Considering Prenatal Alcohol Exposure in a Developmental Origins of Health and Disease Framework

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Effects of prenatal alcohol exposure in humans are impossible to study via controlled experiments; we are limited to observational studies. Although alcohol is considered a teratogen, there is a lack of clarity about the nature of the association between prenatal alcohol exposure, particularly low-level exposure, and offspring development in part because of the potential for unmeasured factors to play a role. In this issue of the *Journal*, an article by Lees and colleagues (1) leverages data from a large, representative sample, the Adolescent Brain Cognitive Development (ABCD) Study, to examine prenatal alcohol exposure in relation to adolescents' neurodevelopmental outcomes based on behavioral assessments, maternal report of psychopathology, and imaging data, with multiple statistical methods to control for other variables. However, review of this article in the context of other studies in the broader field studying the developmental origins of health and disease demonstrates that different research approaches addressing development beginning before birth can lead to divergent conclusions and highlights the importance of considering prenatal exposures in concert with other environmental factors.

The study by Lees et al. follows a behavioral teratology model, focusing on alcohol with the goal of isolating its effects by controlling statistically for other potentially confounding variables that could explain child outcomes—an approach that the large sample of nearly 10,000 participants permits. This model dominates prenatal alcohol exposure research, which began in the 1970s when "fetal alcohol syndrome" was first described in a small study of alcoholic mothers whose infant offspring were assessed to determine the consequences of having an alcoholic mother (2). Research has progressed substantially since, beginning with preclinical models establishing high levels of alcohol as teratogenic—although not before guidelines promoting abstinence from alcohol during pregnancy were swiftly implemented and became commonly accepted. In contrast to other neurodevelopmental disorders, fetal alcohol spectrum disorders, the umbrella term for a range of fetal alcohol exposure effects, including fetal alcohol syndrome, have a unique etiology in that the causal factor (i.e., alcohol) is integral to the diagnosis.

The field of the developmental origins of health and disease, which has come to the fore in developmental psychopathology research, centers on the in utero environment as an influential first home (3). During pregnancy, maternal experiences such as life stress, depression, diet, and exposure to toxins are associated with alterations in gestational biology that affect fetal brain development during critical periods, with implications for future risk for compromised neurodevelopmental trajectories (4). Prenatal exposures are not randomly distributed; typically in studies of the developmental origins of health and disease, substantial effort is made to interrogate observational findings, and any causality is asserted with caution because other possibilities (such as confounding effects and selection bias) may explain associations (5).

Lees et al., in perhaps the largest study of its kind in the United States, examine cognitive and psychological outcomes, assessed via maternal retrospective self-report, in adolescents exposed prenatally to alcohol. Alcohol use was infrequent in the sample: of those with complete data, 2,090 (24%) women drank some alcohol before knowing they were pregnant, and 156 (1.8%) of the sample continued to drink at low levels (<7 drinks/week) after pregnancy awareness. Cognitive outcomes in offspring were assessed at ages 8.9–11 years using the fluid intelligence battery from the National Institutes of Health (NIH) toolbox, as well as the Rey Auditory Verbal Learning Test; the use of an observer-based, standardized neurocognitive test battery is a notable study strength. Covariate-adjusted comparisons showed that youths prenatally exposed to alcohol exhibited enhanced cognitive functioning compared with those born to abstainers (although, similar to all behavioral outcomes, not of a magnitude that is clinically significant). Examination of a dose-response relationship revealed an inverted U-shaped association between the number of alcoholic drinks and Flanker Task performance (a measure of inhibitory control); no association was observed with the other NIH toolbox tasks

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(assessing processing speed, working memory, episodic memory, and executive function) or with outcomes on the Rey Auditory Verbal Learning Test.

At first impression, these findings may seem to contradict common knowledge about the potential harms of prenatal alcohol exposure; in fact, they are remarkably consistent with existing literature. In the majority of cases, prenatal alcohol exposure is not associated with observable cognitive impairment in offspring. Most large, prospective studies using standardized testing have found inverted U- or J-shaped relationships between prenatal alcohol exposure and cognitive ability. Data from the Avon Longitudinal Study of Parents and Children show this pattern of results at ages 8 and 11 (6); similar results were observed in the Millennium Cohort study at ages 3, 5, and 7 (7) and in our previous work in Australia at 12 months of age (8). A meta-analysis pooling results of eight high-quality studies reported an overall small yet statistically significant positive effect of mild to moderate prenatal alcohol exposure on cognitive outcomes relative to control samples (9). This apparent positive effect is unlikely the result of prenatal alcohol exposure itself but a consequence of maternal and sociodemographic factors that differentiate drinkers and abstainers.

Fetal alcohol spectrum disorders are consistently found to be concentrated globally in disadvantaged populations of low socioeconomic status. A systematic review of case-control studies found that maternal demographic factors (lower maternal educational attainment, being single during pregnancy, maternal unemployment, living in a rural area, lower income, and older maternal age) and psychosocial factors (psychiatric comorbidities, history of suicide attempts, having a partner who abuses alcohol, higher number of stressful life events, and physical or sexual abuse) are risk factors for having a child with a fetal alcohol spectrum disorder (10). The overall pattern is that fetal alcohol spectrum disorders are found in a subset of mothers who are marginalized and face a variety of psychosocial stressors—each of which are independently associated with adverse neurodevelopmental outcomes in children. The epidemiology becomes particularly puzzling when these risk factors for fetal alcohol spectrum disorders are examined alongside characteristics of pregnant women who tend to consume alcohol: employment, higher education, and higher income predict alcohol use during pregnancy (11). This is consistent with the characteristics of women who drank alcohol relative to those who abstained in the Lees et al. study, as the mothers were more likely to be white, highly educated, and older.

Were these studies designed such that women from low socioeconomic backgrounds who drank alcohol during pregnancy were adequately represented along with drinkers from high socioeconomic backgrounds, it might have been possible to detect a range of effects of varying levels of prenatal alcohol exposure, even as protective factors associated with higher socioeconomic status may buffer the offspring against any negative effects. A comparison of children born to mothers from both low and high socioeconomic backgrounds who were receiving treatment for alcohol use disorder found a significant difference in the incidence rate of fetal alcohol syndrome: 4.5% in the high socioeconomic status group compared with 70.9% in the low socioeconomic status group (12). Our previous work using exposed and unexposed samples selectively matched on different patterns of sociodemographic factors suggests different effects of prenatal alcohol exposure depending on maternal demographics (8). Because these cross-contextual comparisons show inconsistent effects of prenatal alcohol exposure on development, they suggest that some associations between exposure and outcome are due to residual confounding effects (5). Lees and colleagues have made an important contribution by presenting data from a probability sample, selected to be representative of race, ethnicity, socioeconomic status, and urbanicity, thus avoiding the limitation of our and others' previous work that overrepresents white women of higher socioeconomic status. The authors also attend seriously to the issue of demographic confounding by conducting a sensitivity analysis in which youths exposed to prenatal alcohol were demographically matched to unexposed youths (N=1,271 in each group). In these analyses, some of the previously observed enhanced cognitive outcomes in exposed offspring were no longer apparent, yet enhanced performance on the Flanker Task persisted.

Lees et al. also examined psychological outcomes in youths, measured via maternal report using well-established questionnaires. In covariate-adjusted models and in demographically matched sensitivity analyses, findings remained significant for total problems, externalizing problems, sensation seeking, attention problems, and behavioral inhibition. Although these analyses show robust statistical associations, the differences would not be considered clinically meaningful (i.e., at most, a two-point difference on mean scores). Maternal reports of child psychopathology do not always correlate well with child self-reports or clinician assessments and may be influenced by a parent's anticipation of a "damaged" child based on alcohol use when pregnant; for example, mothers who received ambiguous results on prenatal chromosomal microarray testing (variants of uncertain significance) compared with those who did not perceived their child as being less socially and emotionally competent at 12 months (13).

Lees and colleagues present structural MRI and resting-state functional MRI findings, rare among large studies of prenatal alcohol exposure that also include observer-based outcomes, to examine whether prenatal alcohol exposure may have disrupted brain development, potentially forming biological precursors for disturbance in behavior. Comparing youths prenatally exposed to alcohol with unexposed youths, and using unadjusted or adjusted models, no differences were observed in functional connectivity within and between major networks that previously have been associated with fetal alcohol spectrum disorders (14). Differences in brain morphology were observed, including greater total cerebral volume and greater regional cortical volume and surface area in the temporal, occipital, and parietal lobes. These findings

are in the opposite direction of previous studies of youths with fetal alcohol spectrum disorder that reported reduced brain volume (15). The clinical significance of these differences is unclear, but partial mediation of the effects of prenatal alcohol exposure on psychological outcomes was observed. Among the possible explanations, the authors point to the inverted-U associations between the alcohol dose and regional brain volume and surface area. This means that those with light alcohol exposure compared with those who were unexposed show higher volume and surface area in parietal and temporal regions, a pattern that may be consistent with associations that the authors (and others) observe for cognitive outcomes.

It is interesting to compare the findings of Lees et al. with recently published results from the same ABCD cohort using a data-driven principal component analysis of 39 environmental measures and 30 child behavior and cognitive measures to identify clusters of parental and social factors and clusters of child outcomes (16). Maternal alcohol use was not associated with any child psychopathology, behavioral, or cognitive outcomes. Instead, parent psychopathology showed the strongest associations with child psychopathology, socioeconomic status with cognitive outcomes, and the proximal social environment (e.g., school quality and neighborhood safety) and social interactions (e.g., parenting) with impulsive behaviors. These findings align with converging evidence among studies of the developmental origins of health and disease for the transmission of maternal psychological distress to offspring, perpetuated by exposure to less optimal caregiving and an adverse postnatal environment experienced in the context of parental stress and psychopathology (4). Although Lees et al. adjusted for maternal depression in their primary analyses, demographically matched samples were not matched on maternal depression and other social, parental, and environmental factors that were most strongly associated with child psychopathology in Zhang et al. (16). Taken together, these two studies from the ABCD cohort pose a core conceptual challenge in integrating behavioral teratology studies with the developmental origins of health and disease and other research approaches—are we interested in asking what harm might alcohol cause, or what predicts poorer (or enhanced) development? Evidently the framing of the question, and subsequent choice of analytic methods, will lead to different conclusions.

The study by Lees et al. and existing literature converge to suggest that low-level prenatal alcohol exposure does not lead to clinically meaningful impairment in offspring in most cases, and moreover, that any observed associations between alcohol exposure and poorer developmental outcomes may not be purely causal (5). Prenatal alcohol exposure may more accurately be conceptualized as a risk factor (17)—a necessary, but not sufficient, condition for fetal alcohol spectrum disorders. Viewing alcohol in this way recognizes alcohol as a teratogen yet allows consideration for the probabilistic nature of sequelae for offspring based in part on the many variables in the prenatal and postnatal environments, limiting blame placed on mothers and instead recognizing compromised child outcomes as, in part, manifestations of larger societal issues (18). A possible solution to addressing both pregnant women's alcohol use and seemingly related compromised offspring psychological and cognitive outcomes is to emphasize the too often neglected mental health needs of pregnant women and parents. Parental psychopathology is a leading contributing factor to child psychopathology, and problematic alcohol use is often a manifestation of mental distress. Supportive mental health care, ideally integrated into routine obstetric and gynecological services, would help pregnant women and likely the next generation.

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