

Hypothesis: Is low prenatal vitamin D a risk-modifying factor for schizophrenia?

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Abstract

The central nervous system is increasingly being recognised as a target organ for vitamin D via its wide-ranging steroid hormonal effects and via the induction of various proteins such as nerve growth factor. This paper proposes that low maternal vitamin D may impact adversely on the developing foetal brain, leaving the affected offspring at increased risk of adult-onset schizophrenia. The hypothesis can parsimoniously explain diverse epidemiological features of schizophrenia, such as the excess of winter births, increased rates of schizophrenia in dark-skinned migrants to cold climates, the increased rate of schizophrenia births in urban versus rural setting, and the association between prenatal famine and schizophrenia. Studies that will allow rejection of the hypothesis are proposed. © 1999 Elsevier Science B.V. All rights reserved.

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1. The search for non-genetic risk factors for schizophrenia

The search for non-genetic risk factors for schizophrenia has been a frustrating exercise. Often, the quality of the epidemiological data has out-paced the quality of hypotheses. For example, numerous studies have shown an excess of winter and spring births for individuals who later develop schizophrenia compared to the general population (Torrey et al., 1997). Season of birth acts as a proxy marker, but the nature of the underlying risk-modifying factor remains elusive. Similarly,

research related to migrant studies and urban-birth has only been able to provide broad clues to help identify underlying, risk-modifying factors (e.g. pre- and perinatal exposure to viruses). In this paper I will argue that low prenatal vitamin D should be considered as a candidate risk-modifying factor for schizophrenia as it can provide a unified and parsimonious explanation for diverse epidemiological findings.

2. Vitamin D

Vitamin D is a fat-soluble vitamin and steroid hormone. It is not strictly a vitamin in circumstances where the individual has adequate exposure to sunlight. Where this exposure is lacking, dietary intake of vitamin D is required. Vitamin D is

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found in fish, eggs, vegetable oils, butter, liver and in fortified milk and margarine. The action of ultraviolet light on a cholesterol metabolite found in the epidermis results in the production of previtamin D. After two separate hydroxylations (first in the liver, then in the kidney), the active 1,25 dihydroxyvitamin D₃ is produced. Vitamin D production is strongly and consistently associated with the duration of the photoperiod, which in turn is influenced by latitude and season (Webb et al., 1988; Holick, 1995).

Calcium and phosphorus levels and parathyroid hormone tightly regulate the final step in the production of vitamin D. With respect to its mode of action, vitamin D operates via both nuclear receptors (part of the superfamily of steroid hormone receptors) and nongenomic systems, and has been shown to induce the transcription of a large number of target genes (Darwish and DeLuca, 1993).

Hypovitaminosis D is still relatively common in developed countries, such as the US and the UK (Compston, 1998; Lawson and Thomas, 1999; Thomas et al., 1998; Utiger, 1998). A large epidemiologically based US study reported that, of the women aged 20–39 (peak ages for child-bearing), 12% had low serum 25-hydroxyvitamin D levels (Looker and Gunter, 1998).

3. How does vitamin D impact on brain development?

The links between vitamin D, calcium and bones have long been appreciated; however, in recent years an ever-widening range of actions has been described for this vitamin/steroid hormone. In a recent review, evidence was presented linking vitamin D with cell growth and proliferation, immune response and foetal development (Bouillon et al., 1995). Vitamin D receptors have been found in differentiating zones of the central nervous system of the rat embryo (Veenstra et al., 1998) and in the adult human brain (Stumpf et al., 1982). Vitamin D has been shown to be a potent inducer of nerve growth factor synthesis (Musiol and Feldman, 1997). The precise nature of the links

between vitamin D and the central nervous system are still poorly understood.

4. Vitamin D and schizophrenia

Vitamin D deficiency has not been investigated as a potential risk factor for psychoses; however, polymorphisms in the vitamin D binding protein (also known as group-specific component) have been examined in several genetic marker studies. The results of these studies have been mixed (McGuffin and Sturt, 1986).

4.1. Season of birth

As mentioned previously, one of the most robust findings in schizophrenia epidemiology has been the tendency for people with schizophrenia to be born in winter. Moskowitz (1978) first suggested that the marked seasonal variations in the serum level of vitamin D may be linked to the seasonality of schizophrenia births. In regions with less winter sunlight, low vitamin D levels are frequently reported during winter (Holick, 1995; McKenna, 1992). More vitamin D is required during pregnancy due to the rapid growth of the foetus (especially in the third trimester). In order to optimise foetal vitamin D levels, the placenta has the unusual ability of being able to metabolise the final hydroxylation of vitamin D (Delvin et al., 1985). In women with marginal vitamin D levels, there is evidence that maternal levels fall during the third trimester — this is especially so if the third trimester occurs during winter (MacLennan et al., 1980; Serenius et al., 1984). It is postulated that the excess of winter births noted in schizophrenia may be related to a fall in maternal vitamin D levels associated with the reduced winter photoperiod.

4.2. Migrant studies

One of the most curious epidemiological findings in recent years has been the apparent excess in schizophrenia in groups such as second-generation Afro-Caribbean migrants to the UK (Jarvis, 1998). Recent studies from the UK have shown

high rates of psychosis in Afro-Caribbean migrants (first and second generation) and, to a lesser extent, in migrants of Asian extraction (Bhugra et al., 1997; King et al., 1994; Thomas et al., 1993). Explanations for the higher rates of schizophrenia in these groups have included psychosocial stressors related to immigration, differential patterns of illicit drug use, obstetric complications and prenatal exposure to viruses.

Many of the individuals identified in the second-generation UK migrant studies would have been in utero during the 1970s and early 1980s. At this same time there were many reports of rickets in the children of Afro-Caribbean and Asian migrants in the UK (Anon., 1979, 1981; Dawson and Mondhe, 1972; Dent and Gupta, 1975). Factors that contributed to the low vitamin D levels in these groups include the reduced ability of dark skin to manufacture vitamin D, diet, and reduced exposure to sunlight (as a result of the higher latitude, wearing more clothing and staying indoors due to the cold climate) (Holick, 1995). It is proposed that the increased rate of schizophrenia in dark-skinned, second-generation migrants to cold climates may be related to low maternal Vitamin D levels.

4.3. *Urban birth*

Another ‘proxy’ marker associated with increased risk of schizophrenia is urban birth. Many studies have shown that city-born individuals have an increased risk of developing schizophrenia compared to non-city born individuals (Jablensky, 1999). Recently, two population-based studies have calculated population attributable fractions of between 30 and 35% for this risk indicator (Marcelis et al., 1998; Mortensen et al., 1998). Explanatory theories of the urban-birth risk factor have focused mainly on the increased likelihood of the transmission of viral agents in overcrowded cities environments compared to rural settings.

The risk of vitamin D deficiency is higher in the city compared to the country, which is thought to reflect reduced sun exposure (as a consequence of pollution and the built-up environment), and reduced outdoor activity in city-dwellers (Belton,

1986; Holick, 1995). It is proposed that the urban-birth risk factor for schizophrenia may be the result of increased prevalence of low maternal vitamin D in the city compared to rural settings.

4.4. *Prenatal malnutrition*

Prenatal dietary factors have been implicated by Susser et al. (1996), who reported an increased risk of schizophrenia in individuals who were in utero during a famine in Holland. The authors of this study suggest that a micronutrient deficiency could be a risk-modifying factor for schizophrenia. They draw parallels between their data linking prenatal famine and schizophrenia and the links between folate and neural tube defects.

The current hypothesis would suggest that the effect of the famine described by Susser and colleagues is mediated via low prenatal vitamin D. It is of interest to note that a recent study of the nutritional status of the besieged residents of Sarajevo reported low vitamin D levels in the absence of protein and energy deficits (Mardel et al., 1995).

5. Hypothesis

Low prenatal vitamin D should be considered a candidate risk-modifying factor for schizophrenia. This exposure may be able to account for several key epidemiological findings in schizophrenia in a parsimonious fashion. If true, it seems unlikely that this risk factor could account for more than a small proportion of individuals with schizophrenia.

6. Implications for public health

One attractive feature of the hypothesis is the potential for an intervention at the public health level. Programmes that aim to reduce the prevalence of hypovitaminosis D in pregnant women could translate into a lower incidence of schizophrenia in their offspring. Just as folate supplementation has been shown to reduce the incidence of neural tube defects (Czeizel and Dudas, 1992),

attention to vitamin D status could reduce the incidence of schizophrenia.

7. Testing the hypothesis

One way to test the hypothesis would be to measure vitamin D levels in a large cohort of pregnant women, and to follow-up their offspring for several decades in order to search for a dose–response relationship (a biological gradient) between low vitamin D and increased risk of schizophrenia. If sera from pregnant women and/or cord blood from their offspring were ‘banked down’ during past decades, maternal vitamin D levels and rates of schizophrenia in the offspring could be examined. From an ecological perspective, ‘natural’ and opportunistic experiments that impact on vitamin D may provide exposed and nonexposed cohorts for schizophrenia birthrate comparisons (e.g., famine, clusters of rickets, the introduction of vitamin D supplementation). Animal experiments will be required in order to clarify the mechanisms linking low prenatal vitamin D and the putative neurodevelopmental deviance.

The hypothesis also suggests new directions for genetic research. Candidate genes should include those systems directly or indirectly related to the vitamin D endocrine system (e.g. genes with vitamin D-responsive elements). As the hypothesis implicates a prenatal vitamin D deficiency, maternal genes related to the vitamin D warrant consideration, in addition to those of the affected offspring.

Jablensky (1995) noted that models attempting to understand schizophrenia require grounding against an “epidemiological horizon”. Jablensky stated that a model should “serve to organise large sets of observations into manageable, coherent structures of ideas and hypotheses which allow predictions to be made about the object of study” (p. 242). This paper provides an hypothesis that draws its bearings from some of the most robust features on the epidemiological horizon. Like all scientific hypotheses, elements of the model will need to be elaborated, modified and totally rejected in response to the advancement of knowledge.

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