

## REVIEW

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# Maternal vitamin D deficiency and brain functions: a never-ending story

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A large number of observational studies have highlighted the prevalence rates of vitamin D insufficiency and deficiency in many populations including pregnant women. Vitamin D is well known to have a crucial role in differentiation and proliferation, as well as neurotrophic and neuroprotective actions in the brain. It has been observed that this micronutrient can modulate neurotransmission and synaptic plasticity. Recent results from animal and epidemiological studies indicated that maternal vitamin D deficiency is associated with a wide range of neurobiological diseases including autism, schizophrenia, depression, multiple sclerosis and developmental defects. The aim of this review is to summarize the current state of knowledge on the effect of maternal vitamin D deficiency on brain functions and development.

## 1. Introduction

Challenges during pre-conception, foetal and early postnatal periods of life, such as nutritional and lifestyle imbalances, can cause the onset of diseases during adulthood; this concept is known as the Developmental Origins of Health and Disease (DOHaD).<sup>1,2</sup> These changes can occur *via* various mechanisms including the disruption of the placental function as well as epigenetic modifications such as histone modification, DNA methylation or non-coding RNAs, the consequences of which induce an alteration in the expression of key genes.<sup>2,3</sup>

The perinatal period including gestation and lactation is considered a critical period with high epigenome plasticity and sensitivity, during which time the mother is the only source of nutrients for the foetus.<sup>4</sup> Macronutrients like carbohydrates or proteins as well as micronutrients like minerals and vitamins are essential for the developing foetus and any imbalance induces functional changes and has long-lasting health consequences for the offspring.<sup>1,2,5</sup> It is also interesting to note that several studies have reported that the foetus responds to external signals such as maternal nutritional stimuli in a gender-dependent manner, suggesting that perinatal reprogramming is characterized by sexual dimorphism.<sup>1,2,6</sup>

In this context, the role of vitamin D (VD) in foetal development is widely studied. VD is not only known for its role in

calcium homeostasis and foetal bone development, but also for its implication in many biological functions as a hormone.<sup>7</sup> Due to this, many studies have highlighted its skeletal and non-skeletal roles during pregnancy such as foetal implantation as well as placental formation and function<sup>8</sup> or lung activity.<sup>9–11</sup> Interestingly, VD is also important for brain development, and particularly, in the dopamine system ontogeny, axonal connectivity and neuronal differentiation.<sup>12</sup> In the last decade, several studies have exposed the adverse consequences of gestational VD deficiency (VDD) on brain development and the onset of neurological diseases in the later stages of life. The aim of this review is to assess the existing evidence of the impact of maternal VDD on the neurodevelopment of offspring and its long-term neurological consequences.

## 2. Vitamin D

### 2.1. Biosynthesis, degradation and mechanisms of action of vitamin D

VD is a fat-soluble hormone that has both exogenous and endogenous origins. During endogenous synthesis, VD is produced in the skin under the action of ultraviolet B rays (UVB) and is known as cholecalciferol or vitamin D3 (VD3). For the exogenous origin, VD can be found in different foodstuff; in particular, in animal food sources such as fish, fish oils, egg yolks, and beef liver in the form of VD3, and also in vegetables and mushrooms under the name of ergocalciferol or vitamin D2 (VD2)<sup>13</sup> (Fig. 1).

VD requires two hydroxylation processes in order to be biologically active.<sup>13–15</sup> The first step of VD activation takes place

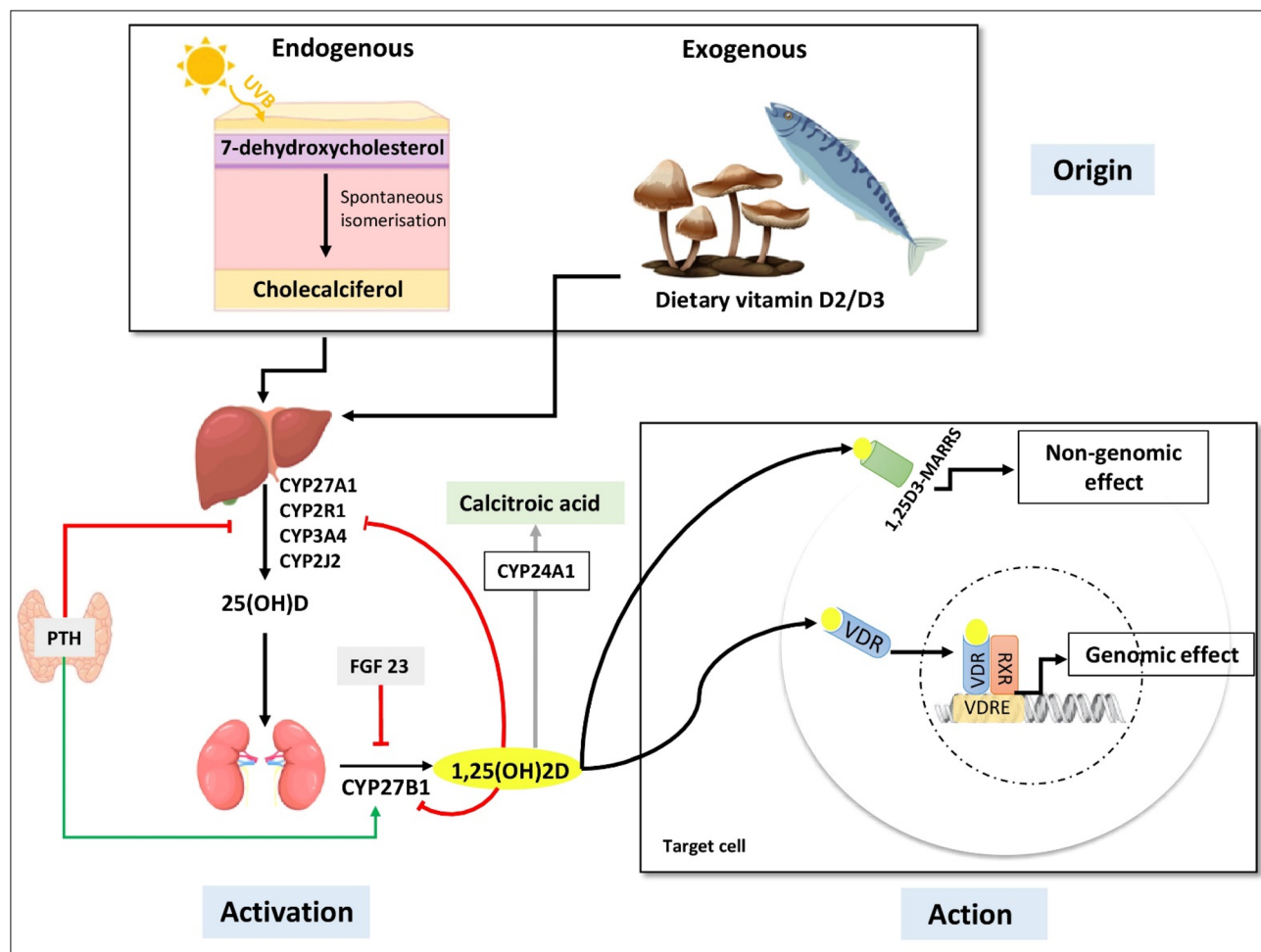
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**Fig. 1** Vitamin D metabolism and mechanisms of action. CYP: cytochrome; FGF 23: fibroblast growth factor 23; PTH: parathyroid hormone; RXR: retinoic X receptor; VDR: vitamin D receptor; VDRE: vitamin D response element; 1,25(OH)<sub>2</sub>D: 1,25-dihydroxyvitamin D; 1,25D3-MARRS: membrane-associated rapid response steroid; 25(OH)D: 25-hydroxyvitamin.

in the liver and generates 25-hydroxyvitamin D (25(OH)D), which represents the main circulating but inactive form of VD with a half-life of three to four weeks.<sup>7,13,14</sup> The adipose tissue is considered as a storage site for 25(OH)D<sup>16–18</sup> as reported in rats,<sup>19</sup> mice<sup>20</sup> and humans.<sup>21</sup> Then, 25(OH)D is transported to the kidneys, where the second step of VD activation will take place, leading to the formation of 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), also called calcitriol, which is the main active form of VD.<sup>13</sup> Kidney production of 1,25(OH)<sub>2</sub>D is highly regulated by calcium and phosphorus levels, PTH (parathyroid hormone) and FGF-23 (fibroblast growth factor 23).<sup>7,13</sup> 1,25(OH)<sub>2</sub>D is involved in the activation of its own catabolism by inducing the expression of the ubiquitous enzyme: CYP24A1, which converts 1,25(OH)<sub>2</sub>D to 1,24,25(OH)<sub>3</sub>D, resulting in the inactive form of VD called calcitriol acid (Fig. 1).<sup>7,13</sup> In the context of this review, it has also been reported that there is a local activation and catabolism of VD in the central nervous system where CYP27B1 and CYP24A1 are expressed in several cell types such as neurons, astrocytes and other glial cells.<sup>22</sup>

The active form of VD is known to have both genomic and non-genomic effects.<sup>7,22,23</sup> The genomic effects result from the binding of active VD to its nuclear receptor VDR (vitamin D receptor), which induces either the activation or repression of the target gene (Fig. 1).<sup>7,23</sup> This gene regulation of VD *via* VDR has epigenetic effects as it modulates the expression of enzymes involved in methylation and acetylation.<sup>23</sup> In addition, VD also regulates the expression of micro-RNAs (miRs), which are small non-coding RNAs that are known for their role in post-transcriptional regulation of gene expression and gene silencing.<sup>23–25</sup> For the non-genomic effects, VD acts *via* a membrane receptor named Pdia3 (Fig. 1). Binding and activation of this receptor by 1,25(OH)<sub>2</sub>D induces the activation of signal transduction pathways which will elicit rapid responses.<sup>23,26–29</sup>

## 2.2. Biological roles of vitamin D

In addition to its primary role in the regulation and maintenance of phosphocalcic homeostasis, VD is known to have several other physiological functions in the immune



system,<sup>13,30–32</sup> cancer<sup>27,31–33</sup> and adipose tissue biology,<sup>14,15,17,34–36</sup> cardiovascular function and arterial pressure.<sup>31,32,37</sup> More interestingly, VD is also considered an essential micronutrient for brain development during foetal life.<sup>38</sup> In accordance with its involvement in foetal neurodevelopment, the lack of VD in later life stages seems to be associated with an increased risk and course of many neurodegenerative and neuroinflammatory diseases as described below.

### 3. Vitamin D deficiency

#### 3.1. Vitamin D status

25(OH)D represents the most abundant circulating form of VD. In addition to being in balance with the spare 25(OH)D, only a fraction of this metabolite is converted to active VD. Thus, the serum concentration of 25(OH)D is the best indicator of VD status.<sup>17</sup> A serum level greater than 30 ng ml<sup>-1</sup> (75 nmol L<sup>-1</sup>) is considered optimal; therefore, the VD standards have been established as follows: sufficiency >30 ng ml<sup>-1</sup> (75 nmol L<sup>-1</sup>), insufficiency 10–30 ng ml<sup>-1</sup> (25–75 nmol L<sup>-1</sup>), and deficiency <10 ng ml<sup>-1</sup> (25 nmol L<sup>-1</sup>). VD deficiency (VDD) or hypovitaminosis D is considered as a risk factor for many diseases such as cardiovascular<sup>39</sup> and autoimmune diseases,<sup>40</sup> type 2 diabetes<sup>41</sup> and cancer.<sup>42</sup> VDD is now regarded as a global epidemic induced by many factors including a diet low in VD, inadequate exposure to the sun or obesity.<sup>13,14</sup>

#### 3.2. Vitamin D deficiency during the perinatal period

The mother is the primary source of VD for the fetus and the placenta is a key structure in fetal development because of its involvement in the diffusion of nutrients such as 1,25(OH)<sub>2</sub>D and 25(OH)D from the mother to the fetus. Due to the presence of 1 $\alpha$ -hydroxylase, 25(OH)D can be activated in both the trophoblast and the decidua. In addition to this enzyme, VDR is also found in the placenta, indicating that this structure not only produces but also responds to 1,25(OH)<sub>2</sub>D.<sup>43,44</sup> It has been shown that VD modulates the synthesis of placental hormones involved in pregnancy such as human chorionic gonadotropin (hCG) and also plays an important role in endometrial decidualization and thus foetal implantation.<sup>44,45</sup>

A large proportion of pregnant women exhibit VDD (8% to 100% in some parts of the world).<sup>46</sup> Several studies showed that maternal VDD induced foetal growth restriction. A prospective cohort that examined the impact of maternal VDD in a multi-ethnic population of 7098 women found that low maternal 25(OH)D levels were associated with foetal growth restriction, low birth weight and increased risk of premature birth.<sup>47</sup> These results are correlated with several other studies.<sup>48,49</sup> Maternal VDD during pregnancy predisposes the offspring to several diseases such as childhood rickets, and severe VDD in the early stages of pregnancy was linked to an increased risk of childhood obesity.<sup>5</sup> In our group, we showed that maternal VDD in mice was associated with a small birth weight in juvenile 5-week-old male offspring, which was

related to an increase in spontaneous activity and energy expenditure.<sup>6</sup> Interestingly, in adulthood, a High Fat Diet (HFD) combined with maternal VDD disrupted glucose homeostasis and adiposity in male offspring but not in females.<sup>6</sup> Under the same experimental conditions, maternal VDD coupled with a HFD induced an increase in white adipose tissue inflammation as well as increased adiposity in male offspring only, thus highlighting the sexual dimorphism in response to developmental VDD.<sup>50</sup> Maternal VDD is also associated with an increased risk of type 1 diabetes in the offspring.<sup>51,52</sup>

Maternal VD status also affects the epigenome of the foetus *via* different epigenetic mechanisms, particularly in the early stages of gestation, which can contribute to the onset and progression of diseases in adulthood.<sup>53</sup> VD also exerts a genomic effect in the developing brain by modulating the proliferation and differentiation of neural stem cells, regulating the development of the dopaminergic system and the release of neurotransmitters such as dopamine. It can also exhibit non-genomic actions by inducing an increase in extracellular Ca<sup>2+</sup> uptake or by modulating kinase-activated signalling pathways in the developing cortex. Taken together, these data highlight the importance of VD and the fact that exposure to low levels of this micronutrient during foetal life alters brain development and predisposes offspring to various neurological disorders.<sup>22,54,55</sup>

In the next sections of this review, an update on the impact of maternal VDD on the onset of neurological and psychological disorders in the offspring has been presented.

### 4. The impact of maternal vitamin D deficiency on cerebral functions

#### 4.1. Maternal vitamin D deficiency and brain development

VD is considered as a potent neurosteroid that acts *via* genomic and non-genomic effects.<sup>56</sup> Interestingly, the brain has the ability to metabolize VD due to the presence of 1 $\alpha$ -hydroxylase and CYP24A1 in neurons and glial cells.<sup>57</sup> VDR is highly expressed in different areas of the mesencephalon during embryonic development as well as in the hippocampus, thalamus, hypothalamus, cortex and substantia nigra, suggesting that VD can modulate brain development and maturation.<sup>57–59</sup>

During brain development, VD inhibits proliferation and potentiates neuronal cell differentiation and apoptosis. In accordance with these observations, it has been demonstrated that VDD in embryonic rats induced an increase in brain cell proliferation and a decrease in apoptosis with dysregulation of pro-apoptotic genes such as *Bak* (BCL2 antagonist/killer 1).<sup>12,60</sup> From a morphological point of view, maternal VDD in rats resulted in a longer and larger brain, a longer and thinner cortex and enlarged lateral ventricles,<sup>12,60</sup> which persist into adulthood.<sup>61</sup> However, the brains of maternal VDD mice were reduced in length with reduced lateral ventricle volume.<sup>62</sup> The absence of VD during foetal development also appears to



affect brain development in C57BL/6J female mice at P0 with a reduction in their hippocampal volume that did not persist in adulthood. In addition, a volumetric decrease in the lateral ventricle and an increase in striatum volume were observed in adult male mice.<sup>63</sup> Altogether, these observations strongly suggest the involvement of VD in the release of many neurotransmitters. In the context of the role of VD in the onset of neurotransmitter systems, it has been shown in a Sprague-Dawley rat maternal VDD model that VD depletion during development reduced factors essential for the onset of dopaminergic phenotypes such as Nurr1 (nuclear receptor-related 1) and p57Kip2 (p57 kinase inhibitory protein 2).<sup>64</sup> The tyrosine hydroxylase (TH) gene expression was reduced in the foetal brain of female offspring from a mouse model of maternal VDD with a decrease of TH protein in the substantia nigra.<sup>62</sup> Regarding the GABAergic system, it has been shown that maternal VD deficiency is associated with a decrease in the expression of GABA-A  $\alpha 4$  (gamma-aminobutyric acid- $\alpha 4$ ), a gene involved in GABA neurotransmission, in the male offspring brains.<sup>61</sup> This micronutrient also promotes the release and expression of neurotrophic factors such as nerve growth factor (NGF),<sup>12,65</sup> glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF)<sup>12,66</sup> in different neuronal and glial cell models. Interestingly, a decrease in the synthesis of NGF as well as the expression of genes involved in the neuronal structure such as MAP-2 (microtubule associated protein-2) was observed in 10-week-old male rats born from VDD dams.<sup>61</sup>

Maternal VDD affects brain development during foetal life and causes alterations that may persist into adulthood, which can lead to the onset of many neurological disorders and diseases.

## 4.2. Maternal vitamin D deficiency and brain pathologies

**4.2.1. Behavioural defects.** In a behavioural context, rats exposed to maternal VDD appeared to have cognitive impairment that reflected in a more impulsive behaviour and decreased inhibitory control in adulthood.<sup>67</sup> Hawes *et al.*<sup>62</sup> showed that maternal VDD in BALB/c mice altered the expression of BDNF and TGF- $\beta 1$  (transforming growth factor beta 1), which are involved in neuronal survival, as well as FoxP2 (forkhead box protein P2), which is known to be involved in speech and language.<sup>62</sup> Maternal VDD also induced spontaneous locomotor hyperactivity in mice and rat offspring<sup>6,68</sup> and similar results were observed in maternal VDD rat offspring exposed to MK-801 (a hyperactivity-inducing agent).<sup>55,69</sup> Interestingly, this hyperactivity was observed in rats exposed to maternal VDD during advanced stages of gestation; however, it was not observed when exposure to the deficiency occurred only at early stages of gestation, emphasizing the importance of critical developmental windows.<sup>55</sup> In a rat model of maternal VDD, adult male rats exhibited alterations in learning and memory, decreased social behaviour and increased grooming behaviour correlated with decreased levels of FoxP2.<sup>70</sup> Impaired learning was also observed in the adult progeny of VDD female mice<sup>71</sup> (Table 1).

Some behavioural defects were also observed in humans as it has been reported in an Australian cohort that there was a 2-fold increase in the risk of language disorder at ages of 5 and 10 years in the offspring of mothers with rates of 25(OH)D  $\leq 46$  nmol L<sup>-1</sup> during the second trimester.<sup>72</sup> The Spanish INMA cohort also showed that there was a positive association between maternal VD levels and social competence in 5-year-old offspring.<sup>73</sup>

**4.2.2. Autism.** Autism spectrum disorder (ASD) is a complex neurodevelopmental disease with repetitive behaviour and difficulties in social interaction, communication and learning.<sup>74</sup> Several murine studies and cohorts have demonstrated that early exposure to low levels of VD during pregnancy could be a risk factor for ASD.<sup>75,76</sup> In 2019, Ali *et al.*<sup>77</sup> aimed to find out the impact of maternal VDD on early post-natal, adolescent and adult offspring. By assessing the righting reflex and negative geotaxis, they found out that the pups from deficient dams showed a delay in their motor development.<sup>77</sup> P12 rats from deficient females also exhibited increased ultrasound vocalization, indicating an alteration in their vocal communication. Adolescent and young adult rats displayed an altered stereotyped repetitive behaviour as they had a reduced digging behaviour. Adolescent rats had less social interaction with a longer latency to interact, which was not found in adult rats; however, adults were more hyperactive but showed no anxiety-like behaviour.<sup>77</sup> In another animal study, maternal VDD induced an increase in the vocalization of pups, accompanied by a decrease in cortical FoxP2 and social behaviour and impaired learning and memory in adult males<sup>70</sup> (Table 1).

Using data from the Stockholm youth cohort, Magnusson *et al.*<sup>78</sup> examined a population of 4–17-year-old children exposed to low levels of VD during gestation and were able to report a positive association between maternal VDD and ASD.<sup>78</sup> Analysing the same cohort, Lee *et al.*<sup>79</sup> suggested that high levels of VD during pregnancy were associated with a moderate decrease in the risk of ASD in the offspring.<sup>79</sup> A prospective study of a multi-ethnic cohort in the Netherlands (generation R study) has also shown an association between maternal mid-gestation VDD and a two-fold increase in the risk of autism in children<sup>80</sup> (Table 2). Interestingly, VD supplementation seems to clinically improve ASD symptoms in affected children.<sup>81,82</sup>

**4.2.3. Schizophrenia.** Schizophrenia is a neurodevelopmental disorder that affects a person's way of thinking, feeling and behaving. Many risk factors are associated with the onset of this disease such as the season of birth,<sup>83</sup> dark skin,<sup>84</sup> malnutrition<sup>85</sup> and VDD.<sup>86</sup> Schizophrenia manifests itself in cognitive, positive and negative symptoms. Positive symptoms reflect psychosis (hallucinations and delusions), while negative and cognitive symptoms refer to emotional, social and intellectual disabilities.<sup>87</sup> Although not all aspects of schizophrenia are observed in the murine model of maternal VDD, some features of this disease can be noticed such as enlarged lateral ventricles and increased behavioral sensitivity to antagonists of NMDA (N-methyl-D-aspartate) receptors<sup>12,60,69,88</sup> as well as





**Table 1** Impact of maternal VDD on brain development and offspring behaviour in rodents

| Growth stage                                | Experimental findings                                                                                                                                                                                                                                   | Ref.        |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| <b>Morphological and functional changes</b> |                                                                                                                                                                                                                                                         |             |
| E12–E15                                     | Reduced Nurr1 levels at E12 and E15<br>Reduced p57Kip2 expression at E12<br>Reduced TH expression at E12                                                                                                                                                | 65          |
| E14.5–E17.5                                 | Reduced lateral ventricle volume<br>Decrease in the expression of BDNF at E14.5 and increase in BDNF and Tgfb1 at E17.5<br>Reduced TH gene expression in females at E17.5<br>Reduced TH protein localization in the substantia nigra of female fetuses  | 63          |
| E19–P7                                      | Enlarged lateral ventricles<br>Down-regulation of pro-apoptotic gene expression with reduced apoptosis<br>Up-regulation of pro-mitotic gene expression with increased cell proliferation                                                                | 61          |
| P0                                          | Increased number of mitotic cells<br>Longer and larger hemispheres<br>Elongated and thin cortex<br>Enlarged lateral ventricles<br>Decreased expression of NGF, GDNF and p75 <sup>NTR</sup>                                                              | 12          |
| P0–P70                                      | Reduction of the hippocampal volume in P0 female mice<br>Volumetric decrease in lateral ventricle and increased striatum volume in adult male mice                                                                                                      | 64          |
| 10 weeks                                    | Decrease in the synthesis of neurotrophic factors such as NGF, the expression of genes involved in the neuronal structure such as MAP-2 and neurotransmission with decreased levels of GABA-A $\alpha$ 4<br>Enlarged lateral ventricles in adult brains | 62          |
| <b>Behavioural impairment/disorders</b>     |                                                                                                                                                                                                                                                         |             |
| E14.5–E17.5                                 | Decreased expression levels of Foxp2 and reduced Foxp2 protein expression in the cortex of females at E17.5                                                                                                                                             | 62          |
| E15                                         | Decreased levels of Nurr1 and TH in the embryonic mesencephalon                                                                                                                                                                                         | 93          |
| P12                                         | Decreased cortical FoxP2<br>Increased vocalization                                                                                                                                                                                                      | 70          |
| Post weaning (P21)                          | Increased impulsive behavior<br>Decreased inhibitory control                                                                                                                                                                                            | 68          |
| P27–P80                                     | Less social interaction observed in adolescents<br>Altered stereotyped repetitive behavior in adolescent and young adult rats<br>Hyperactivity in adults                                                                                                | 81          |
| 10 weeks                                    | Hyperlocomotion                                                                                                                                                                                                                                         | 69          |
| 10 weeks                                    | Dysregulated genes and proteins – identified in multiple sclerosis – in the prefrontal cortex and hippocampus of the DVD-deficient progeny                                                                                                              | 111 and 112 |
| 4 months                                    | Increased grooming behaviour<br>Impaired social, learning and memory behaviour                                                                                                                                                                          | 71          |
| 5–6 months                                  | Spontaneous locomotor hyperactivity                                                                                                                                                                                                                     | 70          |
| 30 weeks                                    | Impaired learning                                                                                                                                                                                                                                       | 72          |

BDNF: brain-derived growth factor; DVD: developmental vitamin D deficiency; Foxp2: forkhead box protein P2; GABA-A $\alpha$ 4: gamma-amino butyric acid A alpha 4; GDNF: glial-derived neurotrophic factor; MAP-2: microtubule associated protein-2; NGF: nerve growth factor; Nurr1: nuclear receptor-related 1; p57Kip2: p57 kinase inhibitory protein 2; p75<sup>NTR</sup>: p75 neurotrophin receptor; Tgfb1: transforming growth factor beta 1; TH: tyrosine hydroxylase.

altered dopamine system development.<sup>64,89–92</sup> The assessment of positive symptoms in the maternal VDD murine model is done by measuring locomotor activity, which often reflects psychomotor agitation and behavioural disruption. As mentioned earlier, rats and mice from VD deficient dams are characterized by spontaneous locomotor hyperactivity<sup>55,68,69</sup> (Table 1). A recent study on Balb/c mice examined the impact of VD on the prefrontal cortex (PFC), which is involved in the pathophysiology of schizophrenia. This study showed that optimal levels of 1,25(OH)<sub>2</sub>D significantly increased Ca<sup>2+</sup> influx through L-VGCCs (L-type Voltage-Gated Calcium Channels), consequently increasing intracellular Ca<sup>2+</sup> levels in a subset of prefrontal cortex neurons, thus suggesting that inadequate levels of VD during foetal growth may modulate the function of L-VGCCs and alter neuronal maturation and excitability.<sup>93</sup>

In humans, the neonatal status of 25(OH)D from dried blood samples demonstrated that newborns with VD levels

below 20.4 nmol L<sup>-1</sup> had a significant increase in the risk of schizophrenia.<sup>94</sup> Interestingly, a prospective Finnish cohort has shown that VD supplementation in males during the first year of life reduced the risk of developing schizophrenia in adulthood<sup>95</sup> (Table 2).

**4.2.4. Depression.** Depression is considered as one of the most common psychological disorders and many studies over the years have associated low levels of VD with depression.<sup>96–98</sup> VD affects brain areas involved in emotional processing and areas associated with depression.<sup>99</sup> This micronutrient can also regulate serotonin or 5-HT (5-hydroxytryptamine) synthesis,<sup>100</sup> which is a neurotransmitter well known for its regulating role in many brain activities such as behaviour or mood<sup>101</sup> and thus its implication in several brain disorders such as depression.<sup>102</sup> In an animal study, the male progeny of female rats that were fed with a VD deficient diet for 6 weeks and then fed with a standard diet 1 week before mating and



**Table 2** Maternal VDD and neurological disorders in humans

| Cohort                                                       | Offspring age                                                                 | Experimental findings                                                                                                            | Ref. |
|--------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|------|
| <b>Autism/developmental disorders</b>                        |                                                                               |                                                                                                                                  |      |
| Australian cohort                                            | 5–10 years old                                                                | Language impairment                                                                                                              | 73   |
| Stockholm Youth Cohort                                       | 4–17 years old                                                                | Positive association between maternal VD deficiency and ASD                                                                      | 79   |
| Stockholm Youth Cohort                                       | 0–17 years old                                                                | Association between high maternal levels of 25OHD and modestly lower risk of ASD                                                 | 80   |
| Generation R study                                           | 6 years old                                                                   | Two-fold increased risk of ASD in children of VDD mothers (mid-gestation)                                                        | 81   |
| <b>Schizophrenia</b>                                         |                                                                               |                                                                                                                                  |      |
| Danish case–control study                                    |                                                                               | Significant increase of schizophrenia for new-borns with 25OHD levels below 20.4 nmol L <sup>-1</sup>                            | 95   |
| Finnish birth cohort                                         | 31 years (follow-up from pregnancy)                                           | VD supplement in the first year of life is associated with a decreased risk of schizophrenia in males                            | 96   |
| <b>Depression</b>                                            |                                                                               |                                                                                                                                  |      |
| DaFO88 cohort                                                | 22 years (follow-up from birth)                                               | Direct association between maternal VDD and offspring depression                                                                 | 105  |
| The Avon Longitudinal Study of Parents and Children (ALSPAC) | Children: 10.6 years old (mean age)<br>Adolescents: 13.8 years old (mean age) | No risk of developing depression during childhood/adolescence was assessed                                                       | 106  |
| <b>Multiple sclerosis</b>                                    |                                                                               |                                                                                                                                  |      |
| Women in the Finnish Maternity Cohort                        |                                                                               | Exposure to maternal 25(OH)D levels <30 nmol L <sup>-1</sup> during early gestational stages increases the risk of developing MS | 113  |
| Cohort study (Nurses' Health Study II)                       |                                                                               | Higher maternal VD dietary intake and higher 25(OH) D levels may be associated with a decreased risk of developing MS            | 114  |
| Longitudinal analysis                                        |                                                                               | Low maternal exposure to UV is associated with an increased risk of MS in offspring                                              | 117  |
| Population-based study                                       |                                                                               | Association between the month of birth of offspring and an increased risk of MS                                                  | 118  |

ASD: autism spectrum disorder; VD: vitamin D; VDD: vitamin D deficiency; MS: multiple sclerosis; UV: ultraviolet.

throughout gestation and lactation showed increased depression-related behaviours.<sup>103</sup>

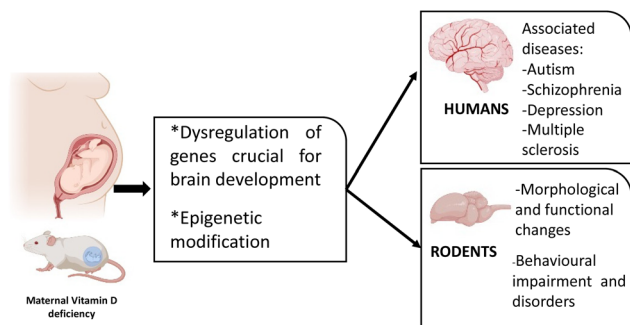
In humans, by using data from a pre-birth cohort with up to 22 years of follow-up, Strøm *et al.*<sup>104</sup> tried to find an association between maternal 25(OH)D levels and the neurodevelopmental outcomes of the offspring, taking into consideration the first admission diagnosis of the offspring or the prescription of medication for depression. A direct association between maternal 25(OH)D levels and offspring depression was observed.<sup>104</sup> However, the Avon Longitudinal Study of Parents and Children (ALSPAC) showed contradictory results. This study included 2938 children (mean age: 10.6) and 2485 adolescents (mean age: 13.8) and had their short moods and feelings questionnaire (SMFQ) assessed at least once, which indicated that maternal VDD during pregnancy did not increase the risk of developing childhood/adolescent depression<sup>105</sup> (Table 2). Several studies<sup>96,97,106</sup> have explored the link between VDD and depression as well as the impact of VD supplementation on reducing depression symptoms.<sup>107,108</sup> However, the exact mechanism by which VD contributes to the aetiology and treatment of depression needs further study.

**4.2.5. Multiple sclerosis.** Multiple sclerosis (MS) is a neurodegenerative and inflammatory disease that affects the brain and the spinal cord. Genetic and environmental factors play a major role in the incidence of this pathology. A growing body of evidence suggests that low VD levels can contribute to the

risk of developing or worsening MS.<sup>109</sup> In an animal model of maternal VDD, 10-week-old progeny exhibited dysregulation of many prefrontal cortex and hippocampus genes and proteins involved in MS<sup>110,111</sup> (Table 1).

Similar observations were made in many human studies. A Finnish study reported an increased risk of developing MS in the offspring of VD deficient mothers with 25(OH)D levels <30 nmol L<sup>-1</sup> early in their pregnancy.<sup>112</sup> Another study assessing the diet of 35 794 pregnant mothers and the follow-up of their daughters found that the offspring of mothers with higher VD dietary intake and higher 25(OH)D predicted levels during pregnancy had a lower risk of developing MS during adulthood.<sup>113</sup> Thus, MS patients with low VD levels have been associated with higher disease activity.<sup>114,115</sup> Many studies on the time and region of birth have found associations between low maternal exposure to ultraviolet rays (UV),<sup>116</sup> the month of birth<sup>117</sup> and the risk of MS in offspring (Table 2). As VD seems to be a risk factor for MS, several studies have tried to investigate the potential therapeutic role of VD supplementation in MS. To address this question, a rodent model of MS was used to explore the impact of VD supplementation during different developmental stages, including supplementation prior to and during gestation and lactation, after weaning, throughout the juvenile/adolescence period and during adulthood.<sup>118</sup> This study highlighted that VD supplementation was associated with a decrease in central nervous system inflammation and





**Fig. 2** The impact of maternal VDD on the development of neurological diseases in rodents and humans.

demyelination. However, these results were dependent on the developmental stage during which this supplementation occurred.<sup>118</sup> However, the benefits of VD supplementation on the disease course of MS are yet to be established as many clinical studies have shown mixed results for the effectiveness of VD supplementation in MS, and the appropriate dose of supplementation still remains undetermined.<sup>119–121</sup>

## 5. Conclusions and perspectives

Many animal and epidemiological studies have been conducted to explore the implication of VDD during foetal life on the developing brain and many have found associations between low gestational VD levels and the onset of many neurological diseases in adulthood. Different animal studies described changes in the expression of many genes related to overall brain development and functions, but the molecular mechanisms by which maternal VDD alters brain development remain poorly understood (Fig. 2).

However, recent research has generated interesting data on the role of epigenetic modifications during gestational VD restriction. For instance, the group of Eyles observed an upregulation of miR-181c-5p that suppressed neurite outgrowth of DA neurons from the ventral mesencephalon.<sup>122</sup> These data suggested that miRNAs can be involved in the onset of psychological disorders such as schizophrenia. In addition, it has been shown that VD plays a role in the DNA methylation state in the germline and soma cells, suggesting a role of this mechanism in brain development.<sup>53</sup> In their preclinical study, Liang *et al.* showed that VDD potentiates maternal diabetes-induced autism-related phenotypes in offspring by epigenetic mechanisms.<sup>123</sup> In the same way, epigenetic modifications were observed in a population-based mother-offspring cohort, in which a negative association between the free maternal 25 (OH)D index and RXR alpha (retinoic X receptor) methylation at a specific site was detected.<sup>124</sup> Altogether, these data indicate that maternal VDD induces epigenetic modifications in the offspring. However, more studies are needed to identify the exact mechanisms underlying the changes and outcomes that developmental VDD has on the brain. Many clinical

studies show that supplementation with VD during pregnancy has beneficial effects on both the mother and the offspring.<sup>125</sup> These studies suggest that maintaining optimal VD levels might reduce the risk of developing a wide range of disorders. Additional rigorous and larger randomised trials are required to evaluate the effects of VD supplementation in pregnancy, particularly in relation to the onset of brain disorders.

## Author contributions

Writing—original draft preparation, L. S. and L. M. Writing—review and editing, H. H., F. S., J.-F. L. and L. M. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

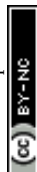
The authors declare no conflict of interest.

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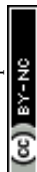
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