REVIEW

The Impact of Maternal Vitamin D Status on Offspring Brain Development and Function: a Systematic Review[1]

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ABSTRACT

Various studies have examined associations between maternal vitamin D (VD) deficiency and offspring health, including offspring brain health. The purpose of this review was to summarize current evidence concerning the impact of maternal VD deficiency on brain development and function in offspring. A systematic search was conducted within Medline (on Ovid) for studies published through 7 May 2015. Animal and human studies that examined associations between maternal VD status or developmental VD deficiency and offspring brain development and function were included. A total of 26 animal studies and 10 human studies met the inclusion criteria. Several animal studies confirmed the hypothesis that low prenatal VD status may affect brain morphology and physiology as well as behavioral outcomes. In humans, subtle cognitive and psychological impairments in offspring of VD-deficient mothers were observed. However, data obtained from animal and human studies provide inconclusive evidence, and results seem to depend on strain or race and age of offspring. To conclude, prenatal VD status is thought to play an important role in brain development, cognitive function, and psychological function. However, results are inconclusive; validation of these findings and investigation of underlying mechanisms are required. Thus, more investigation is needed before recommending supplementation of VD during pregnancy to promote brain health of offspring. *Adv Nutr* 2016;7:665–78.

Keywords: maternal, prenatal, developmental, vitamin D, 25(OH)D, brain, cognition, neuropsychological

Introduction

Over the last decades, the role of maternal nutrient status in fetal development has generated considerable research interest. Many reports worldwide have demonstrated high prevalences of vitamin D (VD)[4] deficiency in pregnant women (1). VD diffuses across the placenta from mother to fetus; hence, the mother is the sole source of VD substrate for her developing child. It has been shown that in cases of maternal VD deficiency, defined as serum 25-hydroxyvitamin D [25(OH)D] status <50 nmol/L (2), the fetus is also deficient (3).

Discoveries have revealed that many tissues and cells in the body express VD receptors (VDRs) (4, 5) and that both placenta and embryonic kidneys exhibit an enzymatic machinery, which converts 25(OH)D, the inactive VD metabolite, into 1,25-dihydroxycholecalciferol [1,25$(OH)_2D_3$], the metabolically active VD metabolite (6). These discoveries have provided new insights into the function of VD. Low VD status during pregnancy has, for instance, been associated with rickets and growth retardation (1, 2) as well as various adverse extra-skeletal outcomes, including type 2 diabetes mellitus and inflammatory disorders in offspring (1, 7, 8). Furthermore, research has suggested that low maternal VD status may affect neuronal development and could result in the onset of various mental illnesses like schizophrenia and autism (1, 7, 8). Therefore, the purpose of this systematic review is to provide a brief overview of current evidence on the impact of maternal VD deficiency on brain development and function and to identify knowledge gaps warranting further research. Two topics will be discussed: *1*) animal studies focusing on biological effects of developmental VD (DVD) deficiency on brain development and function and *2*) human studies examining the impact of maternal 25(OH)D status on both offspring neurocognitive function and psychological health.

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[4] Abbreviations used: ASD, Autism Spectrum Disorder; *Bdnf*, brain-derived neurotrophic factor; *Comt*, catechol-O-methyl transferase; *Cyp24a*, 25-hydroxyvitamin-D-24-hydroxylase; DVD, developmental vitamin D; *Foxp2*, forkhead box protein P2; LCA, lithocholic acid; *Nurr1*, nuclear receptor related 1 protein; *P57Kip2*, cyclin-dependent kinase inhibitor 1C; *P75ntr*, pan-neurotrophin receptor; PPI, prepulse inhibition; *Tgf*-β1, transforming growth factor-β1; *Th*, thyrosine hydroxylase; VD, vitamin D; *Vdr*, vitamin D receptor; 1,25$(OH)_2D_3$, 1,25-dihydroxyvitamin D3; 25(OH)D, 25-hydroxyvitamin D.

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To achieve comprehensive retrieval of relevant articles, a systematic search within Medline (on Ovid) was conducted until 7 May 2015, without time or language limits. Studies investigating potential relations between maternal VD status and offspring brain function and development were systematically reviewed. Gray literature and conference proceedings were not searched. The search string was designed to include search terms on maternal VD intake and status and offspring brain function and development (**Table 1**). Because no search strategy can guarantee completeness, additional hand searches were conducted to identify studies that were not retrieved by the systematic search in Medline. The selection process started with a title and abstract screening based on inclusion and exclusion criteria; articles identified as potentially relevant were ordered as full text. During full-text screening, articles were included if they met both of the following criteria: *1*) providing data on DVD deficiency or maternal 25(OH)D status during gestation obtained before or at delivery and *2*) providing data on offspring brain development and/or function. Studies were excluded if *1*) they were reviews, case reports, letters, editorials, or correspondence; *2*) blood samples to determine maternal 25(OH)D status were obtained after delivery; *3*) the exposure was indirectly related to VD such as season of birth or latitude; *4*) the associations between prenatal 25(OH)D status and brain development, function, and/or behavior were not explored in the study; and *5*) VD mutant or VDR knockout model was used rather than maternal VD–deficient model. In total, 36 articles met the inclusion criteria of this review (**Figure 1**).

Current Status of Knowledge

Vitamin D and brain development and function: what we know from animal studies

VD has been suggested to affect numerous endocrine functions, such as the regulation of serum calcium and phosphorus concentrations, as well as health outcomes, like bone health, muscle function, and type 2 diabetes (reviewed in 1, 2). Furthermore, VD has been proposed to influence brain processes (9–11). Animal studies and in vitro studies have substantially contributed to our understanding concerning the role of VD in brain development and function. In this section, data resulting from animal studies examining the impact of low maternal 25(OH)D status on fetal brain and offspring brain development, function, and behavior are summarized.

Vitamin D and fetal brain development in animals

Most animal studies investigating the effect of maternal VD depletion on brain development and function used the DVD deficiency model as described by Eyles et al. (12). In this DVD deficiency model, female Sprague-Dawley rats were fed a VD-deficient diet from ~6 wk before conception until birth. As a consequence, the developing fetus was exposed to hypovitaminosis D during gestation. When a DVD deficiency model is discussed in this review, it refers to the

TABLE 1 Search strategy

Search no.	Ovid Medline: 7 May 2015	Search results
1	exp vitamin d/ or exp vitamin d deficiency/	55,674
2	(vitamin d or vitamin d2 or vitamin d3 or vitamin-d or vitamin-d2 or vitamin-d3 or vitamin d 2 or vitamin d 3 or ergocalciferol or colecalciferol or cholecalciferol or calciol or calcifediol or calcidiol or calcitriol or 25 hydroxycholecalciferol or 25-hydroxycholecalciferol or 25 hydroxyvitamin D or 25 hydroxyvitamin D2 or 25 hydroxyvitamin D3 or 25-hydroxyvitamin D or 25-hydroxy-vitamin D2 or 25-hydroxy-vitamin D3 or 25OHD or 25-OH-vitamin D or 25-OHD or S-25-OHD or 1,25 dihydroxycholecalciferol or 1,25-dihydroxycholecalciferol or 1,25 dihydroxyvitamin D or 1,25 dihydroxyvitamin D3 or 1,25-dihydroxyvitamin D or 1,25-dihydroxyvitamin D3 or 1,25-dihydroxy-vitamin D or 1,25-dihydroxy-vitamin D3 or 1,25OHD or 1,25-OH-vitamin D or 1,25-OHD or S-1,25-OHD).ti,ab.	54,154
3	Search 1 or 2	72,902
4	exp maternal nutritional physiological phenomena/ or exp maternal exposure/ or exp pregnancy/ or exp prenatal care/ or exp preconception care/ or exp embryology/ or exp embryonic structures/ or exp embryonic development/ or exp fetal development/ or exp prenatal exposure delayed effects/or exp perinatal care/	1,018,871
5	(peri-conception or periconception or periconceptional or peri-conceptional or maternal or intrauterine or intra-uterine or gestation or gestational or pregnancy or pregnant or conception or preconception or pre-conception or early life or early-life or fetal or fetus or fetus or fetal or embryonic or embryo or prenatal or perinatal).ti,ab.	900,584
6	Search 4 or 5	1,361,051
7	Searches 3 and 6	4987
8	exp brain/ or exp neuroimaging/ or exp mental disorders/ or exp neurologic manifestation/ or exp mental competency/ or exp mental health/ or exp mental processes/ or exp psychomotor performance/ or exp psychophysiology/ or exp behavior control/ or exp behavioral sciences/ or exp psychological tests/ or exp psychological techniques/ or exp psychiatric status rating scales/ or exp psychological adaptation/ or exp attitude/ or exp behavior/ or exp defense mechanisms/ or exp emotions/ or exp mental competency/ or exp motivation/ or exp neurobehavioral manifestations/	4,205,228
9	(brain or neurocognitive or neurocognition or memory or attention or information processing or executive function or cognition or cognitive or reactivity or emotions or MRI or neuroimaging or mental or neurological or neurologic or behavior or behavior or behavioral or behavioral or neurodevelopment or neurodevelopmental or neuroprotective or neuroprotection or psychosocial or neurologic or psychological or psychologic).ti,ab.	2,510,335
10	Search 8 or 9	5,375,024
11	Searches 7 and 10	804

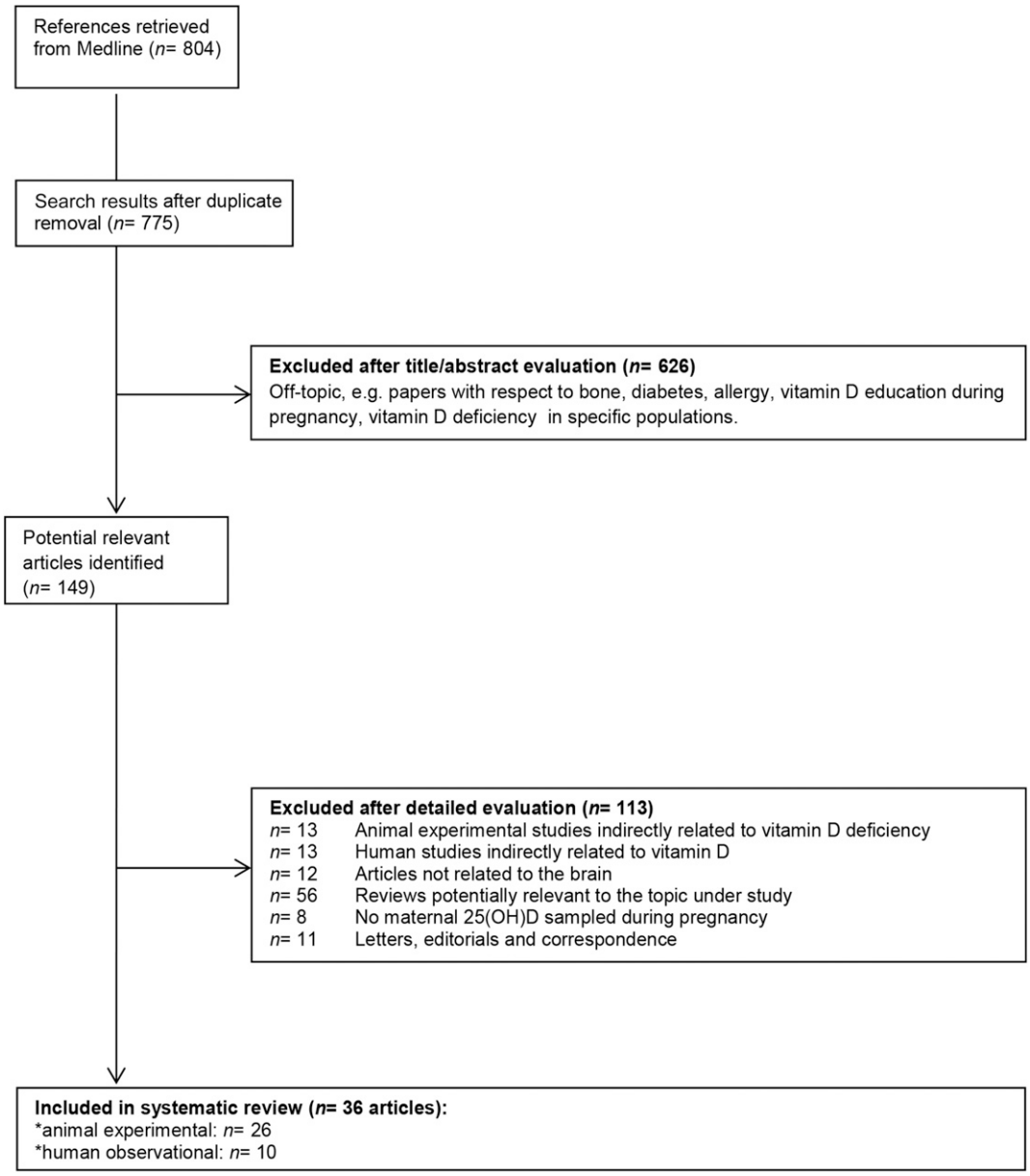

FIGURE 1 Flowchart of the selection process.

model as described by Eyles et al. (12), unless stated otherwise.

DVD and alterations in brain morphology, physiology, and gene expression in rat models. Data resulting from the DVD model have shown that offspring of VD-deficient mothers exhibit differences in brain morphology, physiology, and gene expression (**Table 2**). To illustrate this, neonatal offspring of VD-deficient Sprague-Dawley rats were reported to have longer and thinner cerebral hemispheres in comparison to offspring of normal fed rats (12). Furthermore, cell proliferation and the number of mitotic cells were significantly higher and the number of differentiating cells significantly lower throughout the VD-deficient neonatal brain (12, 14, 22). In addition, in a study by Ko et al. (22), a subtle decline in the number of apoptotic cells in both embryos and pups from VD-deficient rats was observed. This decline was most pronounced at birth (embryonic day 23), suggesting an age-dependent alteration in brain apoptotic activity.

Low prenatal $1,25(OH)_2D_3$ status has also been shown to affect neurotrophin signaling through its effect on the synthesis of nerve growth factor (NGF) and glial cell line neurotrophic factor, and expression of neurotrophin receptor p75 (12). Low fetal $1,25(OH)_2D_3$ status was not related to other neurotrophin receptors, *Vdr* expression, or the neurons:glia ratio (12). DVD deficiency has also been related to larger ventricles, reduced NGF synthesis, decreased expression of genes involved in neuronal structure (17), and decreased cell proliferation (20).

TABLE 2 DVD deficiency and offspring brain development in rodents[1]

Article (y) (ref)	Species	Strain	Gestational period of VD deficiency (animals per group)	Age of testing[2]	Method	Outcome of DVD-deficient vs. DVD adequate rodents
Almeras et al. (2007) (13)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth (n = 4)	10	Silver staining; Western blots	Altered expression of 36 genes and proteins involved in mitochondrial, cytoskeletal and synaptic plasticity
Cui et al. (2007) (14)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth (n = 6)	Day of birth, ±E23	Immunohistochemistry	↑ Neurospheres in SVZ
Cui et al. (2010) (15)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth at E12 or E15 (n = 10)	E12 or E15	Real-time PCR	↓ *Nurr1* at E12,15; ↓ *P57Kip2* at E12
Eyles et al. (2003) (12)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth (n = 11–14)	Day of birth	Histology; immunohistochemistry; brain morphology	↑ Cell proliferation; ↑ mitotic cells; ↓ NGF; ↓ GDNF; ↓ *P75ntr* expression; cortex longer and thinner; enlarged lateral ventricles
Eyles et al. (2007) (16)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth (n = 8)	10	Affymetrix gene microarrays; computational analysis	Dysregulation in oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modifications, synaptic plasticity, and neurotransmission
Eyles et al. (2014) (5)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth at E18 (n = 3)	E18	Western blots	No difference in subcellular *Vdr* distribution in the brain
Féron et al. (2005) (17)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth or weaning (n = 10)	10	Brain morphology; semiquantitative real-time PCR; Brandfort assay, ELISA	↑ Lateral ventricle volume; ↓ GABA-$A_{\alpha 4}$; ↓MAP-2; ↓NF-L and ↓NGF
Grecksch et al. (2009) (18)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth (n = 6–13)	ND	Electrophysiology	↑ LTP both after weak and strong tetanic stimulation
Hawes et al. (2015) (19)	Mice	BALB/c (♀/♂)	From preconception until birth at E14.5 or 17.5 (n = 6–8)	E14.5 or E17.5	Parrafin histology; hemaotoxylin/eosin staining; immunohistohemistry; real-time PCR	↓ Lateral ventricle volume; *Tgf-β1* unchanged at E14.5, increase at E17.5, ♀ 2.2-fold, ♂ 1.5-fold; *Bdnf* reduced at E14.5, increased at E17.5, ♀ 4.5-fold, ♂ 1.5-fold; *Foxp2* reduced at E14.5, increased at E17.5, ♀ 2.4-fold, ♂ 1.5-fold; *Th* unchanged at E14.5, decreased expression and localization at E17.5 in ♀
Keilhoff et al. (2010) (20)	Rats	Sprague-Dawley (♂)	From preconception until birth (n = 10)	10	Immunohistochemistry	↓ Cell proliferation/neurogenesis in the hippocampal DG
Kesby et al. (2009) (21)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth (n = 7–8)	Day of birth, ±E23	Real-time PCR	↓ DOPAC; ↓HVA; ↓*Comt* in the forebrain
Ko et al. (2004) (22)	Rats	Sprague-Dawley (♀/♂)	From preconception until birth at E19, E21, or E23 (n = 5)	E19, E21, E23, or P7	Immunohistochemistry; GEArray	↓ Apoptotic cells, most pronounced at birth; ↑ mitotic cells, no particular period

[1] *Bdnf*, brain-derived neurotrophic factor; *Comt*, catechol-O-methyltransferase; DG, dentate gyrus; DOPAC, dihydroxyphenylacetic acid; DVD, developmental vitamin D; E, embryonic day; *Foxp2*, forkhead box protein P2; GABA-$A_{\alpha 4}$, gamma-aminobutyric acid A; GDNF, glial cell line neurotrophic factor; HVA, homovanillic acid; LTP, long-term potential; MAP-2, microtubule-associated protein 2; ND, not described; NF-L, neurofilament; NGF, nerve growth factor; *Nurr1*, nuclear receptor related 1 protein; P, postnatal day; *P57Kip2*, cyclin-dependent kinase inhibitor 1C; *P75ntr*, p75 neurotrophin receptor; ref, reference; SVZ, subventricular zone; *Tgf-β1*, transforming growth factor β1; *Th*, tyrosine hydroxylase; VD, vitamin D; *Vdr*, vitamin D receptor; ↓, decrease; ↑, increase; ♀, female; ♂, male.

[2] In weeks, unless otherwise noted.

Experimental studies in rats have also suggested a role for VD in dopaminergic systems, which may be of clinical relevance for certain disorders that are associated with abnormal dopaminergic signaling such as schizophrenia (23, 24), Parkinson disease (25), depression (26), and autism (27). For instance, VD deficiency has been shown to alter gene expression of factors such as nuclear receptor related 1 protein and cyclin-dependent kinase inhibitor 1C, which are involved in the dopaminergic development in the embryonic midbrain (15). Changes in dopaminergic metabolic profile were also observed in offspring forebrain, showing a decreased dihydroxyphenylacetic acid:homovanillic acid ratio as well as catechol-O-methyl transferase expression (21).

With the use of Affymetrix gene microarrays, prenatal hypovitaminosis D has been linked to multiple alterations in gene and protein expression patterns involved in neuronal structure later in life. Specifically, DVD deficiency has been shown to affect the expression of 36 protein molecules that are involved in numerous biological pathways in offspring rat brain, including oxidative phosphorylation, synaptic plasticity, and neurotransmission. With the use of computational analyses these impairments were subsequently associated with the pathogenesis of several neurodevelopmental and psychiatric disorders like schizophrenia and multiple sclerosis (13, 16). DVD deficiency did not affect subcellular *Vdr* distribution in Sprague-Dawley rats (5).

DVD and alterations in brain morphology and physiology in mice. A study in prenatal VD-deficient BALB/c mice pointed toward a reduction in lateral ventricle volume and altered expression of genes involved in neuronal survival, specifically brain-derived neurotrophic factor (*Bdnf*) and transforming growth factor-β1 (*Tgf-β1*), and speech and language development, specifically forkhead box protein P2 (*Foxp2*). In DVD-deficient female fetuses dopamine synthesis was also affected, when both brain thyrosine hydroxylase (*Th*) gene expression and *Th* protein localization were reduced (19).

Behavior in DVD-deficient animals

The aforementioned studies suggest that prenatal VD deficiency affects brain development; this may affect offspring behavior. Several studies have associated DVD deficiency with offspring behavioral (dys)function, including developmental milestones, locomotion, exploration, anxiety, learning, memory, and sensorimotor gating (**Table 3**). The influence of prenatal VD deficiency on offspring behavior both in early life and adulthood has predominantly been examined in rats. Most of these animal studies aimed to unravel effects of VD deficiency on developmental disorders such as schizophrenia (30, 33, 38, 39) and autism (12, 32).

Developmental milestones. O'Loan et al. (39) investigated the effect of prenatal VD deficiency on developmental milestones in Sprague-Dawley rats. The offspring was exposed to 1 of 4 prenatal VD conditions: *1*) normal VD status; *2*) VD depletion starting 4 to 6 wk preconception up to conception; *3*) VD depletion from conception until birth; and *4*) VD depletion starting 4 to 6 wk preconception until birth. No significant differences in developmental milestones, including eye/ear opening, ear unfolding, fur growth, upper and lower teeth protrusion, self-righting reflex, posture, and activity, were observed between treatment groups.

Locomotion, exploration, and anxiety in rats. Other studies did, however, point toward behavioral differences triggered by DVD deficiency. For example, DVD deficiency has been related to novelty-induced hyperlocomotion in adult rats, even when pups were fed a VD-replete diet from birth or weaning onwards (30, 31, 34, 38). O'Loan et al. showed that this novelty-induced hyperlocomotion was most pronounced in rats that were DVD deficient from conception until birth (39), suggesting that there might be a critical window for prenatal VD effects on offspring brain development. DVD deficiency from mating to offspring weaning has also been associated with a more anxious and less social phenotype in juvenile Sprague-Dawley rats. Whereas effects related to social behaviors were still present in adulthood, differences pertaining to anxiety-like behaviors did not persist into adulthood (40).

Learning and memory in rats. Maternal VD deficiency has also been suggested to play a role in offspring learning capacities and memory function. For example, maternal VD deficiency in Sprague-Dawley offspring has been related to subtle learning and memory effects, as shown by a disruption in latent inhibition, reduced habituation, and superior relearning skills, whereas memory acquisition as well as memory retrieval remained unaffected (28). In addition, offspring of VD-deficient dams showed an increased impulsivity and a lack of control of inhibitory behavior in adulthood compared with control animals, as measured using a 5-choice continuous performance test (41). Unexpectedly, maternal VD deficiency was also associated with improved retention performance in the brightness discrimination in a Y-maze (28) and enhancement of long-term potentiation (18).

Sensorimotor gating. Burne et al. (29) investigated the impact of both pre- and postnatal VD deficiency on prepulse inhibition (PPI) of the acoustic startle response (ASR) in 5- and 10-wk-old rats. Although 5-wk tests did not suggest differences between treatment groups, impaired PPI—without dysregulation of the ASR itself—was observed in 10-wk-old rats receiving combined pre- and chronic postnatal VD deficiency. No significant impairments were observed in animals exposed to VD depletion during pregnancy or only until weaning. In contrast, another study by Burne et al. (30) did not reveal any significant influence of DVD deficiency on the PPI. Discrepancies between these studies may relate to low calcium levels, which were reported in the former study but not found in the latter approach. Possibly, hypocalcemia instead of pre- and postnatal DVD deficiency impairs PPI.

Behavioral studies in mice. Harms et al. (36) investigated the effect of hypovitaminosis D on the phenotype of 129/SvJ

TABLE 3 DVD deficiency and offspring behavior in rodents[1]

Article (y) (ref)	Species	Strain	Period of VD deficiency (animals per group)	Age of testing[2]	Method	Outcome
Becker et al. (2005) (28)	Rats	Sprague-Dawley (♂)	During preconception until birth (n = 8)	10	Holeboard test; brightness discrimination in a Y-chamber; avoidance learning in a shuttle-box and radial maze	DVD deficiency was related to reduced habituation in the holeboard test and better maintenance of previously learned rules in a Y-chamber. No effect on radial maze or shuttle-box performance was observed.
Burne et al. 2004) (29)	Rats	Sprague-Dawley (♀/♂)	During preconception until birth or until weaning, or remained until 10 wk of age (n = 9–23)	5, 10	PPI of ASR	The combination of prenatal and chronic postnatal VD deficiency resulted in an significantly impaired PPI, despite normal ASR, at 10 wk.
Burne et al. (2004) (30)	Rats	Sprague-Dawley (♀/♂)	During preconception until birth or until weaning, or remained until 10 wk of age (n = 23–30)	10	Holeboard test; elevated plus maze test; ASR test; forced swim test; PPI of ASR; social interaction observation	DVD deficiency increased locomotion in holeboard test and increased activity in the elevated plus maze. No effects on other outcome measures were observed.
Burne et al. (2006) (31)	Rats	Sprague-Dawley (♀/♂)	During preconception until birth (n = 14)	8	Open field test	DVD deficiency enhanced locomotion in open field test. DVD rats spent significantly less time in corners and more time on the side compared with DVD-adequate rats.
Burne et al. (2011) (32)	Rats	Sprague-Dawley (♀/♂)	During preconception until birth (n = 24)	12–18[3]	Day of birth pup-retrieval test; isolation-induced USV	VD-deficient dams showed more pup-directed activities and less time was needed to retrieve their pups. Maternal diet did not affect the calling rate of isolation-induced ultrasonic vocalizations by pups.
Burne et al. (2014) (33)	Rats	Sprague-Dawley (♀/♂)	During preconception until birth (n = 6–12)	6[3]	Injection of 2.5 mg THC or vehicle/kg before PPI of ASR or open field test; injection of 0–2.5 mg THC or vehicle/kg 15 min before DMTS	DVD deficiency enhanced the PPI in DVD-deficient animals after THC injection. DVD-deficiency was not shown to affect other outcome measures under investigation.
Eyles et al. (2006) (34)	Rats	Sprague-Dawley (♂)	During preconception until birth (n = 5)	10	Open field test	DVD deficiency resulted in a significantly increased activity pattern, more specifically, distance traveled and rearing.
Fernandes de Abreu et al. (2010) (35)	Mice	C57BL/6J (♂)	During preconception until birth (n = 8–12)	30, 60, 70	MRI; olfactory tubing maze	Compared with DVD-adequate mice, DVD-deficient mice showed significantly impaired learning abilities at 30-wk-old and reduced ventricle volumes.
Harms et al. (2008) (36)	Mice	129/SvJ, C57BL/6J (♀/♂)	During preconception until birth (n = 22–35)	10	Holeboard test; open field test; elevated plus maze; forced swim test; PPI of ASR; SHIRPA screening; social interaction test	DVD-deficient 129/SvJ and C57BL/6J mice showed significantly higher levels of exploration than did DVD-adequate mice. In addition, 129/SvJ showed significantly higher levels of spontaneous locomotion than did DVD-adequate mice. No effects with respect to the other outcome measures were observed.

(Continued)

TABLE 3 (*Continued*)

Article (y) (ref)	Species	Strain	Period of VD deficiency (animals per group)	Age of testing[2]	Method	Outcome
Harms et al. (2012) (37)	Mice	129/X1Sv, C57BL/6J (♀/♂)	During preconception until birth (n = 6–11)	P0, 70	MRI; open field test, injection of saline, MK-801, or amphetamine	DVD-deficient C57BL/6J females had a reduced hippocampal volume. DVD-deficient C57BL/6J males had a lower lateral ventricle volume and increased striatum volume. No DVD-deficiency effect was shown for any of the other outcome measures under investigation.
Kesby et al. (2006) (38)	Rats	Sprague-Dawley (♂)	During preconception until birth (n = 9–124)	10	Holeboard test open field test, injection of MK-801 and/or haloperidol; PPI, injection of apomorpine or MK-801	DVD deficiency was related to an increased baseline locomotion on the holeboard test and in response to MK-801. Haloperidol antagonized this effect. No DVD-deficiency effect on baseline or drug-mediated PPI was observed.
O'Loan et al. (2007) (39)	Rats	Sprague-Dawley (♂)	Early, 4 wk before conception VD deplete, thereafter replete; late, conception to birth VD deplete; full, 6 wk before conception until birth VD deplete (n = 123–134)	P7, 14, 21, 70	Developmental milestones; open field test, injection of MK-801	No effects of DVD deficiency on developmental milestones were observed. Full and late VD deficiency resulted in MK-801-induced hyperlocomotion.
Pan et al. (2014) (40)	Rats	Sprague-Dawley (♀/♂)	From mating to weaning, range 0–10.0 IU VD/g (n = 10–12)	P35–40, 100–105	Elevated plus maze; locomotor activity box; social behavior and learning	In juveniles, DVD deficiency was related to enhanced anxiety and reduced locomotion. DVD deficiency also affected social behavior and learning in both juveniles and adults.
Turner et al. (2013) (41)	Rats	Sprague-Dawley (♀/♂)	During preconception until birth (n = 6–8)	20	5-CPT; 5-CRT	DVD-deficient rats exhibited increased impulsivity and a lack of inhibitory control. DVD deficiency did not affect accuracy.

[1] ASR, acoustic startle response; DMTS, delay match to sample test; DVD, developmental vitamin D; P, postnatal day; PPI, prepulse inhibition; ref, reference; SHIRPA, SmithKline Beecham, Harwell, Imperial College, and Royal London Hospital phenotype assessment; THC, tetrahydrocannabinol; USV, ultrasonic vocalization; VD, vitamin D; 5-CPT, 5-choice continuous performance test; 5-CRT, 5-choice serial reaction time test; ♀, female; ♂, male.
[2] In weeks, unless otherwise noted.
[3] In months.

and C57BL/6J mice in 10-wk-old offspring using a behavioral test battery. DVD-deficient mice of both strains had higher levels of exploratory behavior than did DVD-adequate mice. In 129/SvJ mice locomotion was also increased, but sensorimotor gating and social behavior were unaffected. No differences were observed for simple behavioral and morphological characteristics as assessed by SHIRPA (SmithKline Beecham, Harwell, Imperial College, and Royal London Hospital phenotype assessment) primary screen, nor for anxiety or depressive behavior. These findings were in line with another study of Harms et al. (37) in which brains of both C57BL/6J and 129/X1SvJ mice were imaged using MRI at postnatal day 0 (neonatal) and postnatal day 70 (adulthood), and locomotion sensitivity to psychotomimetic drugs (amphetamine and MK-801) was studied using an open field test. When DVD deficiency was related to reduced hippocampal volume in female neonatal C57BL/6J mice, adult DVD-deficient males had lower lateral ventricle volumes when compared with control animals. No DVD-deficiency effects were observed in 129/X1SvJ mice, nor was there a difference in behavioral phenotype in both strains. Fernandes de Abreu et al. (35) investigated the impact of prenatal VD deficiency on learning abilities in C57BL/6J mice. Offspring of VD-deficient mothers underwent an associative hippocampal dependent memory test at 30 and 60 wk old, and MRI at 30 and 70 wk old.

Results showed problems with learning as well as smaller lateral ventricles at 30 wk. However, none of these alternations were observed during the follow-up measurement at 60 and 70 wk.

Vitamin D and brain development and function: what we know from human studies

Based on animal studies, VD deficiency has been proposed to contribute to brain development and function in humans. The aim of this section is to provide an overview of available human data on the potential relation between VD- and brain-related outcomes. The systematic literature search resulted in 10 human observational studies that dealt with maternal 25(OH)D serum status during pregnancy and offspring neurocognitive and psychological outcomes. Characteristics of the included studies are summarized in **Table 4**. No intervention studies have yet been published.

Vitamin D, cognition, and behavior

Several studies examined the association between maternal serum 25(OH)D concentrations and offspring neurocognitive development. For instance, Keim et al. (45) did not observe associations of maternal 25(OH)D measured at ≤26 wk of pregnancy or cord blood 25(OH)D with early childhood development among 3308 8-mo-old American boys and girls [Bayley mental score β: 0.02; 95% CI: −0.03, 0.07 per 5 nmol/L increment]. In contrast, after adjustment for child sex and maternal country of origin, significant associations were reported between maternal serum 25(OH)D concentrations and Bayley mental and psychomotor scores in 1820 14-mo-old Spanish offspring. Specifically, mental and psychomotor scores were higher in children of mothers with 25(OH)D status ≥75 nmol/L compared with serum VD concentrations ≤50 nmol/L (reference) (Bayley mental score β: 2.60; 95% CI: 0.63, 4.56; Bayley psychomotor score β: 2.32; 95% CI: 0.36, 4.28) (47).

Studies on maternal VD deficiency and offspring intelligence scores also showed contradictory results. Maternal serum 25(OH)D status during gestation was not associated with total intelligence quotient scores or tests of scholar achievement, reading and spelling, language impairments, or verbal intelligence quotient among Danish, English, and American children (43, 45, 48). However, data of Whitehouse et al. (50) did suggest an association between low prenatal VD status at 18 wk of pregnancy and an increased risk of language impairment, as measured by the Peabody Picture Vocabulary Test-Revised, in 929 Australian boys and girls aged 5 and 10 y [adjusted OR: 1.97; 95% CI: 1.00, 3.93 for maternal 25(OH)D ≤46 nmol/L compared with levels >70 nmol/L]. Previous research has shown that cortical structures critical for language development are formed around the fourteenth week of gestation (52, 53). Therefore, measured 25(OH)D concentrations in studies other than Whitehouse et al. (50) may not have reflected circulating 25(OH)D concentrations during critical phases of neurodevelopment. In a prospective cohort study among 960 Vietnamese mother-offspring pairs, language scores were, however, significantly lower in children who were prenatally exposed to 25(OH)D concentrations <38 nmol/L than in children prenatally exposed to 25(OH)D concentrations >75 nmol/L. In this study, maternal 25(OH)D blood was sampled at 32 wk of gestation (adjusted estimated mean difference: −3.48; 95% CI: −5.52, −1.44) (44).

Vitamin D and neuropsychological disorders

Language impairment is often a prominent feature of the autism spectrum disorder (ASD) phenotype, and previous studies have suggested involvement of maternal VD deficiency in the etiology of ASD. However, to date, only 1 observational study has examined the association between deficient maternal VD status and the risk of the ASD phenotype (51). In the 18th week of gestation, 929 Australian mothers donated blood. During the 17 y of follow-up, parents were asked whether their child ever received a diagnosis of ASD. In early adulthood children were asked to complete the autism spectrum quotient. No significant association was revealed between maternal 25(OH)D status and offspring total score on the autism spectrum quotient. However, offspring of mothers with 25(OH)D concentrations <49 nmol/L did have higher scores on the Attention Switching subscale than offspring of mothers with sufficient VD status (≥67 nmol/L), after adjusting for a range of confounders (adjusted OR: 5.46; 95% CI: 1.29, 23.05). Within that same Australian cohort the link between DVD deficiency and another neuropsychological condition was examined as well, namely, the association between prenatal VD deficiency and the development of eating disorders (EDs) at 14, 17, and 20 y of age. ED risk was assessed with the Child Eating Disorder Examination and Eating Disorder Examination Questionnaire (n = 308). When children were 20 y old, multivariate logistic regression showed an ~2-fold increase in ED risk among female offspring in the lowest 25(OH)D quartile (<46 nmol/L) when compared with those in the highest quartile (>71 nmol/L), after adjusting for BMI (in kg/m^2), depressive symptoms, and season of birth (adjusted OR: 2.09; 95% CI: 1.03, 5.27) (42).

Similar to autism, maternal VD deficiency during pregnancy has been proposed as an early life risk factor for the development of psychosis (54, 55). However, a case-control study among American women, including 26 cases of schizophrenia and 51 race, sex, and date of birth matched controls, did not show an association between prenatal 25(OH)D concentrations during the third trimester of pregnancy and psychosis risk. Although not statistically significant, subgroup analysis did suggest that black individuals with schizophrenia were more likely to be prenatally exposed to low 25(OH)D concentrations (OR: 0.78; 95% CI: 0.66, 1.08) (46). The null findings of this study were recently replicated by a British study, which also did not observe associations between maternal 25(OH)D status and psychotic experiences (Psychosis-Like Symptoms Interview) (177 cases) or diagnosis of a psychotic disorder when children were 18 y old (29 cases) (49). Because both studies are

TABLE 4 Cohort and case–control studies on low maternal 25(OH)D status and offspring neurocognitive and psychological outcomes[1]

Article (y) (ref)	Type of study	Location	Participants	Maternal 25(OH)D determination	Mean 25(OH)D	Method	Main findings
Allen et al. (2013) (42)	Prospective cohort	Australia (RAINE)	929 mother-child pairs	18-wk gestation	Maternal serum: 60 nmol/L	C-EDE and EDE-Q in ♀ offspring (age 20 y)	Female offspring exposed to the lowest prenatal 25(OH)D concentrations (<46 nmol/L) had a significantly higher ED risk at age 20 y than those exposed to the highest prenatal 25(OH)D concentrations [>71 nmol/L, reference; adjusted OR for lowest 25(OH)D quartile: 2.09; 95% CI: 1.03, 5.27].
Gale et al. (2008) (43)	Prospective cohort	United Kingdom	596 mother-child pairs	28–42 wk gestation	Maternal serum: 50 nmol/L	WAIS; SDQ (age 9 y)	No associations were observed between maternal 25(OH)D concentrations and child's intelligence or psychological health.
Hanieh et al. (2014) (44)	Prospective cohort	Vietnam	960 mother-child pairs	32-wk gestation	Maternal serum: 70 nmol/L	BSID-III (age 6 mo)	Infants exposed to the lowest prenatal 25(OH)D concentrations (<38 nmol/L) had lower language scores than those exposed to 25(OH)D concentrations (≥75 nmol/L, reference; adjusted estimated mean difference: −3.48; 95% CI: −5.52,1.44). Prenatal 25(OH)D status was not associated with cognitive, motor, or socio-emotional scores.
Keim et al. (2014) (45)	Prospective cohort	United States	3896 mother-child pairs	≤26-wk gestation	Maternal serum: 45 nmol/L Cord serum: 32 nmol/L	WISC (age 7 y); BSID (age 8 mo); behavior (ages 4 and 7 y), SBIC (age 4 y); WRAT (age 7 y)	Lower maternal/cord 25(OH)D concentrations were associated with lower WISC intelligence quotient scores [adjusted β for 5-nmol/L increment in maternal 25(OH)D concentration: 0.10; 95% CI: 0.00, 0.19; adjusted β for cord blood 25(OH)D concentrations: 0.16; 95% CI: 0.03, 0.19]. No associations were observed for the other outcome measures under study.
McGrath et al. (2003) (46)	Case-control	United States	26 cases 51 race, sex, and date of birth matched controls	2nd trimester	Maternal serum: 47 nmol/L	DSM-IV criteria schizophrenia/schizoaffective disorder	Overall, no association was observed between maternal 25(OH)D status and schizophrenia risk. In a subgroup of black individuals, however, a nonsignificant inverse association between maternal 25(OH)D concentrations and psychosis risk was observed: adjusted OR: 0.78; 95% CI: 0.55,1.08.

(Continued)

TABLE 4 (*Continued*)

Article (y) (ref)	Type of study	Location	Participants	Maternal 25(OH)D determination	Mean 25(OH)D	Method	Main findings
Morales et al. (2012) (47)	Prospective cohort	Spain	1820 mother-child pairs	2nd trimester	Maternal plasma: 75 nmol/L	BSID (age 14 mo)	Offspring exposed to the highest prenatal 25(OH)D concentrations (≥75 nmol/L) had higher mental and psychomotor scores (adjusted β: 2.60; 95% CI: 0.63, 4.56 and β: 2.32; 95% CI: 0.36, 4.28, respectively) than offspring exposed to the lowest prenatal 25(OH)D concentrations (≤50 nmol/L).
Strøm et al. (2014) (48)	Prospective cohort	Denmark	965 mother-child pairs	30-wk gestation	Maternal serum: 76 nmol/L	First admission diagnosis or prescription of medication for depression and ADHD (age 22 y); scholastic achievement based on the mean grade on standardized written exams (9^{th} grade)	*P*-trend analysis showed a significant positive association between maternal 25(OH)D concentrations and offspring depression risk ($P = 0.02$). No association was observed between maternal 25(OH)D status and ADHD.
Sullivan et al. (2013) (49)	Prospective cohort	England	2047 mother-child pairs	Random, adjusted to date corresponding with individuals' midpoint of 34 wk of gestation	Median maternal serum: 64 nmol/L	PLIKSi (age 18 y)	Maternal 25(OH)D concentration was not associated with psychiatric experiences.
Whitehouse et al. (2012) (50)	Prospective cohort	Australia (RAINE)	929 mother-child pairs	18-wk gestation	Maternal serum: 60 nmol/L	CBCL (follow-up age 2–17 y); PPVT-R (age 5 and 10 y)	No associations were observed between maternal 25(OH)D concentrations and behavioral/emotional problems at any age. A higher risk of language impairment was observed in offspring of mothers with VD levels ≤46 nmol/L than in offspring of mothers with VD levels >70 nmol/L (adjusted OR: 1.97; 95% CI: 1.00, 3.93).
Whitehouse et al. (2013) (51)	Prospective cohort	Australia (RAINE)	929 mother-child pairs	18-wk gestation	Maternal serum: 58 nmol/L	ASQ (early adulthood); DSM-IV criteria ASD (ages 5, 8, 10, 14 and 17 y)	Higher Attention Switching subscale scores were observed in offspring of mothers with VD status <49 nmol/L than in offspring of VD-sufficient mothers (≥50 nmol/L) (adjusted OR: 5.46; 95% CI: 1.29, 23.05). No associations were observed between maternal VD concentrations and the other subscales/autism-related outcomes.

[1] ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ASQ, autism spectrum quotient; BSID, Bayley Scales of Infant Development; CBCL, child behavior checklist; C-EDE, Child Eating Disorder Examination; DSM, Diagnostic and Statistical Manual of Mental Disorders; ED, eating disorder; EDE-Q, Eating Disorder Examination Questionnaire; PLIKSi, psychosis-like symptom interview; PPVT-R, Peabody Picture Vocabulary Test–Revised; RAINE, Western Australian pregnancy cohort; ref, reference; SBIC, Stanford-Binet Intelligence Scale; SDQ, Strengths and Difficulties Questionnaire; VD, vitamin D; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children; WRAT, Wide Range of Achievement Test; 25(OH)D, 25-hydroxyvitamin D; ♀, female.

limited by their sample sizes, these studies lack power to yield conclusive results.

Finally, no associations have been observed between prenatal VD deficiency and offspring behavior as measured with the Childhood Behavior Checklist and/or Strengths and Difficulties Questionnaire (43–45, 50). These instruments assess internalizing/emotional problems and externalizing/hyperactivity and might therefore reflect key features of depression and attention-deficit hyperactivity disorder (DHD), respectively. Results of a Danish cohort study by Strøm et al. (48) also reported no association between maternal serum levels measured at 30 wk gestation and offspring risk of depression or DHD, as defined as first admission diagnosis or prescribed medicine.

Discussion

As stated previously, the primary goal of this systematic review was to provide an overview of current evidence from animal and human studies investigating the impact of maternal VD status on offspring brain development and function. Results of the systematic search predominantly yielded animal experimental studies, in which DVD-deficient animal model experiments suggest an important role for VD in brain development. More specifically, significant differences were observed between DVD-deficient offspring and offspring exposed to normal prenatal VD concentrations with respect to brain morphology and physiology as well as gene expression. In addition, prenatal VD deficiency was found to alter offspring phenotype. Only a few observational studies have examined the association between maternal 25(OH)D status and offspring psychological health and behavior in humans, providing inconclusive data.

When current scientific evidence is evaluated, there are several aspects that warrant discussion. First, most animal studies were conducted in Sprague-Dawley rats, limiting extrapolation of current data to other animals or humans. Second, not all animal studies reported whether calcium concentrations were measured in offspring animals and whether these levels fell within the normal range. Therefore, some of the observed alterations in offspring behavior may be due to low calcium levels affecting musculoskeletal function and thereby offspring behavior during experimental tasks. Third, even though animal studies offer the opportunity to study more contrasting exposures, e.g., absolute VD deficiency compared with a normal VD status, and to control for many factors, rodent studies do not yet provide conclusive evidence. It may be postulated that the lack of clear differences in offspring health between DVD-deficient and nondeficient animals relates to the presence of lithocholic acid (LCA) (56). Nehring et al. (57) presented data in which LCA acted as a substitute for VD. More specifically, LCA resulted in increased serum calcium levels, replaced VD in the mobilization of calcium from bone, and induced 25-hydroxyvitamin-D-24-hydroxylase (*Cyp24* expression in DVD-deficient rats.

The first point of discussion with respect to human studies relates to the fact that most human studies exploring the potential link between prenatal VD exposure and brain development and function in later life studied factors serving as a proxy for maternal VD status, including season of birth, migrant status, urban-rural status, and latitude gradient. Because evidence obtained from these studies may not reflect VD effects but effects caused by other characteristics of sunlight, these studies were not included in this review. Second, most of the included observational studies in this review were conducted in Caucasian populations, limiting extrapolation of these findings to other ethnic populations. Only the study of McGrath et al. (46) reported race-dependent study outcomes. Third, there is some heterogeneity in timing of maternal blood sampling between the included studies. Because there may be a critical window for the impact of maternal VD deficiency during gestation on offspring health, this heterogeneity in timing of maternal blood sampling may explain some of the discrepancies between the different studies. Fourth, differences in outcomes between human studies may also relate to differences with respect to statistical analyses, including use of different cutoffs and potential confounders taken into account (**Table 5**). Fifth, whereas some studies used validated test batteries, others used data collected using self-reported questionnaires filled in by offspring or their caretakers (Table 5); self-report questionnaires may be more likely to introduce bias. Sixth, several studies experienced difficulties with sample attrition over time. For instance, during the last follow-up round at age 9 y, Gale et al. (43) obtained follow-up data for only 30% of the original study population. Moreover, in the study of Whitehouse et al. (50) only 14% of all participants eventually participated after reaching adolescence (Table 5). Seventh, studies examining the impact of maternal 25(OH)D deficiency on developmental disorders are likely to have lacked power due to the low number of offspring eventually developing a disorder. These limitations pinpoint that the potential link between maternal VD deficiency and offspring brain development and function still warrants further investigation.

Future animal studies could add to our understanding if the clinical window during which the brain is particularly vulnerable to VD deficiency is examined. Furthermore, it would be valuable to obtain data on optimal dosage and timing of VD supplementation for offspring brain development and function. Effects on brain development and brain function could be investigated by studying morphological, physiological, and behavioral outcomes from gestation throughout adulthood while at the same time monitoring offspring calcium concentrations. Given the lack of conclusive human data, there is also a critical need for longitudinal cohort studies with maternal 25(OH)D sampling in all 3 trimesters and long-term offspring monitoring by means of regular blood sampling, imaging techniques, and neurocognitive, behavioral, psychiatric, and neurological assessments. In addition to the techniques that have already been applied in studies, serial 3-dimensional ultrasound scans during gestation could be conducted to visualize (ab)normal embryonic brain development (58–60). Cord blood samples,

TABLE 5 Study characteristics of included human cohort studies[1]

Article (y) (ref)	Potential confounders adjusted for in the analysis	Method of status assessment	Method of outcome assessment	Number at Start with Complete Exposure Data, Loss to Follow-up	Funder
Allen et al. (2013) (42)	Presence of maternal kidney dysfunction at 18 wk gestation, family income, biological father living at home at age 14 y, offspring BMI at age 14 y, and offspring depressive symptoms at age 14 y	EIA	C-EDE; EDE-Q	Baseline: *n* = 802 Caucasian mothers; follow-up: *n* = 526 (66%) pairs with available outcome data in adolescence, of which 308 were mother-daughter pairs included in the analyses	Nonprofit
Gale et al. (2008) (43)	No adjustment for potential confounders	RIA	WASI; SDQ	Baseline: *n* = 466; follow-up: *n* = 178 with available outcome data at 9 y	Nonprofit
Hanieh et al. (2014) (44)	Maternal age, maternal education, month of blood sampling, maternal BMI, gravidity, maternal depression, and treatment group during RCT	LC-MS	BSID	Baseline: *n* = 960; follow-up: *n* = 886	Nonprofit
Keim et al. (2014) (45)	Maternal education, maternal age, parity, race, maternal BMI, marital status, smoking, gestational age, month of blood sampling, and study site	LC-MS/MS	BSID; SBIC; behavior; WISC; WRAT	Baseline: *n* = 4444; follow-up: 8 mo, *n* = 3587; 4 y, *n* = 3146; 7 y, *n* = 3237	Nonprofit
Morales et al. (2012) (47)	Study site, offspring sex, birth weight, maternal country of origin, maternal age, parental social class, maternal education, parity, maternal prepregnancy BMI, and maternal smoking and alcohol consumption during pregnancy	HPLC	BSID	Baseline: *n* = 2389; follow-up: *n* = 1820	Nonprofit
Strøm et al. (2014) (48)	Parity, maternal age, maternal prepregnancy BMI, maternal smoking during pregnancy, maternal education, offspring sex, and season of blood sampling	LC-MS/MS	Depression and ADHD: first admission diagnosis or medication prescription. Scholastic achievement: mean grade of standardized written exams in grade 9.	Baseline: *n* = 851; follow-up: *n* = 798 for scholastic achievement, *n* = 850 for depression and ADHD	Vitamin D biomarkers in maternal sera were funded by a grant from the Novo Nordisk Foundation.
Sullivan et al. (2013) (49)	Maternal age, parity, maternal BMI, maternal smoking, maternal alcohol intake, maternal symptoms of depression, social economic position of head of household, maternal educational level, housing tenure, and season of blood sampling	LC-MS/MS	PLIKSi	Baseline: *n* = 6780; follow-up: *n* = 2399; analysis sample: *n* = 2047, due to missing data on covariables (*n* = 352)	Nonprofit
Whitehouse et al. (2012) (50)	For PPVT-R model: maternal age at conception, family income, maternal smoking during pregnancy, offspring parity, and season of blood sampling. Analyses on CBCL were not adjusted for confounders.	EIA	CBCL; PPVT-R	Baseline: *n* = 813; follow-up: *n* = 743	Nonprofit
Whitehouse et al. (2013) (51)	Maternal race, maternal alcohol intake during pregnancy, maternal education, family income, offspring gestational age at birth, offspring parity, offspring Apgar scores 5 min after birth, and season of blood sampling	EIA	AQ	Baseline: *n* = 929; follow-up: *n* = 406	Nonprofit

[1] Baseline: *n*, number of participants with available 25(OH)D data. ADHD, attention-deficit hyperactivity disorder; AQ, autism spectrum quotient; BSID, Bayley Scales of Infant Development; CBCL, child behavior checklist; C-EDE, Child Eating Disorder Examination; EDE-Q, Eating Disorder Examination Questionnaire; EIA, enzyme immunoassay; PLIKSi, psychosis-like symptom interview; PPVT-R: Peabody Picture Vocabulary Test-Revised; RCT, randomized controlled trials; ref, reference; SBIC, Stanford-Binet Intelligence Scale; SDQ, Strengths and Difficulties Questionnaire; WASI, Wechsler Abbreviated Scale of Intelligence; WISC, Wechsler Intelligence Scale for Children; WRAT, Wide Range of Achievement Test; 25(OH)D, 25-hydroxyvitamin D.

analyzed with microarrays, may also provide insight into the potential impact of DVD deficiency on gene and protein expression patterns already observed in rats (13, 16). Finally, studies in non-Caucasian mother-offspring pairs are warranted in order to obtain a better understanding of ethnic differences in the link between maternal VD status and brain development and function.

Conclusion

As summarized in the body of this review, VD is thought to play an important role in brain development and offspring cognitive and psychological function. Rodent studies suggest deviations in brain morphology and physiology of DVD-deficient offspring. However, observed impairments in behavior are subtle and inconsistent. Furthermore, robust human data supporting the link between 25(OH)D status or maternal VD supplementation and offspring brain development and/or function are lacking. Because the developing fetus is completely dependent on the nutritional status of its mother, the impact of low VD status during gestation needs further clarification by future research efforts.

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