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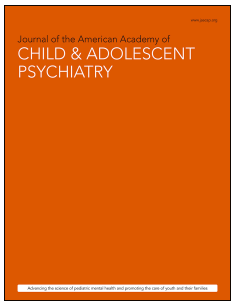

Editorial: *In Utero* Exposure to Maternal Affective Symptoms: Prenatal Programming of Child Psychopathology is Independent of Shared Genes of Risk

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Editorial: *In Utero* Exposure to Maternal Affective Symptoms: Prenatal Programming of Child Psychopathology is Independent of Shared Genes of Risk

RH = Editorial

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The womb is an influential first home. This felicitous phrase is attributed to David Barker, often called the father of the late 20th century Developmental Origins of Health and Disease (DOHaD) hypothesis, which asserts that maternal experiences during pregnancy are biologically transmitted to, and embedded in, the fetus, shaping child development. [1] Specifically, Barker focused on maternal inadequate nutrition as a key *in utero* exposure to which the fetus biologically adapts, leading to biologically programmed changes, meaning long-lasting, that potentially put the offspring at risk for future metabolic diseases.[1] In more recent DOHaD publications, the impact of pregnant women's affective symptoms—defined broadly to include perceived stress, depression, and anxiety—on fetal and infant brain–behavior development has been identified. There is a third pathway for the familial inheritance of risk for psychiatric illness beyond shared genes and compromised parental postnatal mental health and care giving: prenatal programming of risk for psychopathology originating in mothers' mental health symptoms[1] However, despite decades of experimental, pre-clinical studies demonstrating maternal prenatal stress predicting altered offspring outcomes,[2] the alternative interpretation—that shared genes of risk account for the outcomes—has remained challenging to disprove for human studies, perhaps particularly when the mother reports on her own and her child's mental health (a common study design further addressed below). In this context, the article by Chen et al. [3] utilizing polygenic risk scores providing a single measure of genomic risk for complex phenotypes provides rigorous and original results demonstrating effects of maternal affective symptoms on child psychiatric outcomes while controlling for genomic risk.

Chen *et al*. [3] leverage a subset of the Avon Longitudinal Study of Parents and Children (ALSPAC) (n=4,980) which included participants who had been genotyped to demonstrate that

maternal prenatal depressive and anxiety symptoms at 32-weeks gestation are positively associated with child/adolescent emotional/behavioral problems at 4,7,8,9,11, 13, and 16 years of age independent of child genomic risk for mental disorders (GEE Est.=0.096, 95% CI: 0.065–0.121, p=2.66E-10 and GEE Est.=0.065, 95% CI: 0.037–0.093, p=1.62E-05, respectively). In other analyses, results showed that both prenatal environment and genes were independently and additively (though not multiplicatively) associated with child/adolescent outcomes. Furthermore, based on genetic sensitivity analyses, maternal prenatal affective symptoms still were associated with child/adolescent symptoms while shared genetic risk accounted for approximately 40% of the variance. Of note, there was little evidence of domain-specific effects of maternal depression on child/adolescent symptoms, suggesting instead that maternal depression may serve as an overall risk factor for child psychopathology. Finally, the main findings were replicated in a sample from the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) (n=514), specifically the independent effect of maternal depression on child symptoms (B=0.156, 95% CI: 0.066–0.246, p=0.001).

Chen *et al.*,[3] identify the very limited number of studies that have aimed to address the potential genomic confounding in prenatal programming research, especially with respect to maternal prenatal mental health symptoms and children's mental health trajectories. The statistical models include key covariates such as gestational age at birth, maternal prenatal substance use, and household crowding index. Study authors also ran models examining a subset with clinically significant maternal affective symptoms and child/adolescent mental health symptoms showing that at 4 and 16 years of age, maternal depression and anxiety were associated with compromised

child mental health independent of children's genomic risk. These important analyses are reassuring as there can be statistically significant results independent of clinical relevance.

However, some of the report's methodologies and unexpected findings should be identified, with the acknowledgement that the original ALSPAC data was collected in the early 1990s and with the intent of potentially improving future similar work. In ALSPAC mothers reported on their own mental health during pregnancy and at later time points as well as on their child's/adolescent's. To address this weakness, the researchers ran sensitivity analyses excluding women with significant depression at any postpartum time point, reporting their original results held. Yet it remains troubling to have the independent and dependent variables obtained from the same reporter; bias still could account for the outcomes. Recent papers (eg,[4] and others resulting from two large NIH consortiums, Environmental Influences on Child Health Outcomes (ECHO: https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program) and Healthy Brain Child Development Study (HBCD: https://hbcdstudy.org), enrolling 50,000 and 7,500 dyads respectively from pregnancy and including observer-based child outcomes will be ideal, publicly-available, data sets that can address this confound in prenatal programing studies. Postpartum depression in ALSPAC was measured at 8 months, potentially missing the impact of these symptoms on child development prior to this period; some reports indicate peak incidence much closer to birth [5]. If postpartum depression had been measured at an earlier time point, would the results hold? It also is curious that both gestational age at birth and birth weight were included in their models as they are so highly correlated. The authors note the lack of diversity in their sample, which the ECHO and HBCD data sets will address—and they also will include child and mother genotype. Finally, two outcomes are unexpected: there was no

interactive effects of maternal affective symptoms with child genomic risk or between maternal affective symptoms or child genomic risk and child sex assigned at birth. On the former, the authors consider the results in relation to varying genomic risk methodologies, though not conforming to the Genes X Environment equation still warrants further investigation. When examined, sex effects are common in prenatal programming studies [4,6], which is unsurprising given the sexually dimorphic outcomes in developmental psychopathology [4]. Finally, while Barker emphasized fetal adaptation in his programming hypothesis, this report, and most DOHaD studies, are described within a teratogenic model: exposure to maternal affective symptoms is an adverse exposure likely associated with compromised outcomes. Future studies with observational child outcomes and greater assessment of the child's postnatal context may consider short-term advantages to what are labelled as, or later become, mental health symptoms.

This report's robust findings demonstrating the association between prenatal exposure to maternal affective symptoms and increased risk for child psychopathology independent of genomic risk is a clarion call to address the mental health needs of pregnant individuals in the transition to parenthood—for the mothers and two-generation impact. In the United States, there are innovative approaches to improving access to treatment such as psychiatry access programs[7] and collaborative care models,[8] and others re-imagining the perinatal care ecosystem to focus on whole-person care and preventative programs for mental health issues.[9] We have the tools for effective intervention; we lack equitable funding schemes for mental health across regions, disciplines, and demographics, which also drives providers away from insurance-based care and into private practice, further exacerbating access issues. Chen *et al*. [3] note the annual $18 billion cost of untreated perinatal mental illness, largely a consequence of the adverse effects of

untreated illness on child outcomes. Results from this and other high-caliber papers could contribute to calculating the Return on Investment from improved access to affordable care for maternal mental health. As the authors point out, the human cost of maternal mental health conditions must be addressed; If examined, the financial equation likely also would support the urgency for systems-change to address mental health needs in the perinatal period.

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