Malnutrition's Role to the Risk of Developing Schizophrenia: A Literature Review

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Some evidence suggests that nutritional factors in-utero may contribute to the development of schizophrenia in offspring. To better understand the relationship between in-utero exposure to nutritional deficiency as a determinant of schizophrenia, a narrative review was conducted. Natural studies involving prenatal exposure to famines were identified and described. The relationship between malnutrition, low birth weight, and obstetric complications was evaluated as implicated in schizophrenia development. In addition to malnutrition, various micronutrients and the complementary biological mechanisms were reviewed including, iron, Vitamin D, and folate. Given the inherent link between poverty and malnutrition, associations between income and risk of schizophrenia were examined. The review concluded that prenatal malnutrition may be associated with an increased risk of schizophrenia. Given the relatively high prevalence of nutritional deficiencies during pregnancy, this work has the potential to offer substantial benefits for the intervention and prevention of schizophrenia in the population. More work and research are needed to directly observe malnutrition's impact on schizophrenia, but such opportunities are limited due to ethical considerations. To address these limitations, future research could explore innovative methodologies to bridge the gap in understanding and provide insights into the complex interplay between prenatal malnutrition and schizophrenia.

Keywords

malnutrition • pregnancy • schizophrenia • prenatal health

Introduction

Schizophrenia is a debilitating disease characterized by a range of symptoms such as lack of insight, hallucinations, delusions, distorted or illogical speech, and social withdrawal. It affects an estimated

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7.2 in 1000 persons in the United States (McGrath, 2008). Schizophrenia is not solely a mental illness but rather a physical brain disease, as evidenced by the smaller whole brain volumes and larger lateral ventricles observed in individuals with schizophrenia (Picchioni, 2007). The disease typically develops in young adulthood, with an earlier onset and greater incidence for males compared to females (Venkatesh, 2008). The etiology of schizophrenia is complex, involving genetic predisposition, environment, and brain structure and function (National Institute of Mental Health, 2023). Risk of schizophrenia development has further been found to involve obstetric complications, low birthweight, and perinatal hypoxia (Piccioni, 2007; Brown, 2008). Malnutrition serves as one example of an obstetric circumstance that can detrimentally impact overall health. Undernutrition or malnutrition is described by a deficiency, excess or imbalance of nutrients that can increase the risk for disease, prolonged illness, low birth weight, low immunity, and impaired physical and neurological development (Saunders, 2010); (Wahlbeck, 2001). These negative health effects associated with malnutrition may be recognized as components of biological injury that heighten the risk of developing schizophrenia.

To better understand the relationship between in-utero exposure to nutritional deficiency as a determinant of schizophrenia, a narrative search was conducted. This review aims to explore the existing evidence on the association between prenatal malnutrition and the risk of schizophrenia. Understanding the role of nutrition during pregnancy in the etiology of schizophrenia is crucial for developing effective preventive strategies and interventions.

Natural Experiments

The findings of natural experiments and the examination of specific micronutrients provide valuable insights into the potential impact of prenatal malnutrition on schizophrenia.

Tragic events, like periods of famine, though not a controlled experiment, can provide a valuable foundation for conducting stronger experiments that surpass mere observation (Stein, 1975).Two separate and notable natural studies observed the association between prenatal exposure to famine and the later development of schizophrenia — the Dutch Hunger Winter and Chinese Famine.

The Dutch Hunger Winter occurred between 1944–1945 after a Nazi blockade of Holland, exacerbated the already compromised food access that had been further endangered by a frozen winter for those living in the Netherlands. The daily food rations during this time were severely limited, consisting mainly of just bread and potatoes. The event has allowed for the study of the impact of famine on health outcomes, due to detailed records of food rations and impacted individuals for decades after (Susser, 1992; Schultz, 2010). The Dutch psychiatric registry compared psychiatric outcomes in adulthood for unexposed and exposed birth cohorts in cities that experienced and did not experience the height of the famine from October 15–December 31, 1945. These babies were then followed throughout their life and evaluated periodically for mental health outcomes between 1970–1992, when the subjects were aged 24–48 years. Studies from this cohort highlight an increase in neurodevelopmental tube defects, a common precursor to the development of schizophrenia (Stein, 1975; Brown, 2008). More notably, the study found a significant, 2-fold increase in the risk of schizophrenia in the exposed birth cohort compared to non exposed cohorts (Brown, 2008).

A study in the Anhui Province of China in the 1950s amidst a massive famine also looked into the development of schizophrenia. Caloric data was not available but the cohort had a much larger

sample size and perhaps more accurate results than that of the Dutch cohort. Researchers relied on the birth cohorts of 1960 and 1961 at the height of the famine to observe schizophrenia incidences and trends. Similar to the Dutch famine study, there was an approximate 2-fold increase in the risk of schizophrenia (St. Clair, 2005).

However, given that the diagnostic criteria for schizophrenia has changed over time, it is hard to make accurate associations between these natural experiments' famine and schizophrenia development. The last evaluation of outcomes in Dutch winter famine were given in 1992. Since then, the Diagnostic and Statistical Manual of Mental Disorders (DSM) has gone through a total of five revisions, with numerous changes in the requirements needed to make a schizophrenia diagnosis (Substance Abuse and Mental Health Services Administration, 2016; Regier, 2013).

Therefore, applying the most recent edition, DSM V, when examining associations would offer the most accurate information. The research may still hold value, but there is a need for caution and nuanced interpretation of the findings, taking into account the changes in diagnostic criteria over time. Researchers should consider reexamining the data using the latest criteria to ensure the continued relevance and applicability of the study's conclusions.

Specific Nutritional Deficiencies

Various micronutrients and their biological mechanisms were reviewed to potentially identify specific associations between prenatal malnutrition causing nutrient deficiencies and schizophrenia development including folate, essential fatty acids, vitamin D, iron, and protein-calorie malnutrition.

Folate: Folate deficiency can impede the synthesis and repair of DNA and hinder the production of methyl donors and the methylation of DNA. Specifically, inadequate folate can inhibit the conversion of homocysteine (hcy) to methionine, leading to a buildup of hcy, which has been shown to cause adverse effects on fetal brain development, and is implicated in schizophrenia development (Hama, 2020; Moustafa, 2014). Maternal folate supplementation immediately before pregnancy lowers neural tube defects by up to 80% (Wald, 2011). Neural tubes are crucial structures that form in early embryonic development and eventually develop into the spinal cord and brain (Singh, 2023). Supplementation, in this context, refers to the intentional intake of additional folate through dietary sources or supplements to address potential deficiencies. Supplementation has also been shown to lower risk of severe language delay, improve cognitive function, and reduce neurodevelopmental delays overall which have been associated with an increased risk of schizophrenia (Kirkbride, 2012). A limitation falls in the fact, however, that no clinical cohort has directly examined the relationship between maternal folate and schizophrenia.

Essential Fatty Acids: Docosahexaenoic acid (DHA), an omega-3 fatty acid, has been correlated with decreased neonatal neurological abnormalities, which are implicated in schizophrenia development (Sun, 2017).

Vitamin D: A study suggests that individuals born during the winter months, particularly in urban areas, face a higher risk of Vitamin D deficiency due to reduced sunlight exposure. This deficiency has been associated with an elevated likelihood of developing schizophrenia (McGrath, 2008).

Iron: Iron deficiency reduces hemoglobin, increases anemia, and compromises oxygen levels (Mayo Clinic, 2022). When a fetus is exposed to iron deficiency in utero, this can result in fetal

hypoxia. Fetal hypoxia is associated with an increased susceptibility to schizophrenia. Further, iron affects dopaminergic neurotransmission and myelination both of which have been implicated in the pathway of schizophrenia (Cannon, 2002).

Protein-Calorie Malnutrition: A deficit in protein-calories increases dopamine and serotonin, which causes turnover and dysfunction in the hippocampus (Bronzino, 1997). This is associated with low cell counts, low dendritic branching, long-term potentiation, bad spatial performance, and reduced prepulse inhibition all of which are associated with risk of schizophrenia development when exposed in-utero (Bronzino, 1997). An appropriate and well-proportioned amount of protein supplementation reduced the incidence of small for gestational age births by 21%, while supplementing too much increased the risk of schizophrenia (Ota, 2015).

All micronutrients supplemented together (Vitamin A, zinc, calcium, iron, iodine, magnesium, Vitamin C, Vitamin E, Folic acid, marine oil, fatty acid) led to a decrease of 11%–14% in the number of babies born with LBW (da Silva Lopes, 2017).

The influence of bodily functions during refeeding must be accounted for, however. When people are malnourished, thiamine (or Vitamin B) stores become depleted. Refeeding, the process of reintroducing and increasing the intake of nutrients to address malnutrition or starvation, however, seems to prompt an even greater thiamine deficiency, which may increase the development of schizophrenia, not the malnutrition itself (Mehanna, 2009; Ishida, 2023). Under normal circumstances, vitamin B supplementation has been shown to reduce the symptoms of schizophrenia (Firth, 2017).

Income

The link between poverty and malnutrition has been well-established, and there is evidence of associations between income and the risk of schizophrenia (Hakulinen, 2020; Ridley, 2020). The psychiatric stress responses due to social class in the face of famine is a confounding factor that may increase low birth weight pregnancies and affect schizophrenia risk (Borders, 2007; Khashan, 2008). Low income can be both a casual factor for schizophrenia and a result of a downward drift or decrease in social status (Ridley, 2020; Werner, 2007). Chronic psychosocial stress has been associated with low birth weight neonates in low-income women, with factors such as food insecurity, chronic illness in the home, increased crowding, unemployment, and poor coping skills significantly contributing to this outcome (Borders, 2007). Furthermore, research has established a bidirectional causal relationship between poverty and mental illness, with negative income shocks and poverty-related risks contributing to the development and worsening of mental health conditions (Ridley, 2020; Jensen, 2017). Poverty-related risks such as food insecurity, infectious diseases, environmental contaminants, and psychological stressors have been shown to converge and affect children's neurocognitive development through various biological pathways, including malnutrition, inflammation, and neuroendocrine stress responses (Jensen, 2017). Furthermore, maternal psychological stress and distress during pregnancy have been found to be predictors of low birth weight, prematurity, and intrauterine growth retardation (Rondó, 2003). The release of catecholamines, placental hypoperfusion, and restriction of oxygen and nutrients to the fetus are believed to contribute to fetal growth impairment and preterm delivery, both examples of biological injury that increase schizophrenia development risk (Omer, 1986; Copper, 1996). Additionally, maternal exposure to severe adverse life events, particularly death of a close relative during the first trimester,

has been associated with an increased risk of offspring schizophrenia, independent of other risk factors (Khashan, 2008). The mechanisms underlying these associations involve neurodevelopmental abnormalities and potential programming of abnormal brain growth due to the effects of stress hormones on fetal development (Khashan, 2008). These findings highlight the importance of assessing and addressing psychosocial stressors during pregnancy to mitigate adverse outcomes and reduce the risk of schizophrenia in offspring.

A significant obstacle hinders the undertaking of experiments aimed at directly studying the impact of malnutrition on the development of schizophrenia. Specifically, conducting extensive randomized trials that involve exposing pregnant women to suboptimal nutritional conditions to assess adverse effects on their offspring raises crucial ethical considerations. Further, malnutrition is associated with other health problems, such as vitamin deficiencies, weakened immune system, and cardiovascular issues, which may increase the risk of schizophrenia separate and apart from a state of malnutrition itself (Picchioni, 2007).

Conclusion

The review concluded that prenatal malnutrition may be associated with an increased risk of schizophrenia. This work has the potential to offer substantial benefits for the intervention and prevention of schizophrenia in the population. In addition, this work may benefit those who are at higher risk of stress-inducing life events, including those impoverished, famished, and those with other health complications. Proper maternal nutritional supplementation or even pregnancy education may decrease the risk of schizophrenia in offspring later in life. More work and research are needed to directly observe malnutrition's impact on schizophrenia.

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