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Developmental exposure to vitamin D deficiency and subsequent risk of schizophrenia

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ABSTRACT

Over the last half century, a body of convergent evidence has accumulated linking disruption of early brain development with an increased risk of mental disorders, including schizophrenia. The orderly cascade of brain development may be disrupted by exposure to suboptimal concentrations of a range of biological substrates and micronutrients. We hypothesized that those exposed to vitamin D deficiency during early life, have an increased risk of neurodevelopmental disorders, including schizophrenia. The hypothesis was based on the link between an increased risk of schizophrenia in (a) those born in winter and spring, when vitamin D deficiency is more prevalent, and (b) the offspring of dark-skinned migrants living in cold climates, who have a markedly increased risk of vitamin D deficiency. In this review, we summarize evidence from analytic epidemiology related to this hypothesis. Two case-control studies based on Danish neonatal dried blood spots have found that neonatal vitamin deficiency is associated with an increased risk of schizophrenia. However, recent genetic analyses have also suggested that common variants linked to schizophrenia may lead to lower vitamin D concentrations (possibly mediated via reduced outdoor activity). We summarize limitations of the current evidence and outline suggestions that can guide future research. Based on currently available data, there is insufficient evidence to support public health recommendations related to this topic. However, we cannot reject the hypothesis that the provision of vitamin D supplementation to pregnant women and/or offspring in groups vulnerable to vitamin D deficiency may subsequently reduce the incidence of schizophrenia in the offspring.

1. Introduction

Neurodevelopmental disorders such as schizophrenia and autism spectrum disorders (ASD) are major contributors to the burden of disease (Whiteford et al., 2015). Because they have onsets in childhood or early adulthood, and because they are often associated with persistent disability, they are major contributors to morbidity-related health metrics, such as years-lived-with-disability (i.e. the non-fatal burden of disease). In addition, both disorders are associated with premature mortality (Plana-Ripoll et al., 2019), which contributes to years-of-life-lost. In light of the fact that even our best treatments for these disorders are suboptimal, we need to invest in research that may lead to the

prevention of neurodevelopmental disorders. Even a slight reduction in the incidence of schizophrenia and ASD would translate into an appreciable reduction in the burden of mental health.

From a public health perspective, researchers seek candidate risk factors that can be prevented via population-wide interventions – ideally, these interventions should be cheap and safe (Rose, 1992). Thus, it is not surprising that researchers have been drawn to nutritional factors as attractive candidate exposures. It is hard not to be impressed by the association between folate supplementation and a reduction in the incidence of spina bifida (a neurodevelopmental disorder that impacts on closure of the spinal tube during early development) (Pitkin, 2007). With respect to schizophrenia and ASD, researchers have examined a range of exposures (McGrath et al., 2011), including: (a) choline

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Abbreviations

25OHD	25 hydroxyvitamin D
ASD	autism spectrum disorders
DBS	dried blood spot
DVD	Developmental Vitamin D
LC-MS/MS	liquid chromatograph tandem mass spectroscopy
PRS	polygene risk score

supplementation (Freedman and Ross, 2015), (b) maternal anaemia related to iron deficiency (Wieggersma et al., 2019), (c) folate (Roza et al., 2010; Schmidt et al., 2012; Steenweg-de Graaff et al., 2012) and (d) vitamin D (Cui et al., 2021). As part of this volume summarizing research related to the neurodevelopmental hypothesis of schizophrenia, we will present a concise summary of past research related to the hypothesis that exposure to developmental vitamin D deficiency is associated with an increased risk of schizophrenia, outline the limitations of the current studies, and make recommendations for future research.

2. Early clues from ecological epidemiology

People born in winter and spring have a slightly increased risk of subsequently developing schizophrenia (Radua et al., 2018). For example, based on a systematic review of northern hemisphere studies, the risk of schizophrenia in those born in winter/spring (birth compared to summer/autumn) was 1.04 (95% confidence interval 1.02–1.06) (Davies et al., 2003). While not always replicated (e.g. the finding is less prominent at equatorial or subtropical sites (Davies et al., 2003; Parker and Balza, 1977; Parker et al., 2000), this finding suggests that seasonally-varying prenatal or early post-natal exposures may influence the subsequent risk of developing schizophrenia. Candidate exposures that might explain the season-of-birth finding include infection (e.g. respiratory viruses tend to be more common in colder months), or temperature- and sunlight-related exposures. There is robust and consistent evidence that the concentration of 25 hydroxyvitamin D (25OHD), the transport form of vitamin D widely used as a marker of general vitamin status (Holick et al., 2011), is lower in winter and early spring in pregnant women and their offspring (Vinkhuyzen et al., 2016). This is because the production of 25OHD depends on sun exposure – specifically, the action of ultraviolet radiation on the skin, which converts a cholesterol derivative into the precursor of 25OHD (Webb et al., 1988). Ultraviolet radiation during winter at high latitude sites is insufficient to trigger this conversion, thus vitamin D deficiency is more prevalent during winter and spring (compared to summer and autumn) (Lips, 2010).

Epidemiological research indicates that the risk of schizophrenia is higher in the offspring of dark-skinned migrants to some, but not all, countries (Cantor-Graae and Selten, 2005; Dealberto, 2011; McGrath et al., 2004b). This finding has been hard to explain. Factors related to social marginalization and migration-related stress are linked to an increased risk of mental disorders in general, including schizophrenia (Selten and Cantor-Graae, 2005). While not detracting from the importance of socially mediated risk factors, dark-skinned individuals who live in cold climates are also at increased risk of vitamin D deficiency, because pigmented skin acts as a natural sunscreen, and reduces the production of the precursor of 25OHD (Holick, 2007). Thus, the prevalence of exposure to vitamin D deficiency during prenatal and early life is higher in the offspring of dark-skinned migrants (Vinkhuyzen et al., 2016). Curiously, a study found that those who migrated to the Netherlands as young children are at increased risk of later schizophrenia (compared to those who migrate as adults) (Veling et al., 2011), which may suggest that the critical window of exposure (i.e. the

age window when exposure to vitamin D deficiency may increase the risk of neurodevelopmental disorders) may remain open in the first years of life. A study from Finland also lends weight to this hypothesis (McGrath et al., 2004a). There was an increased risk of schizophrenia in men (but not women) who did not receive vitamin D supplements during the first year of life.

However, these studies do not actually measure 25OHD in infants and thus are not able to directly examine the risk of subsequent schizophrenia, nor do they provide clues as to the mechanism of action linking vitamin D deficiency with a neurodevelopmental disorder such as schizophrenia. These issues will be addressed below.

3. Biological plausibility and potential mechanisms of action – animal models

Animal experiments have provided a solid body of convergent research indicating that vitamin D deficiency during early life causes subtle changes in brain development, which can persist into adulthood. These have been summarized in detail in a recent review (Cui et al., 2021). The Developmental Vitamin D (DVD) deficiency model has been mostly based on Sprague Dawley rats, and involves feeding female rats a vitamin D deficient diet for several weeks, followed by mating. After the birth of the litter, the animals are returned to normal vitamin D-replete chow. Thus, the fetus is exposed to vitamin D deficiency throughout gestation, and suboptimal vitamin D in the first few days after birth (maternal vitamin D concentrations will normalize over several days back on the standard diet, and be available to the pups via maternal lactation) (Eyles et al., 2013). Compared to control animals, rodents exposed to DVD deficiency had (a) enlarged lateral ventricles in neonates and in adult offspring (Eyles et al., 2003; Feron et al., 2005), (b) altered expression of genes involved in mitochondrial, cytoskeletal, and synaptic plasticity (Almeras et al., 2007; Eyles et al., 2006), (c) altered expression of calcium-binding proteins (McGrath et al., 2008), (d) hyperlocomotion in novel settings (Kesby et al., 2006; Kesby et al., 2010) and (e) altered dopamine transporter expression and dopaminergic neurotransmission (Kesby et al., 2010).

Recent animal studies have found that the active form of vitamin D (1,25 dihydroxyvitamin D) influences calcium influx in prefrontal cortical tissue, which appears to be mediated by non-genomic mechanisms that influence L type calcium channels (Gooch et al., 2019). This finding is of particular interest with respect to schizophrenia and autism-related research, as there is an increased risk of these disorders in those with common or rare variants in genes that code for subunits of these receptors (e.g. CACNA1C) (Bhat et al., 2012; Breitenkamp et al., 2014; Dedic et al., 2017). The active form of vitamin D is a seco-steroid, which shares mechanisms of action and metabolic pathways with other steroid hormones (e.g. sex hormones), and other hormones that operate via nuclear receptors (e.g. thyroid hormone) (Ali et al., 2020; Eyles, 2021). Early studies reported that the vitamin D receptor was widely expressed in the rodent and human brain (Cui et al., 2013; Eyles et al., 2005), and recent studies using gene editing have confirmed that the cells expressing the vitamin D receptor are enriched in multiple brain regions, including the cortex, amygdala, caudate putamen, and hypothalamus (Liu et al., 2021).

In summary, the evidence from experimental studies based on animal models has provided robust evidence linking exposure to developmental vitamin D deficiency and altered brain development. While this provides biological plausibility to the hypothesis that neonatal vitamin D deficiency increases risk for schizophrenia, animal models do not necessarily translate to humans. The evidence that directly examines the links between observed neonatal vitamin D deficiency and subsequent risk of schizophrenia is outlined in the next section.

4. Analytical epidemiology

Two studies examining the association between neonatal 25OHD

concentration and risk of schizophrenia have been published (Eyles et al., 2018; McGrath et al., 2010). Both were based on archived dried blood spots from a Danish biobank. The vitamin D status of neonates is dependent on maternal gestational 25OHD concentration, thus if neonatal vitamin D deficiency is identified in neonatal samples, this would suggest suboptimal maternal vitamin D status in at least the last trimester. (Hollis et al., 2011; Karras et al., 2013; Kuroda et al., 1981; Vinkhuyzen et al., 2016). The first study (McGrath et al., 2010) was based on a total of 848 individuals with schizophrenia and age- and sex-matched controls (case-control matching 1:1). While the study confirmed the hypothesis that neonatal vitamin D deficiency was associated with an increased risk of schizophrenia, the relationship between 25OHD concentration and risk of schizophrenia was non-linear (those in the highest quintile of 25OHD concentration had an increased risk compared to the second quintile). These findings raise concerns that providing vitamin D supplements to women who were already within the normal range could result in higher concentration of 25OHD may be associated with an increased risk of schizophrenia in their offspring.

The second study was based on a larger case-control study (2602 individuals with schizophrenia and age- and sex-matched controls, case-control matching 1:1) (Eyles et al., 2018). This study confirmed the association between neonatal vitamin D deficiency and an increased risk of schizophrenia. There was no increased risk of schizophrenia in neonates in the highest quintile. When meta-analysed, the two studies suggested that the increased risk of schizophrenia was associated with the two lower quintiles of 25OHD distribution, with no significant increased risk of schizophrenia in the offspring exposure to the highest quintile of 25OHD concentration.

5. What can we learn from genetics?

Genome-wide association studies have identified a range of common variants associated with 25OHD in adults. As expected, these involve variants in genes related to the vitamin D binding protein (coded by Group-specific Component; GC) and enzymes involved in the production of cholesterol and in the modification of seco-steroid ring structure of 25OHD (Jiang et al., 2018; Manousaki et al., 2020; Revez et al., 2020). Therefore, it is now feasible to explore if people who carry alleles of variants associated with lower 25OHD concentration have an altered risk of schizophrenia.

Early studies found no genetic evidence that low 25OHD causally increases risk of schizophrenia by utilizing a small number of 25OHD-associated variants (Taylor et al., 2016). A study using a more robust set of common variants found a more complex pattern of association between mental disorders and 25OHD (Revez et al., 2020). When genetic correlation estimates were examined, there was a substantial proportion of common variants contributing to both (a) 25OHD and (b) a range of mental disorders including schizophrenia, depression, bipolar disorder, attention deficit and hyperactivity disorder, and autism spectrum disorder in individuals of European ancestry. Of interest, the study by Revez et al. (2020) performed bidirectional mendelian randomization using Generalised Summary-data-based Mendelian Randomization (GSMR) methods (Zhu et al., 2018). This method tests for putative causal association between a risk factor (e.g. vitamin D concentration) and a disease (e.g. mental disorders) using summary-level data from genome-wide association studies.

In these analyses, despite the genetic correlations, there was no evidence linking genetic variants associated with 25OHD deficiency and an increased risk of schizophrenia (nor other mental disorders), consistent with the study of Taylor et al. However, there was evidence that genetic variants associated with several mental disorders were associated with lower 25OHD concentration, including major depression, bipolar disorder and schizophrenia. In addition, genetic variants associated with a range of traits and phenotypes were found to predict 25OHD concentrations. Reassuringly, this genetic study confirmed the findings from many observational studies that common variants

associated with outdoor activity (e.g. duration of walks) were inversely associated with 25OHD concentrations, while variants linked to chronic disability were also associated with lower 25OHD concentration. This provides a useful sanity check, as reduced outdoor activity results in less exposure to ultraviolet light and therefore should be associated with reduced vitamin D.

These findings suggest that regardless of the presence or absence of the clinical diagnosis, those who have risk alleles associated with mental disorders may also have lower 25OHD concentration. This could be related to reduced outdoor behaviour and thus lower 25OHD. Alternatively, the mechanisms underlying the finding could include pleiotropic mechanisms not detected in the analyses. For example, common variants associated with 25OHD concentration via cholesterol and lipid metabolisms could directly or indirectly influence brain development, and subsequent risk of schizophrenia. Of note, these findings suggest possible confounding between the variables of interest, which may provide an alternative explanation for the finding that lower neonatal vitamin D exposure is associated with schizophrenia. If mothers with genetic variants associated with schizophrenia engage in behaviours that lead to reduced time outdoors, this could lead to a spurious association between reduced neonatal 25OHD and increased risk of schizophrenia in the offspring that inherits one allele of each risk gene from the mother. It remains to be seen if this association would be sufficient to explain the observed association between vitamin D deficiency and risk of schizophrenia in the two Danish case-control studies. This mechanism cannot explain the season of birth effect seen in epidemiological studies, which suggest that seasonally-fluctuating exposures influence the risk of schizophrenia.

These findings demonstrate the value of modern genetics in re-evaluating and refining hypotheses. It is feasible that there is a (cross-generational) bidirectional association between schizophrenia and neonatal vitamin D. Several scenarios may operate, which can guide future research:

1. Maternal genetic risk of schizophrenia could lead to reduced 25OHD during pregnancy, which may confound the association between the variables of interest. If this is the case, maternal supplementation will not reduce the risk of schizophrenia in the offspring. While 25OHD may be lower in the offspring of women with genetic risk for schizophrenia, because vitamin D deficiency is prevalent in the community, it would not be feasible to use 25OHD as a biomarker indicative of schizophrenia or genetic risk.
2. Maternal genetic risk of schizophrenia could lead to reduced 25OHD during pregnancy, which (if the guiding hypothesis is correct), could amplify the risk of schizophrenia in the offspring. In this scenario, the offspring would be exposed to 'two hits'. The offspring would carry genetic risk alleles inherited from the mother, and be exposed to vitamin D deficiency as a possible result of maternal behaviour. In this scenario, the provision of vitamin D supplements to the mother and offspring may be of benefit, and lead to a reduction in risk of schizophrenia in the offspring, regardless of the inherited genetic risk variants.

The potential confounding between maternal genetic risk variants for mental disorders and exposure to putative risk factors has been found elsewhere – for example between maternal polygene risk score (PRS) scores for ADHD and putative prenatal risk factors including heavy metals and infection (Leppert et al., 2019).

The most recent Danish case-control study was able to explore models that included both neonatal 25OHD and neonatal genetic information. A PRS associated with schizophrenia was derived based on offspring genotype. While both 25OHD and the PRS score both predicted schizophrenia, there was no significant interaction between neonatal 25OHD concentration and the PRS score. The two risk factors combined in an additive fashion. However, the assessment of gene-environment interaction requires very large sample sizes, and in light of the fact

that the explained genetic variance of 25OHD is currently modest (less than 10.5% in external samples) (Revez et al., 2020), the study lacked power to confidently explore these research questions. However, if future studies confirm additive properties of genetic variants and 25OHD-associated risk, then this could have implications for public health – the provision of vitamin D supplements may be of benefit regardless of common genetic variants associated with schizophrenia.

6. Improvements in the measurement of 25OHD in dried blood spots

In some nations, neonatal dried blood spots (DBS) collected as part of routine neonatal screening are stored in biobanks and can be used for analytical epidemiological research. However, neonatal DBS are a precious resource. They contain small amounts of whole blood and require highly sensitive assays. Although several analytical methods for assessing vitamin D are available, the development of the sensitive liquid chromatograph tandem mass spectroscopy (LC-MS/MS) method was a breakthrough for measuring 25OHD in DBS (Eyles et al., 2009). In brief, the assay includes a simple extraction clean-up of endogenous 25OHD, as well as deuterium labelled internal standard and calibration standard, in order to reduce sample loss. In order to enhance ionization, chemical derivatization with 4-Phenyl-1,2,4-triazoleline-3,5-dione (PTAD) is performed. Then, the 25OHD is separated and quantified on an LC-MS/MS mass spectrometer coupled with a multiple reaction monitoring (MRM) setup. The method was adapted and further optimized for high-throughput research projects and used to demonstrate the association between the concentration of neonatal vitamin D and the risk of schizophrenia in samples from the Danish biobank (McGrath et al., 2010). In the following years, the methods were refined, leading to substantial improvements in the sensitivity, stability, robustness and reliability of the measurements. For example, removal of the interfering and ion-suppressing phospholipids (Eyles et al., 2018; Kvaskoff et al., 2016).

At the Statens Serum Institut (SSI) laboratory, removal of the ion-suppressing matrix compounds is achieved using an online two-dimensional post-extraction step. It consists of a TurboFlow technology column and an analytical separation of the analytes by a reverse phase column prior to the LC-MS/MS quantification. In addition, the solvent used for the online HPLC setup contains methyl amine, which forms an adduct and enhances the ionization of the metabolites together with the PTAD derivatization. For external quality control, the assay was further optimized and validated according to standards reference material (SRM 972a and 972) from the National Institute of Standards and Technology. The SSI laboratory also participates in the Vitamin D External Quality Assessment Scheme. The improved assay was used to clarify the association between neonatal concentration of 25OHD and a broad range of health outcomes (Handel et al., 2017; Jacobsen et al., 2016; Keller et al., 2018a; Keller et al., 2018b; Nielsen et al., 2017; Thorsteinsdottir et al., 2020). The LC-MS/MS system can also be used to assay a range of vitamin D metabolites in addition to 25OHD (including the concentration of 1,25 dihydroxyvitamin D, the active hormonal form of vitamin D). However, assays for these and other less abundant vitamin D metabolites have not yet been optimized for high throughput LC-MS/MS. Proteins can also be extracted from DBS, which allows for the quantification of the vitamin D binding protein concentration, an important factor in determining total and bioavailable 25OHD (Ko et al., 2021; Xie et al., 2020). Finally, DBS can be used to extract DNA for genotyping (Hollegaard et al., 2007), which can provide important insights into how neonatal genetic factors can interact with 25OHD concentrations.

7. Limitations of past research, implications for public health, and future directions

There are several important limitations to the hypothesis linking

neonatal vitamin D deficiency and risk of schizophrenia. Firstly, the analytical epidemiology is based on two case-control samples with relatively modest sample sizes. Additional replications in other settings are needed. Issues of specificity with respect to other types of neurodevelopmental disorders require more research. For example, other analytic epidemiology studies have reported an association between developmental vitamin D deficiency and (a) an increased risk of autism-related phenotypes (Lee et al., 2021; Magnusson et al., 2016; Vinkhuyzen et al., 2018; Vinkhuyzen et al., 2017) and (b) attention deficit hyperactivity disorder (Mossin et al., 2017; Sucksdorff et al., 2021). It remains to be seen if the putative link between developmental vitamin D deficiency is non-specifically linked to a range of neurodevelopmental disorders, or if it is specific to schizophrenia. Ideally, future studies should include a broader range of psychiatric phenotypes and have access to both observed 25OHD concentration and PRS scores for the mental disorders of interest. Ideally, maternal samples could be collected during different trimesters, as well as from cord blood or neonatal dried blood samples. This would allow the examination of potential critical developmental windows where vitamin D deficiency during different periods of gestation may be differentially associated with neurodevelopmental outcomes.

Access to genetic instruments that allow the prediction of 25OHD are providing important insights into the complex factors that influence the association between vitamin D status and health outcomes. However, because these common variants would influence 25OHD across the lifespan, and (based on current samples) only explain a modest proportion of the variance in 25OHD concentration, genetic instruments may be better suited to predicting long-latency disorders such as osteoporosis (Heaney, 2003). They would not be suitable as instruments to predict transient deficiencies related to environmental factors, which can result in substantial variation in 25OHD. Regardless of genetic variants and PRS scores related to 25OHD, if an individual is not exposed to bright sunshine, they will not make any 25OHD. In addition, during development, transient environmental disruptions can have persistent health consequences, which may not be readily detected by genetic instruments that are better able to capture persistent genetically-mediated variation in 25OHD.

The gold-standard test of causality remains the randomized controlled trial. However, it is neither feasible nor ethical to enrol pregnant women with vitamin D deficiency, randomize them to vitamin D supplementation, and then follow their offspring for two to three decades in order to detect the rate of schizophrenia in the offspring (McGrath, 2010). In the meantime, there have been several large, well-controlled randomized controlled trials of vitamin D supplements in adults, with a range of health outcomes (e.g. bone density, respiratory infections, cancer, cardiovascular outcomes) with disappointing results (Lucas and Wolf, 2019; Manson and Bassuk, 2015). For example, with respect to depression, a systematic review and meta-analysis of randomized controlled trials of supplementation with vitamin D versus placebo in those with depression (Lazaro Tome et al., 2021) found that vitamin D supplementation was not associated with a significant improvement on depression outcomes. A large randomized controlled trial (n = 18,353, median treatment duration = 5.3 years) found that vitamin D supplementation was not associated with a reduced incidence of depression, nor any improvement in those with prior depression (Okereke et al., 2020). Randomized controlled trials for other mental disorder are based on smaller samples and the findings are mixed (Jamilian et al., 2019).

It may be that neonates should be screened for vitamin D deficiency routinely in order to make targeted interventions to optimise the use of neonatal vitamin D supplement. Rickets still occurs in developed countries (Elder and Bishop, 2014) and the use of vitamin D supplementation can easily avert this disorder. Mindful of the ecological study from Finland that found an association between the lack of vitamin D supplementation during the first year of life and an increased risk of subsequent schizophrenia in male cohort members (McGrath et al.,

2004a), there is lack of evidence about the critical window during which time exposure to vitamin D deficiency continues to disrupt brain development. If future studies lend weight to this hypothesis, then we speculate that prompt treatment of infants with neonatal vitamin D deficiency (as observed on neonatal dried blood spots) may avert or 'rescue' mental health related adverse health outcomes.

8. Conclusions

After 20 years of research, much progress has been made on understanding the links between developmental vitamin D deficiency and risk of schizophrenia. However, much more work is required. Animal experiments have provided important clues related to potential mechanisms of action, however findings from animal models may not translate to humans. Sensitive methods are now available to measure 25OHD in neonatal dried blood spots, but access to neonatal biobanks remains a rate-limiting step. Genetic studies have allowed us to explain at least part of the variance associated with 25OHD concentrations; however, vitamin D is strongly linked to environmental factors, which may also interact with genetics. Analytic epidemiology has supported an association between neonatal vitamin D deficiency and an increased risk of schizophrenia, however to date this is based on only two studies. Randomized controlled trials of prenatal or neonatal vitamin D supplementation are not feasible for adult-onset disorders such as schizophrenia.

In summary, we lack sufficient data at this time to justify an attempt to translate this hypothesis into population-based prevention efforts. Based on current data, we cannot recommend the use of prenatal or neonatal vitamin D supplements as a method to reduce the risk of schizophrenia. Nor do we have sufficient evidence to confidently reject the hypothesis. This is the task ahead.

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CRedit authorship contribution statement

JM was responsible to the conceptualization of the manuscript. All authors contributed to the Writing- Original draft preparation and reviewing and editing.

Declaration of competing interest

We have no conflicts to disclose.

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