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HOT TOPICS

Neuropsychopharmacology reviews 2022 hot topics: the prenatal environment and risk for mental illness in young people

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Perturbations in fetal brain development have long been implicated in risk for subsequent mental illness. Birth cohort studies have associated varied prenatal exposures – spanning obstetric complications to maternal infection, stress, and substance use – with risk for multiple neurodevelopmental disorders that emerge years (e.g., autism) to decades (e.g., schizophrenia) after birth. Emerging research may further shift how we conceptualize the origins of mental illness, and, relatedly, the best time to intervene.

Although adverse prenatal exposures can have large effects (~1.5–2-fold increased risk of disease), these exposures are also common and frequently co-occur, raising questions about additive effects. Using Adolescent Brain Cognitive Development (ABCD) Study data, we assessed cumulative effects of adverse prenatal exposures on psychopathology at ages 9–10 [1]. Each adversity associated independently with modest effects on psychopathology scores. However, when linearly combined, risk for *clinically significant* symptoms risk rose sharply (7% for no exposures vs. 29% for ≥4 exposures, OR 3.53, Fig. 1). More systematic, fully prospective efforts to characterize the prenatal "exposome" may account for even greater proportions of risk.

Maternal infections during pregnancy also augment psychopathology risk in offspring. However, relatively few pathogens (e.g., TORCH, Zika virus) associated with poor neurodevelopmental outcomes cross the placenta. Further, the severity of maternal

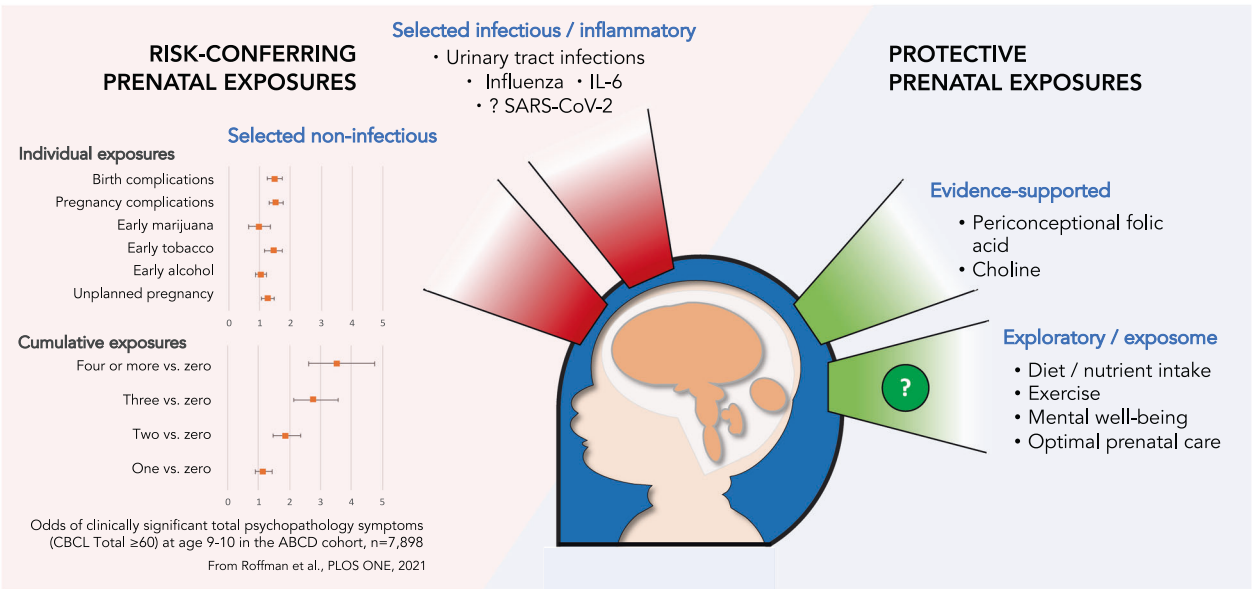

Fig. 1 Prenatal exposures that exacerbate, or potentially mitigate, risk for neurodevelopmental disorders. Left panel: infectious and non-infectious exposures contribute to risk, and selected non-infectious exposures have been found to confer additive risk. Right panel: candidate neuroprotective exposures that may be developed through prenatal interventional studies.

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infection does not necessarily predict the degree of risk to the fetus, as demonstrated in a recent Swedish birth registry study where even uncomplicated maternal urinary tract infections predicted a 1.3-fold increase in depression, and 1.9-fold increase in autism in the offspring [2]. These and other findings have implicated the maternal immune response – elements of which do cross into the fetal circulation – as a more proximal culprit than the pathogens themselves. Accordingly, lack of routine vertical transmission of SARS-CoV-2, the virus that causes COVID-19, does not alleviate concerns that it may predispose to subtle fetal brain injury. Such concerns are potentially compounded in the setting of (1) increased frequency of neonatal complications following maternal SARS-CoV-2 infection [3], and (2) pandemic-related social stressors, which themselves likely confer risk in utero, if these too combine linearly.

Importantly, recognition of fetal life's importance to subsequent mental illness risk has also catalyzed efforts to discover protective, and potentially preventative, interventions during pregnancy. For example, large, prospective studies have consistently associated periconceptional folic acid intake with ~50% reduction in autism risk – including among children at increased genetic risk [4]. Our work has also related increased prenatal folic acid exposure to neuroprotective effects on cortical development that persist through adolescence [5].

Efforts to identify additional modifiable factors in the prenatal environment that mitigate risk are ongoing, including through the planned NIH HEALthy Brain and Child Development Study which will study ~7500 children from the second trimester of pregnancy through the first decade of life. These efforts may also provide greater temporal specificity, as effects of both risk-conferring and protective exposures likely vary by gestational stage. In parallel, efforts to develop objective, non-invasive markers to document prenatal environment risks, including the study of primary teeth [6], may ultimately enhance personalized risk assessment, and herald more sophisticated and effective early interventions.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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