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Prenatal Nutritional Deficiency and Psychosis:

Where Do We Go From Here?

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In this issue of *JAMA Psychiatry*, Mackay et al[1] report that extremely inadequate gestational weight gain is linked to non-affective psychosis in offspring. This result is concordant with several previous studies[2] designed as natural experiments that linked prenatal maternal famine to offspring nonaffective psychosis. The present study, based on Swedish national registries, represents a substantial advance by providing evidence that a similar association is detectable among individuals in a generally well-fed population in more ordinary circumstances. Also notable, the study included strengths of design not possible in the natural experiments, such as rigorous control for parental psychiatric conditions and comparison of affected and unaffected siblings. Thus, it contributes to an increasingly robust body of convergent evidence for a role of prenatal nutritional deficiency in the early origins of psychosis and strengthens the argument for examining prenatal nutritional supplements and dietary patterns as a means of prevention.

Another strength is that the study highlights puzzling questions that have yet to be resolved. Why was the association with psychosis robust only at the extreme of low weight gain? Why did the investigators find no association of high or low early prenatal body mass index with psychosis, contrary to prevailing views and some prior reports on schizophrenia and other neurodevelopmental disorders?

Inevitably, the study also had limitations. For example, the timing of nutritional deficiency could not be specified using registry data, results were inconclusive at the extremes of body mass index, and the potential role of maternal stress as a co-factor could not be examined. These limitations should be noted but without losing sight of the authors' substantial achievements.

In this commentary, we focus henceforth on how we could build on the convergent evidence to identify mechanisms and preventive interventions for nonaffective psychoses and other neurodevelopmental disorders that fall within the domain of psychiatry. Studies of extreme prenatal exposures remain useful but not sufficient to reach these goals. We propose that the endeavor requires a guiding framework that embraces mutually informative lines of investigation being conducted in tandem. Given limited space, we hope to spark discussion

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of this framework by focusing on 2 of the central challenges and how they might be overcome.

The first challenge is that translational science is generally presented as a linear progression, with knowledge transferred from basic science to clinical research (step 1), from clinical research to clinical care (step 2), and from clinical care to implementation of public health interventions (step 3). For more than 50 years, however, studies of prenatal nutritional deficiencies and neurodevelopmental disorders have followed a more circuitous route and holistic bridging of disciplines.[2] Studies have been performed in tandem at many levels and have informed one another, including natural experiments based on tragic historical famines, discoveries in basic sciences such as genomics and epigenetics, trials of prenatal micronutrients, clinical research, and epidemiologic studies of risk factors. The interplay has generated hypotheses about mechanisms, such as epigenetic effects and de novo mutations, and supported studies of preventive effects of micronutrients. At present, evidence is being sought for preventive effects of periconceptional folic acid, prenatal choline supplementation, and prenatal vitamin D, and all these efforts are grounded in basic science, animal studies, epidemiologic studies, and clinical research. We propose that translational science as a linear progression is not an appropriate framework for research on prenatal nutrition and neurodevelopmental disorders. Instead, this field should adhere to a conceptual framework that explicitly promotes multiple levels of inquiry proceeding in parallel and not in isolation from one another. We should also encourage cross-level research, exemplified by an investigation by Roffman et al[3] that compares neuroimaging data for children and adolescents born before, during, and after the rollout of folate fortification of food in the United States. Such multileveled and cross-disciplinary efforts fit conceptual frameworks of ecoepidemiology and population health science,[4,5] in which there is an interplay between macro and micro levels, interacting and iteratively learning from and informing preventive interventions in the population. These efforts are also compatible with calls for translational epidemiology.[6]

The second challenge is that typically in studies of neurodevelopmental disorders, specific prenatal micronutrients have been considered in isolation, prominent examples being the studies noted earlier of choline, folic acid, and vitamin D. These studies should be continued and may yet produce definitive evidence of preventive effects for a single micro-nutrient. All 3 of these micronutrients are fundamental to neurodevelopment. For example, folate plays a crucial role in 1-carbon pathways that shape epigenetic effects, DNA synthesis and repair, and neuronal migration. However, we have increasing evidence that these 3 (and other) micronutrients have a dynamic influence on one another.[7] In a simple example, folate intake mitigates the consequences of low choline intake, and most likely vice versa. Just as we now recognize that mutations in any one of a set of genes could disrupt a pathway of neurodevelopment, we could recognize that deficiencies in any one of a set of micronutrients could do so, and furthermore that a deficiency of one might be partly compensated by another. This leads us to the view that a set of micronutrients may often best be considered in tandem. Further supporting this view is the fact that the influence of any single factor on an outcome in a given population is inherently dependent on the prevalence of other factors that belong to the same causal set.[4,5] At the same time, the boundaries among neurodevelopmental disorders are uncertain and the same early disruption might influence

the pathways to more than one of them. We therefore propose that our framework embrace the selection and study of sets of micronutrients and sets of neurodevelopmental disorders.

It is beyond the scope of this comment to spell out the many implications of these 2 starting points. We shall simply note that a framework incorporating these features would help generate hypotheses to explain apparent discrepancies between results at different levels, such as between societal trends and individual-level studies of micronutrients as preventive interventions; would encourage us to consider micronutrient sets as buffers against a host of insults ranging from toxins to maternal stress; and last but not least, would facilitate study of a rich array of gene-environment interactions.

We close by emphasizing that as we seek to advance toward mechanisms and preventive interventions, we should not dismiss the ongoing relevance of famine per se. Famines have been common throughout the history of human evolution and afflict a wide array of populations today. They tend to be man-made, resulting more from the maldistribution of food than the inability to produce it. The manifold tragic consequences of famine for population health present an urgent challenge for social justice.

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