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LETTER TO THE EDITORS

# Comment on "Perinatal risk factors for the onset of bipolar disorder in young adulthood: a 22-year birth cohort"

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We would like to congratulate the editors for their valuable and extensive study, which contributes significant results on perinatal risk factors associated with bipolar disorder in people up to 22 years of age. The study used rigorous methodology and a robust population sample representative of the Brazilian context based on a 1993 birth cohort study in the city of Pelotas. The investigation of factors such as maternal smoking and passive tobacco exposure fills an important gap in the literature on early environmental influences on bipolar disorder.

However, we would like to suggest other contextual factors that can be explored using the theoretical framework of the Developmental Origins of Health and Disease (DOHaD) to enrich the results.

Research indicates that both malnutrition and overnutrition during pregnancy can be harmful,[1] reinforcing the relevance of the DOHaD approach, which demonstrates how environmental factors during early development can cause permanent epigenetic changes, with lasting impacts on mental and physical health.

The DOHaD theory, which emphasizes the role of early life environmental factors in shaping health outcomes, could provide a valuable lens for understanding perinatal risk factors for bipolar disorder. In DOHaD, the brain is considered most vulnerable to environmental factors and nutritional deficiencies in the perinatal phase.[1] DOHaD argues that exposure to external environmental events during critical periods of development in early life, from the fetal period to the first two years of life, can program the body's physiology and metabolism.[2] This programming occurs through epigenetic modifications, such as DNA methylation and changes in chromatin structure, without altering the genetic sequence.[3,4]

Analysis of the maternal family history of mental disorders is an important aspect that was neglected in this study, in addition to other factors such as medication use, exposure to toxic substances, maternal stress, and infections during pregnancy, which have been associated with adverse health outcomes throughout life, including neuropsychiatric disorders.[5] Factors such as protein-calorie malnutrition, nutrients such as essential fatty acids, iron, retinol (vitamin A), and vitamin D, and environmental insults, such as perinatal stress and hunger, can impair brain development, leading to mental health consequences and neuropsychiatric disorders, such as schizophrenia, depression, and other disorders.[1,6,7]

Thus, future studies on bipolar disorder could incorporate DOHaD theory, which emphasizes environmental aggression during the perinatal period. That is to say, maternal malnutrition, gestational infections, psychological stress, lack of social support, difficulty accessing health services, financial stress, and inappropriate use of medications, alcohol, and drugs can influence epigenetic adaptations associated with disorders such as bipolar disorder.

Finally, considering factors such as the mother's nutritional status, family history of mental disorders, the psychosocial context, and the importance of a balanced diet in early childhood can result in a more integrated approach to mental disorders throughout life, strengthening prevention measures. We congratulate the authors on the study's relevance and suggest that future investigations explore these nutritional and psychosocial factors for a deeper understanding of bipolar disorder, from the perinatal period to the later stages of life. We look forward to an enriching dialogue with the authors on these topics.

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## Disclosure

The authors report no conflicts of interest.

## Data availability statement

Not applicable.

## Author contributions

RC: Conceptualization, Writing – original draft.
AET: Writing – review & editing, Supervision.
PBP: Writing – original draft.
JPSJ: Conceptualization.
EVCB: Writing – review & editing, Supervision.
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