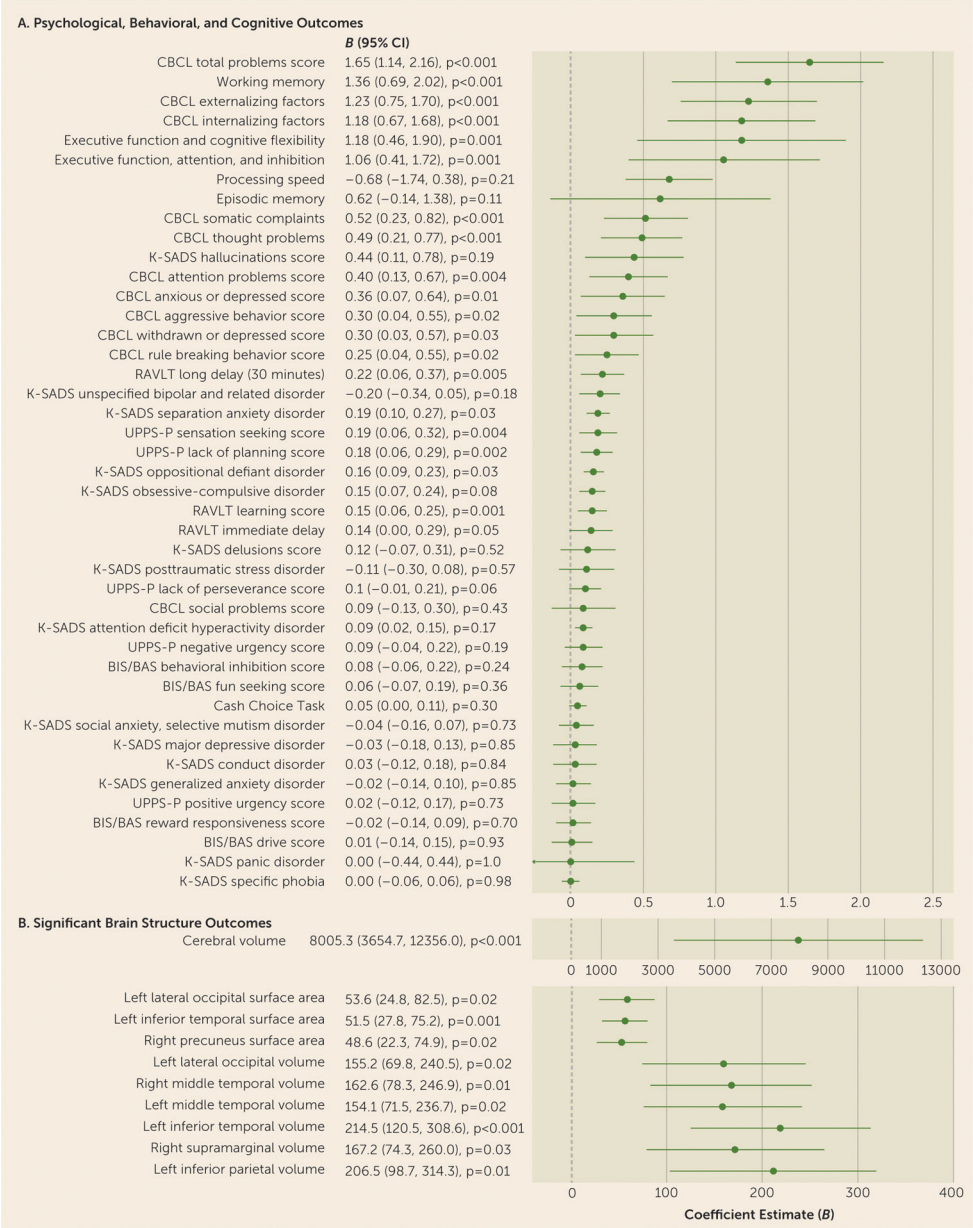


**FIGURE 2.**

Association of prenatal alcohol exposure of any severity, compared with no exposure, with psychological and behavioral problems, cognitive functioning, and cortical volume and surface area in preadolescent children[a]

[a] Unstandardized regression coefficients and associated 95% confidence intervals, as well as p values or false-discovery-rate-adjusted p values for neural outcomes, are presented for the effects of prenatal alcohol exposure compared with no exposure. Only brain regions where the model passed the false-discovery-rate correction for volume or surface area are presented. These generalized additive mixed models controlled for fixed and random effects. Fixed effects included race/ethnicity, sex, age, whether the child was born premature, child birth weight, school grade, prenatal tobacco exposure, prenatal cannabis exposure, prenatal

heroin exposure, prenatal cocaine exposure, maternal age at birth, level of parental education, and maternal depression. Random effects included family and MRI scanner site. Working memory was measured by the Toolbox Working Memory Test. Executive function and cognitive flexibility were measured by the Toolbox Dimensional Change Card Sort Task. Executive function, attention, and inhibition were measured by the Toolbox Flanker Task. Processing speed was measured by the Toolbox Pattern Comparison Processing Speed Test. Episodic memory was measured by the Toolbox Picture Sequence Memory Test. BIS/BAS=behavioral avoidance and behavioral inhibition scales; CBCL=Child Behavior Checklist; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; RAVLT=Rey Auditory Verbal Learning Test; UPPS-P=Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form.

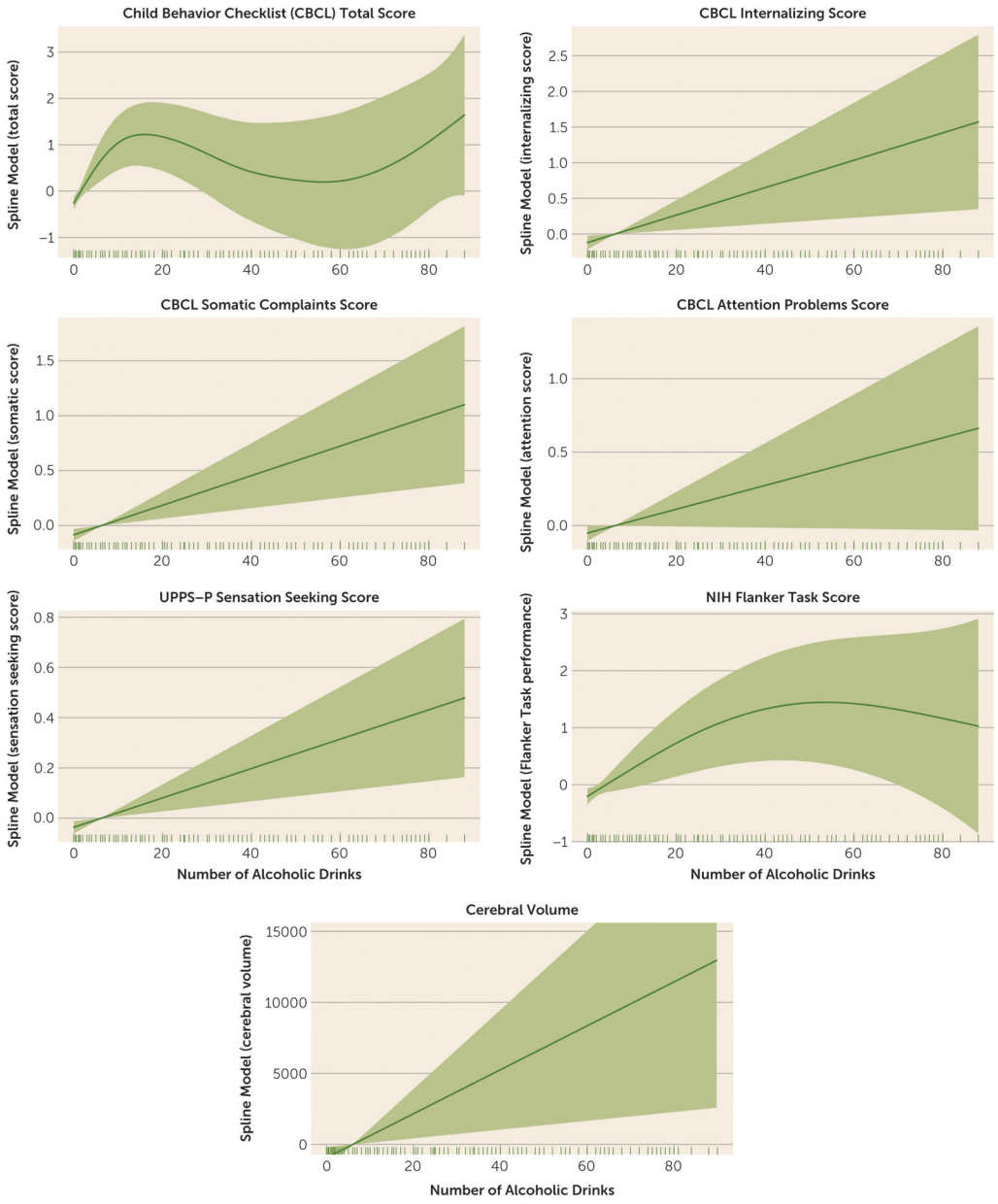


**FIGURE 3.**

Spline models demonstrating a significant dose-dependent relationship between the estimated total number of alcoholic drinks consumed during pregnancy and offspring psychopathology, cognitive functioning, and brain volume, adjusted for fixed and random effects[a]

[a] NIH=National Institutes of Health; UPPS-P=Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children–Short Form.

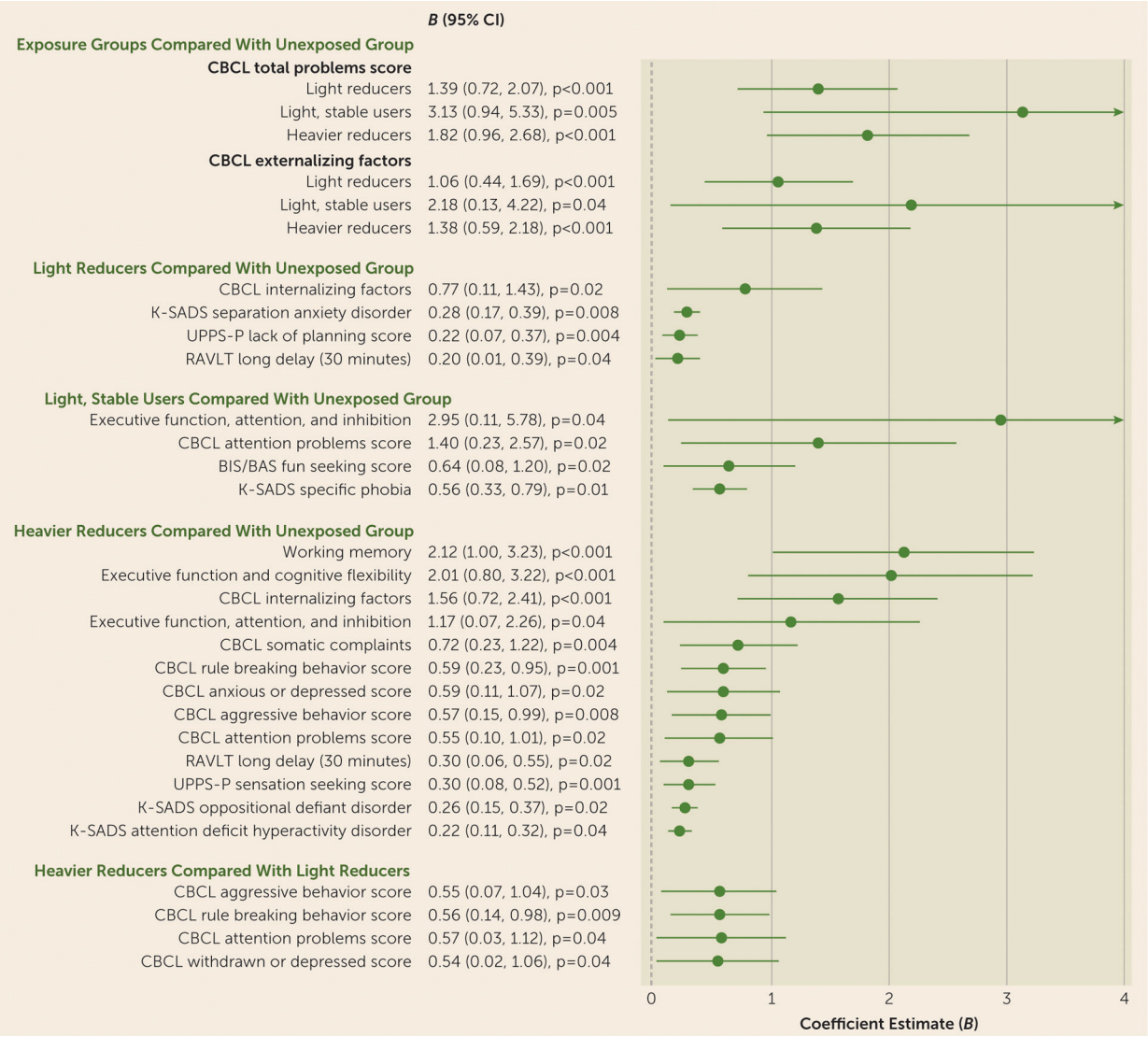


**FIGURE 4.**

Association of prenatal alcohol exposure patterns with varying psychological and behavioral problems among children[a]

[a] Results of all psychological, behavioral, cognitive, and neural indices analyses are provided in Table S10 in the online supplement. Unstandardized regression coefficients, associated 95% confidence intervals, and p values are presented for significant associations. These generalized additive mixed models controlled for fixed and random effects. Fixed effects included race/ethnicity, sex, age, whether the child was born premature, child birth weight, school grade, prenatal tobacco exposure, prenatal cannabis exposure, prenatal heroin exposure, prenatal cocaine exposure, maternal age at birth, level of parental education, maternal depression, and the week the mother became aware of pregnancy. Random effects included family and MRI scanner site. Executive function, attention, and inhibition were measured by the Toolbox Flanker Task. Executive function and cognitive flexibility were measured by the Toolbox Dimensional Change Card Sort Task. Working memory was measured by the Toolbox List Sorting Working Memory Test. BIS/BAS=behavioral

avoidance and behavioral inhibition scales; CBCL=Child Behavior Checklist; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; RAVLT=Rey Auditory Verbal Learning Test; UPPS-P=Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form.

**TABLE 1.**

Youth and parental characteristics in a study of prenatal alcohol exposure and mental health outcomes in children (N=9,719)

| Characteristic | Unexposed Youths (N=7,201) | | Youths With Prenatal Alcohol Exposure (N=2,518) | | p |
|---|---|---|---|---|---|
| **Youth Variables** | | | | | |
| | **N** | **%** | **N** | **%** | |
| Sex | | | | | 0.32 |
| Male | 3,776 | 52.4 | 1,291 | 51.3 | |
| Female | 3,425 | 47.6 | 1,227 | 48.7 | |
| Race/ethnicity | | | | | <0.001 |
| White | 3,631 | 50.4 | 1,630 | 64.7 | |
| Black | 1,126 | 15.6 | 216 | 8.6 | |
| Hispanic | 1,574 | 21.9 | 407 | 16.2 | |
| Asian | 139 | 1.9 | 27 | 1.1 | |
| Other | 731 | 10.2 | 238 | 9.5 | |
| Born premature | | | | | 0.07 |
| Yes | 1,417 | 19.7 | 443 | 17.6 | |
| No | 5,757 | 79.9 | 2,065 | 82.0 | |
| Unknown | 27 | 0.4 | 10 | 0.4 | |
| Prenatal tobacco exposure | | | | | <0.001 |
| Yes | 637 | 8.8 | 628 | 24.9 | |
| No | 6,551 | 91.0 | 1,865 | 74.1 | |
| Unknown | 13 | 0.2 | 25 | 1.0 | |
| Prenatal cannabis exposure | | | | | <0.001 |
| Yes | 204 | 2.8 | 325 | 12.9 | |
| No | 6,987 | 97.0 | 2,150 | 85.4 | |
| Unknown | 10 | 0.1 | 43 | 1.7 | |
| Prenatal cocaine exposure | | | | | <0.001 |
| Yes | 9 | 0.1 | 44 | 1.7 | |
| No | 7,187 | 99.8 | 2,446 | 97.1 | |
| Unknown | 5 | 0.1 | 28 | 1.1 | |
| Prenatal heroin exposure | | | | | <0.001 |
| Yes | 7 | 0.1 | 8 | 0.3 | |
| No | 7,190 | 99.8 | 2,482 | 98.6 | |
| Unknown | 4 | 0.1 | 28 | 1.1 | |
| School grade performance | | | | | <0.001 |
| A | 3,233 | 44.9 | 1,190 | 47.3 | |
| B | 2,408 | 33.4 | 788 | 31.3 | |
| C | 776 | 10.8 | 226 | 9.0 | |
| D | 130 | 1.8 | 43 | 1.7 | |

| Characteristic | Unexposed Youths (N=7,201) | | Youths With Prenatal Alcohol Exposure (N=2,518) | | p |
|---|---|---|---|---|---|
| F | 28 | 0.4 | 7 | 0.3 | |
| Ungraded | 626 | 8.7 | 264 | 10.5 | |
| Consumed full drink of alcohol | 10 | 0.1 | 6 | 0.2 | 0.44 |
| | **Mean** | **SD** | **Mean** | **SD** | |
| Age (years) | 9.9 | 0.6 | 9.9 | 0.6 | 0.89 |
| Birth weight (lb) | 6.6 | 1.5 | 6.7 | 1.4 | <0.001 |
| **Parent Variables** | | | | | |
| | **N** | **%** | **N** | **%** | |
| Highest level of education | | | | | <0.001 |
| Less than high school diploma | 547 | 7.6 | 59 | 2.3 | |
| High school diploma or General Equivalency Diploma | 838 | 11.6 | 155 | 6.2 | |
| Some college | 2,191 | 30.4 | 687 | 27.3 | |
| Bachelor's degree | 1,999 | 27.8 | 809 | 32.1 | |
| Postgraduate degree | 1,626 | 22.6 | 808 | 32.1 | |
| Maternal depression | | | | | <0.001 |
| Yes | 1,530 | 21.2 | 656 | 26.1 | |
| No | 5,495 | 76.3 | 1,763 | 70.0 | |
| Unknown | 176 | 2.4 | 99 | 3.9 | |
| | **Mean** | **SD** | **Mean** | **SD** | |
| Maternal age at delivery (years) | 29.2 | 6.3 | 30.1 | 5.9 | <0.001 |
| Week of pregnancy knowledge | 6.9 | 7.0 | 6.9 | 5.7 | 0.93 |