

COMMENT



An expansive approach to examining the paternal origins of mental disorders

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In this issue of *Pediatric Research*, Vervoot, Delger, and Soubry review what is known about the impact of paternal age at conception and the development of mental disorders in offspring. They focus on six conditions for which paternal age may play a role: autism spectrum disorder, schizophrenia, attention-deficit/hyperactivity disorder, bipolar disorder, obsessive-compulsive disorder, and Tourette syndrome. They also comment on the paucity of epidemiological evidence for a role of paternal age in other psychiatric conditions such as suicidality and substance abuse.

In reviewing prior studies focused on the etiology of the conditions of interest, the authors note the interplay between contributing genetic, epigenetic, and environmental factors in the development of symptomatic disease. Not only do multiple influences contribute to the manifestation of phenotype, they note, but distinct etiological mechanisms likely interact to enhance or suppress disease development. For example, genetic factors contributing to a specific phenotype in the father might predispose him to behavior that results in fathering a child earlier or later in life. Earlier parenting results in childrearing by less mature parents in an often less socioeconomically secure household, resulting in a social environment that could potentially enhance specific phenotypes in the offspring. Thus, paternal genetics directly influences the environment that the child experiences. In contrast, later parenting allows for increased toxic environmental exposures that could impact epigenetic marks on gametes, enhancing or suppressing transmission of the father's phenotype.

Vervoot et al. thereby apply a wide-angle developmental lens to the question of the origins of these six conditions, adapting the "Barker Hypothesis" or Developmental Origins of Health and Disease framework¹ to build upon the *Paternal Origins of Health and Disease* paradigm that has been circulating in the literature since at least 2018.² As such, they take an "exposomics" approach to the question of disease prediction, proposing a conceptual framework with which to address the role of paternal age in the development of specific disorders in offspring. This approach, conceptualized by Christopher Wild in 2005, stresses the need to include environmental influences in the understanding of human disease progression. Specifically, the exposome is defined as "encompassing life-course environmental exposures (including lifestyle factors), from the prenatal period onwards"³ and is intended to complement genome-wide association studies in the search for predictors of and contributors to disease.

In addition to recommending broad consideration of predisposing environmental and genetic factors, the authors suggest that both clinicians and researchers would benefit from avoiding the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition⁴ categorizations as outcomes of focus. Instead, they advocate the prioritization of phenotypic features to unmask common gene-by-environment interactions in the causal pathway.

The application of an exposomics approach to key problems in behavioral health with a focus on clinical utility is both novel and a much-needed addition to the care armamentarium for a complex and impactful class of diseases. The significant increase in mental health disorders—particularly among children and adolescents⁵—during the COVID19 pandemic has highlighted the importance of environmental factors in the development, unmasking, or exacerbation of psychiatric conditions. It is critical that both the research and clinical communities take a broad view of disease predisposition to facilitate early identification and appropriate treatment for those at risk.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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