

## Developmental Vitamin D Deficiency and Risk of Schizophrenia: A 10-Year Update

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**There is an urgent need to generate and test candidate risk factors that may explain gradients in the incidence of schizophrenia. Based on clues from epidemiology, we proposed that developmental vitamin D deficiency may contribute to the risk of developing schizophrenia. This hypothesis may explain diverse epidemiological findings including season of birth, the latitude gradients in incidence and prevalence, the increased risk in dark-skinned migrants to certain countries, and the urban-rural gradient. Animal experiments demonstrate that transient prenatal hypovitaminosis D is associated with persisting changes in brain structure and function, including convergent evidence of altered dopaminergic function. A recent case-control study based on neonatal blood samples identified a significant association between neonatal vitamin D status and risk of schizophrenia. This article provides a concise summary of the epidemiological and animal experimental research that has explored this hypothesis.**

*Key words:* vitamin D/schizophrenia/epidemiology/animal models/neurodevelopment/prevention

### Introduction

There is robust evidence demonstrating that the risk of schizophrenia varies according to season of birth, place of birth, and migrant status.<sup>1</sup> We propose that developmental vitamin D (DVD) deficiency underlies these gradients.<sup>2</sup> Over the last decade, we have undertaken a coordinated program of animal experiments, assay development, and analytic epidemiology in order to explore this hypothesis. This article summarizes the current research related to this hypothesis and makes recommen-

dations for future research. Key features of the evidence are summarized in table 1.

### Vitamin D—The Basics

Ultra Violet B (UVB) radiation on the epidermis converts a cholesterol metabolite to vitamin D<sub>3</sub> (cholecalciferol; a prohormone). This is subsequently hydroxylated to 25-hydroxyvitamin D<sub>3</sub> (25OHD), a prohormone commonly used to measure vitamin D status. A second hydroxylation of this molecule converts 25OHD to the active secosteroid hormone 1,25-dihydroxyvitamin D<sub>3</sub> (1,25OHD). This hormone binds the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. In concert with a range of binding partners and coactivators (including the retinoid X receptor), this phylogenetically ancient system influences the expression of many genes in mammals. Vitamin D is a potent prodifferentiating and antiproliferative agent.

Vitamin D deficiency (<25 nmol/l) and insufficiency (25–50 nmol/l) are common in many nations.<sup>6–8</sup> Hypovitaminosis D is more prevalent in winter, in high latitudes, and in dark-skinned individuals. Migrants to European countries are at higher risk of hypovitaminosis D compared with native-born.<sup>9</sup> Compared with nonimmigrants, those from Africa have the highest adjusted ORs for vitamin D deficiency (about 7-fold), followed by migrants from Arab-Islamic countries (about 6-fold) and Turkey (about 4-fold).<sup>10</sup> Apart from darker skin color, variables related to dress (eg, wearing a veil), behavior (eg, less outdoor activities), and diet also contribute to an increased risk of deficiency in certain ethnic groups.<sup>11,12</sup> Urban residence is associated with an increased risk of hypovitaminosis, due to factors such as reduced outdoor activity and access to UVB radiation.<sup>13,14</sup>

**Table 1.** Summary of Evidence Related to the Vitamin D Hypothesis of Schizophrenia

Analytic Epidemiology	
Finnish birth cohort	Absence of vitamin D supplement in first year of life associated with increased risk of schizophrenia in males. <sup>51</sup>
US banked maternal sera	25-Hydroxyvitamin D <sub>3</sub> (25OHD) was detectable in 30-y-old banked maternal sera. Low vitamin D associated with winter birth and maternal African American ethnicity. Inconclusive results with respect to schizophrenia. <sup>45</sup>
Danish case-control study	Low vitamin D associated with season of birth and migrant status. Low 25OHD associated with an increased risk of schizophrenia but nonlinear relationship. <sup>48</sup>
Biological plausibility and assay development	
Human postmortem study	Vitamin D receptor (VDR) and key enzyme (CYP27B1) widely distributed in normal adult brain. High expression of VDR in substantia nigra. <sup>28</sup>
Rat studies	VDR first expressed in embryo at day 15 in proliferative zones. <sup>3</sup>
Assay technique	25OHD measured in 20- to 30-y-old neonatal dried blood spots (DBS). Concentrations in DBS correlated with neonatal cord blood. <sup>46,47</sup>
Developmental vitamin D rodent models	
Brain structure	Enlarged lateral ventricles in neonates and in adult offspring repleted at weaning. <sup>31,33</sup>
Genomics and proteomics	Altered expression of genes and proteins involved in mitochondrial, cytoskeletal, and synaptic plasticity (whole brain, adult offspring). <sup>34,35</sup> Altered expression of calcium-binding proteins (nucleus accumbens, adult offspring). <sup>36</sup>
Behavior	Hyperlocomotion in novel settings. <sup>38,39</sup> Hyperlocomotion phenotype associated with late (but not early) gestational hypovitaminosis D. <sup>39</sup> Increased exploratory behavior in mouse. <sup>4</sup> Sensitivity to MK-801 and amphetamine. <sup>38,40</sup> Increased sensitivity to dopaminergic antagonist (haloperidol). <sup>38</sup> Altered latent inhibition. <sup>42</sup> Altered prepulse inhibition in offspring with chronic adult exposure. <sup>5</sup>
Cellular neuroscience	Altered dopamine transporter expression and dopaminergic neurotransmission. <sup>40</sup> Altered catechol- <i>O</i> -methyl transferase and dopamine metabolites. <sup>41</sup> Altered neurogenesis in cell culture and altered sensitivity to 1,25-dihydroxyvitamin D <sub>3</sub> . <sup>29</sup> Increased neuronal proliferation and reduced differentiation and apoptosis. <sup>31,32</sup>

## Ecological Epidemiology

Individuals born in winter and spring have a slight but significantly increased risk of later developing schizophrenia.<sup>15</sup> The effect size of this within-year fluctuation is correlated with latitude, with greater variation found in sites further away from the equator.<sup>16</sup> If seasonally fluctuating risk factors for schizophrenia have a latitude gradient, then one would predict that the incidence of schizophrenia should be greater at higher latitudes. Recent systematic reviews have lent support to this hypothesis.<sup>17,18</sup> While some infectious agents also have seasonal variation, vitamin D seems an obvious candidate exposure because of its robust seasonal fluctuations.<sup>19,20</sup>

Some migrant groups have a markedly increased risk of developing schizophrenia.<sup>21</sup> Evidence from the United Kingdom, Europe, and Scandinavia (ie, counties at relatively high latitudes) suggests that those with darker skin are at most risk.<sup>22</sup> Regardless of recent migrant status, there is also evidence to suggest that some dark-skinned ethnic groups have an increased risk of schizophrenia.<sup>23</sup> Independent of migrant status, individuals born and raised in cities also have a significantly increased risk

of developing schizophrenia compared with those from rural settings.<sup>24–27</sup> The evidence related to season of birth, urban-rural gradient, and migrant studies strongly implicate the presence of environmental risk factors for schizophrenia. While the research community needs to keep an open mind about the factors underpinning these gradients, vitamin D is an unusually parsimonious candidate exposure in the sense that it may explain diverse findings from the epidemiology of schizophrenia.<sup>2</sup>

## Biological Plausibility and Animal Models

Until recently, little was known about the role of vitamin D and brain function. In order to explore the biological plausibility of vitamin D with respect to schizophrenia, we mapped the distribution of the VDR in the human brain.<sup>28</sup> The receptor has a widespread pattern of expression in the adult brain, being especially prominent in the dopaminergic neuron-rich substantia nigra. In the developing rodent brain, the expression is most pronounced in proliferating zones.<sup>29</sup> As expected based on its general properties, the addition of 1,25OHD to embryonic brain

cultures decreases cell proliferation and increases differentiation.<sup>30</sup>

In order to explore the biological plausibility of low prenatal vitamin D as a risk factor for schizophrenia, an animal model was developed. Female rats were depleted of vitamin D prior to mating and throughout pregnancy but returned to normal diet after the litter is born. This model is called the DVD deficiency model. The brains from DVD-deficient neonates have larger lateral ventricles, increased cellular proliferation, reduced apoptosis, and altered neurogenesis.<sup>29,31,32</sup> Ventricular enlargement persists in these animals as adults.<sup>33</sup> Genomic and proteomic studies based on DVD brain samples have identified alterations in biological pathways related to neurotransmission, synaptic plasticity, cytoskeletal function, and calcium-binding proteins.<sup>34–36</sup> Behaviorally, adult DVD-deficient rats are more active than controls in novel environments.<sup>37,38</sup> DVD-deficient rats also have enhanced locomotion in response to psychomimetic agents such as the N-methyl-D-aspartic acid antagonist MK-801<sup>38,39</sup> and amphetamine.<sup>40</sup> The DVD-deficient adult rat is more sensitive to haloperidol, a dopamine receptor antagonist,<sup>38</sup> and has altered dopamine transporter expression.<sup>40</sup> Neonatal catechol-*O*-methyl transferase expression and dopamine metabolism are also altered in the DVD brain.<sup>41</sup> DVD-deficient rats have altered attentional processing, as indicated by impaired latent inhibition,<sup>42</sup> altered learning,<sup>43</sup> and altered synaptic plasticity.<sup>44</sup>

### Analytic Epidemiology and Assay Development

In order to examine the feasibility of measuring 25OHD in archived samples, we undertook a pilot study that assessed the association between third trimester maternal 25OHD serum levels and risk of schizophrenia, based on a case-control sample (26 cases and 51 controls).<sup>45</sup> We confirmed that 25OHD could be quantified after 3 decades of storage and that 25OHD concentrations varied by season and were lower in African American women, as predicted. However, there was no significant association between low vitamin D and risk of schizophrenia. Within the African American mothers, a subgroup with markedly lower levels of 25OHD, a trend-level association emerged.

Many developed nations routinely screen neonatal dried blood spots (DBS) for a range of disorders. If stored appropriately, DBS can be used to explore the association between various neonatal exposures and risk of later disorders. In order to measure 25OHD in DBS, we developed a highly sensitive assay using a derivatization step and tandem mass spectroscopy.<sup>46</sup> Based on Danish and Australian samples, we confirmed that the new assay could reliably detect plausible concentrations of 25OHD in samples stored for over 2 decades. Reassuringly, we found significant fluctuations according to season of birth and also confirmed that 25OHD

concentrations in DBS were significantly correlated with measures based on paired cord blood samples.<sup>47</sup> Because neonates are reliant on maternal vitamin D supplies, neonatal DBS provide indirect evidence of prenatal exposures.

We have recently completed the first examination of the relationship between neonatal vitamin D status and risk of schizophrenia.<sup>48</sup> This study was based on a linkage between the Danish Psychiatric Central Register and neonatal DBS. We identified 424 cases with schizophrenia and matched controls (based on sex and day of birth). As predicted, we found significant seasonal variation in 25OHD and significantly lower levels of 25OHD in the offspring of migrants. We found that the risk of schizophrenia was significantly associated with neonatal 25OHD concentrations. As predicted, those with lower concentrations had an increased risk of schizophrenia. Unexpectedly, neonates with the highest levels also had an increased risk (ie, the exposure-risk relationship was nonlinear). With respect to population attributable fraction, shifting all subjects to the optimal level could potentially avert 43.6% of cases in this sample. We speculate that the unexpected increased risk associated with the upper range of 25OHD concentrations may reflect a subgroup of individuals who are less efficient in converting 25OHD (the prohormone that is used as a measure of vitamin D status) into the active hormone (1,25OHD). It is feasible that a subgroup with apparently adequate concentrations of 25OHD may need a higher recommended range in order to overcome mild vitamin D “resistance.” If we can clarify the genetic architecture of vitamin D, then we may be able to identify subgroups with common single nucleotide polymorphisms in vitamin D-related genes that contribute to the nonlinear relationship.<sup>49</sup>

### Implications for Future Research and Caveats

We speculate that prenatal vitamin D supplements in women at risk of hypovitaminosis D could reduce the risk of schizophrenia in their offspring. Because of the long lag between the exposure and the outcome, undertaking randomized clinical trials to test this hypothesis will be a challenge. However, prenatal supplementation trials are currently underway that focus on a range of neonatal and child health outcomes.<sup>50</sup> These studies could provide the schizophrenia research community with the opportunity to follow-up the long-term mental health of these offspring. If these studies failed to establish an association between prenatal hypovitaminosis D and an increased risk of schizophrenia, the hypothesis could be rejected.

To date, our research has focused on prenatal hypovitaminosis D. However, it is feasible that hypovitaminosis D during childhood and puberty could also influence brain development. The risk of schizophrenia is increased

in both (a) second-generation dark-skinned migrants (who would be exposed to low vitamin D prenatally and postnatally) and (b) first-generation migrants (who would only be exposed postnatally).<sup>22</sup> There is some indirect evidence to support a link between postnatal hypovitaminosis D and risk of schizophrenia. A birth cohort study<sup>51</sup> found a link between the absence of vitamin D supplementation during the first year of life and an increased risk of schizophrenia in men. If the critical window extends into childhood, one would predict that those with rickets (a bone disorder associated with chronic hypovitaminosis D and poor calcium intake during childhood) would have an increased risk of schizophrenia.

With respect to hypovitaminosis D during adulthood, there is currently a lack of convincing evidence to link this exposure with short-term cognitive or behavioral impairment.<sup>52</sup> However, there is strong evidence from in vitro studies showing that vitamin D has neuroprotective properties.<sup>53–57</sup> Thus, it is feasible that chronic hypovitaminosis D could leave individuals more vulnerable to subsequent neurobiological insults. For example, migrant groups exposed to both “social defeat”<sup>58</sup> and hypovitaminosis D may be less able to buffer neurotoxicity related to stress-related mechanisms.<sup>59</sup> Inspired by recent studies suggesting a protective effect for fish oil supplements,<sup>60</sup> we speculate that the risk of developing psychosis in vulnerable individuals may be amplified in those with low vitamin D and that recovery from first episode psychosis may be enhanced by optimal vitamin D concentrations. These research questions are tractable and could be addressed with pragmatic randomized controlled trials. Because vitamin D is safe, cheap, acceptable to the general public, and could help a range of physical health outcomes, there is a public health case to undertake these exploratory trials promptly.<sup>61</sup>

Based on lessons learned from cancer epidemiology, we must remain mindful that some promising nutritional candidates identified from observational epidemiology are subsequently found to be ineffective when assessed in randomized controlled trials.<sup>62</sup> Currently, we lack sufficient evidence to make public health recommendations about the use of vitamin D for the prevention of schizophrenia. We lack crucial information about the critical window during which time hypovitaminosis D impacts on brain function, and we do not understand the mechanisms underpinning the apparent nonlinear relationship between neonatal vitamin D and risk of schizophrenia.

## Conclusions

A recent editorial in *Nature*<sup>63</sup> drew attention to the relative lack of research devoted to exploring the environmental influences related to schizophrenia. In light of the appreciable effect size, consistency of findings, and population attributable fractions associated with environmentally mediated risk factors for schizophrenia,<sup>64</sup> the

research community needs to actively investigate novel biological candidates that may underlie these clues. While more research needs to be done with respect to the links between vitamin D and schizophrenia, we present our findings as a practical demonstration of how coordinated research programs can efficiently translate clues from epidemiology into neuroscience discovery.<sup>65</sup>

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