Maternal vitamin D deficiency and developmental origins of health and disease (DOHaD)

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Abstract

Vitamin D is an essential nutrient that is metabolized in the body to generate an active metabolite (1,25(OH)$_2$D) with hormone-like activity and highly diverse roles in cellular function. Vitamin D deficiency (VDD) is a prevalent but easily preventable nutritional disturbance. Emerging evidence demonstrates the importance of sufficient vitamin D concentrations during fetal life with deficiencies leading to long-term effects into adulthood. Here, we provide a detailed review and perspective of evidence for the role of maternal VDD in offspring long-term health, particularly as it relates to developmental origins of health and disease (DOHaD). We focus on the roles in neurobehavioral and cardiometabolic disorders in humans and highlight recent findings from zebrafish and rodent models that probe potential mechanisms linking early life VDD to later life health outcomes. Moreover, we explore evidence implicating epigenetic mechanisms as a mediator of this link. Gaps in our current understanding of how maternal VDD might result in deleterious offspring outcomes later in life are also addressed.

Key Words

- vitamin D deficiency
- DOHAD
- metabolic disorders
- autism
- neurobehavioral disorders
- animal models

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Introduction

Vitamin D is obtained through various plant and animal dietary sources and can also be synthesized in the skin through sunlight exposure (Fig. 1). All forms of vitamin D are metabolized in the liver via 25-hydroxylases to generate 25 hydroxyvitamin D, 25(OH)D, the predominant but inactive circulating form of vitamin D. (Fig. 1). As shown, the kidney is the primary site of conversion of 25(OH)D to the active form 1,25(OH)$_2$D *via* the 1-alpha-hydroxylase CYP27B1. However, extrarenal expression of CYP27B1 also generates 1,25(OH)$_2$D in numerous target tissues including the placenta and brain (Townsend *et al.* 2005, Adams & Hewison 2012). Vitamin D deficiency (VDD) is commonly defined as 25(OH)D concentration <50 nmol/L (Holick *et al.* 2011) and represents one of the most

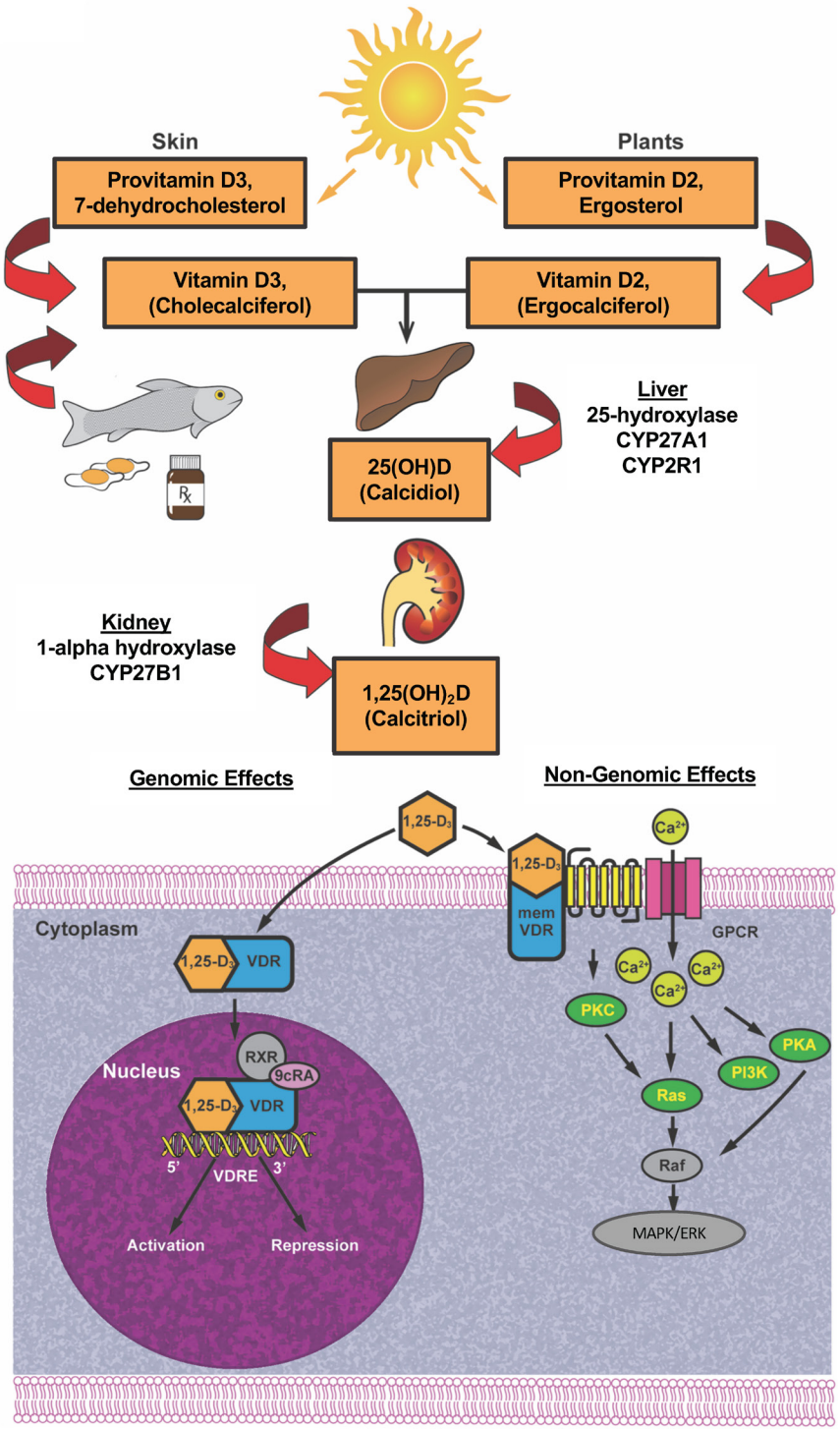

Figure 1
Synthesis and functions of active hormonal vitamin D metabolite 1,25$(OH)_2$D. As shown, the liver is essential in converting vitamin D to 25(OH)D. Within the kidney, it is then further metabolized to 1,25$(OH)_2$D, although it is increasingly being recognized that other organs can convert 25(OH)D to 1,25$(OH)_2$D. Once formed, 1,25$(OH)_2$D can induce both genomic and non-genomic effects mediated by VDR, some of which are illustrated in this diagram. Adapted, under the terms of the original CC-BY licence, from Vuolo *et al.* 2012; and adapted by permission from Springer Nature, *Journal of Pharmaceutical Investigation*, Vitamin D in cancer: effects of pharmaceutical drugs on the vitamin D pharmacokinetics, Soo-Jeong Lim, So Hee Kim, copyright (2014) (Lim & Kim 2014). A full colour version of this figure is available at https://doi.org/10.1530/JOE-18-0541.

widespread but treatable nutrient deficiencies (Holick *et al.* 2011). VDD has been attributed to dietary depletion, insufficient sunlight exposure, adiposity and genetic variants (Ross 2011). Pregnant women are especially at high risk (Fiscaletti *et al.* 2017), and global rates range from 7% in Southern Africa up to 100% in some parts of Northern Europe (Hossein-nezhad & Holick 2013). In the United States (US), up to 80% of pregnant women, including those prescribed prenatal vitamins, are estimated to have low vitamin D status (McAree *et al.* 2013).

VDD during pregnancy is associated with increased risk of gestational diabetes and preeclampsia, which can indirectly affect offspring health (Bodnar *et al.* 2007,

Brannon 2012, Senti *et al.* 2012). It is also associated with direct effects on offspring health such as low birth weight, poor skeletal health, impaired brain development, autoimmune disease, obesity and insulin resistance (Krishnaveni *et al.* 2011, Crozier *et al.* 2012, Reichetzeder *et al.* 2014, Hawes *et al.* 2015, Gur *et al.* 2016, Maia-Ceciliano *et al.* 2016). Recent randomized controlled trials involving vitamin D supplementation in high-risk pregnancies demonstrated decreased cesarean section rate and maternal hospitalization, decreased macrosomia and hospitalization in newborns of women with gestational diabetes (Karamali *et al.* 2016). Favorable effects on insulin metabolism parameters, serum HDL cholesterol and total cholesterol concentrations in women with pre-eclampsia risk factors were also reported (Karamali *et al.* 2015).

Maternal VDD likely impacts offspring health by altering fetal and newborn vitamin D availability. Although 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the primary bioactive form, does not readily cross the placenta, umbilical cord concentrations of its precursor, 25(OH)D, are similar to maternal concentrations (Hillman & Haddad 1974, Fleischman & Cole 1980, Gray *et al.* 1981, Marshall *et al.* 2013). Findings from a recent human study provide evidence that the placenta, working as the interface between mother and fetus, modulates circulating vitamin D metabolites in pregnant women and that it favors the uptake of DBP-bound 25(OH)D3 through a specific receptor system (LRP2-CUBN) (Park *et al.* 2017). In the placenta, CYP27B1 activity is detectable in both maternal decidua and fetal trophoblast, which then allows for local production of 1,25$(OH)_2$D from maternal 25(OH)D via 1-alpha-hydroxylase (Ganguly *et al.* 2018). Likewise, both decidua and trophoblast also express VDR (Liu & Hewison 2012). Placental production of 1,25$(OH)_2$D is proposed to be essential for immunosuppressive effects required for immune tolerance of implantation. However, *ex vivo* and *in vitro* studies provide evidence for a more extensive role of vitamin D in placental function, including trophoblastic differentiation and extravillous trophoblast invasion of the decidua and myometrium (Ganguly *et al.* 2018).

Studies are ongoing to better understand the potential genomic and non-genomic mechanisms responsible for effects of maternal VDD on offspring health (Fig. 1). Vitamin D has both calciotrophic and noncalciotrophic functions (Maalouf 2008). It plays a major role in calcium ion homeostasis by regulating calcium transport and bone mineralization. Noncalciotropic functions of vitamin D occur *via* vitamin D receptor (VDR) activity in many tissues across the body. 1,25$(OH)_2$D acts as a nuclear receptor ligand primarily binding to the vitamin D receptor (VDR) – retinoic X receptor (RXR) complex to activate or repress gene transcription at vitamin D response elements across the genome (Fig. 1). The calciotropic function of vitamin D does not sufficiently explain all the adverse effects of VDD on offspring health since calcium absorption during pregnancy is increased in an estrogen-dependent and vitamin D-independent manner in vitamin D receptor (VDR)-knockout mice (Heaney & Skillman 1971, Van Cromphaut *et al.* 2003, Fudge & Kovacs 2010). Additionally, maternal–fetal calcium transfer in both VDD rats and VDR-knockout mice is unaffected (Glazier & Sibley 1995, Kovacs *et al.* 2005). Thus, VDD-related offspring health outcomes are likely in part due to non-calciotropic functions of vitamin D. However, whether these are direct vs indirect effects and mediated by VDR genomic activity remains unclear.

Recently, the focus on the relationship between maternal VDD and long term offspring health has shifted to roles of vitamin D as a regulatory agent in 'fetal programming' of disease in later life, also termed developmental origins of health and disease (DOHaD) (Brannon 2012, Reichetzeder *et al.* 2014, Chango & Pogribny 2015). Animal models have been designed to elucidate the DOHaD effects of this secosteroid hormone nutrient. The purpose of this review is to discuss the findings, strengths and limitations of DOHaD-focused VDD studies in current and emerging rodent and zebrafish models, primarily as they relate to human metabolic and neurobehavioral health. We also discuss emerging evidence of epigenetic activity of vitamin D and implications of a mechanistic role in DOHaD.

Neurobehavioral health

Recent findings link low vitamin D status to adverse neurological outcomes such as autism spectrum disorder (ASD), schizophrenia, depression, multiple sclerosis and dementia (Eyles *et al.* 2011, 2013, Yates *et al.* 2018). Accumulating evidence suggests that vitamin D is metabolized in various cells within the central nervous system, such as glial cells, neurons and astrocytes (Cui *et al.* 2017). 1,25$(OH)_2$D genomic activity is responsible for activating transcription of genes critical for early brain development (Eyles *et al.* 2011). VDR's regulation of the dopaminergic system implicates a direct association with neurodegenerative diseases (Stednitz *et al.* 2015).

Low vitamin D status, at early developmental stages and throughout adulthood, results in impaired dopamine (DA) turnover (Kesby *et al.* 2009, Pertile *et al.* 2016). Impaired DA turnover can cause oxidative stress, neuron degradation and hyperactivity (Beninger 1983, Nowicki *et al.* 2015, Takeshima *et al.* 2016). Given the essential role of vitamin D in promoting healthy brain development, VDD has been proposed as a contributing factor to neurobehavioral health outcomes such as ASD and attention deficit hyperactivity disorder (ADHD) (Berridge 2018, El-Ansary *et al.* 2018).

Human studies

Autism and ADHD

In an extensive epidemiological study, Childhood Autism Risks from Genetics and the Environment (CHARGE) showed an association between autism spectrum disorders (ASDs) and several functional polymorphisms in genes within the vitamin D pathway, including *Bsm1*, *Taq1*, *Cdx2* and *FokI* in the vitamin D receptor (*VDR*) gene (Schmidt *et al.* 2015). Importantly, this study pinpointed that the genotype AA/A-allele of GC *rs4588*, encoding the vitamin D-binding protein, was strongly associated with ASD in children (Schmidt *et al.* 2015). Additionally, supplementation with high doses of vitamin D (ranging from 300 IU/kg/day to 5000 IU/day) in two open-label trials has been found to improve clinical core symptoms of autism in ~75% of affected children (Cannell 2017).

Assessment of the Generation R study, a population-based cohort of mother–child dyads ($n = 4229$) from Rotterdam, The Netherlands, revealed that gestational VDD (defined by the study as maternal 25(OH)D <25 nmol/L) was associated with an increase in autism-related traits in 6-year-old offspring (Vinkhuyzen *et al.* 2018). Analogous findings were reported with a birth cohort that included 4334 individuals where mid-gestational VDD was associated with increased risk of ASD (Vinkhuyzen *et al.* 2018). A prospective study with 1650 mother–children pairs included as part of the INMA Project (Spain 1997–2008) assessed maternal 25(OH)D concentrations in relation to child ADHD-like symptoms (attention deficit and hyperactivity-impulsivity) evaluated using the ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders fourth edition form. It was found that increasing maternal 25(OH)D concentrations were linked with a lower risk of ADHD-like symptoms in resulting children (Morales *et al.* 2015).

Other neurological disorders

Assessment of later receptive language ability in children aged 5 and 10 born to Caucasian women in Perth, Western Australia discovered that maternal VDD (≤46 nmol/L of 25(OH)D) during pregnancy was associated with higher incidence of later language difficulties in children (Whitehouse *et al.* 2012). It has also been hypothesized that maternal VDD during pregnancy may increase offspring risk for later adult-onset schizophrenia (McGrath 1999). Two studies, Finnish Maternity Cohort and the Nurses' Health Study II, collectively sampled ~ 36,000 mothers and identified a positive link between maternal VDD and risk of adult offspring developing multiple sclerosis (MS) (Mirzaei *et al.* 2011, Munger *et al.* 2016).

Polymorphisms in vitamin D pathway genes such as *VDR* have been shown to affect binding to calciferol and contribute to VDD (Zumaraga *et al.* 2017). Therefore, several studies have also assessed the link between MS and genetic variants in vitamin D pathway genes. However, not all reports agree. A study of Canadian MS patients and unaffected relatives did not detect any significant associations between vitamin D pathway genetic variants that were previously linked to serum 25(OH)D concentrations and disease status (Orton *et al.* 2011). A meta-analysis with 303 Caucasian Spanish MS patients and 310 healthy Caucasian Spanish controls also did not find any association with *VDR* variants *rs2228570* (*Fok1*) or *rs731236* (*Taq1*) and risk of MS (García-Martín *et al.* 2013). In contrast, another study that examined 726 MS patients and 604 controls from the United Kingdom (UK) found that the *VDR Taq1* polymorphism *rs731236* was associated with MS such that there was overrepresentation of the minor allele (C) in MS patients (Cox *et al.* 2012). This latter study also suggested a trend of increasing risk for MS specifically in individuals homozygous for the *HLA-DRB1*501* allele in association with the *Fok1* allele known to generate a more active form of VDR. Genetic variants in *CYP27B1*, which catalyzes the conversion of 25(OH)D to $1,25(OH)_2D$, have also been linked with MS susceptibility. A genome-wide association study performed with 1618 MS patients of European ancestry from Australia and New Zealand and 3412 controls of European ancestry from the UK and US found alleles at the *CYP27B1* variant *rs703842* were associated with increased risk of MS (Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene) 2009). Alleles at *rs703842* were associated with circulating 25(OH)D levels in a study comparing twins concordant or discordant for MS (Orton *et al.* 2008).

Rodent models

Rodent models of VDD during pregnancy reproduce the human condition by depleting the maternal diet of vitamin D and establishing an *in utero* environment deficient in vitamin D. Mouse dams were fed diets lacking vitamin D (0 IU/g of vitamin D) or gradient levels of reduced vitamin D (described below) to induce VDD during critical windows of pre- and perinatal development. VDD effects were assessed by comparing mice on VDD diet to mice on vitamin D-sufficient diets. The exact amount of vitamin D in sufficient diets varies by diet. Various rodent strains have been tested depending on the phenotype of interest to be examined. Outbred (not genetically identical) strains such as Sprague–Dawley rats, Wistar rats or Swiss Webster mice were presumably used to maximize phenotypic robustness, while genetically identical (inbred) mouse strains such as C57BL/6, BALB/c or BTBR were likely used to ensure biological reproducibility. Strains from recombinant inbred mouse lines such as the Collaborative Cross (CC) both maximize phenotypic robustness and ensure reproducibility (Churchill *et al.* 2004). Lines carrying targeted/naturally occurring genetic mutations in genes of interest have also been used to elucidate effects of specific genetic changes in response to VDD.

Learning and memory

Progeny of VDD C57BL/6J dams exhibited later in life impairments in learning and memory, as assessed by an olfactory-based test and smaller lateral ventricles (Fernandes de Abreu *et al.* 2010). Pre- and post-natal VDD increased learning and memory deficits and resulted in elevated depressive-like and anxiety-like behaviors in male mice (Fu *et al.* 2017). Similar learning and memory deficits were reported in male rats subjected to VDD during the perinatal period (Yates *et al.* 2018). Deviations in pup ultrasonic vocalizations reduced social behaviors, and an increase in stereotypical behaviors was also detected in this group, which might be attributed to reduced maternal care provided by VDD dams. One report, however, suggests inbred mice differ in prenatal VDD effects on later neurobehavioral disruptions (Langguth *et al.* 2018). Assessment of the effect of prenatal VDD on autism-related behaviors (ultrasonic vocalizations, social interaction, hyperlocomotion, grooming, rearing and spatial learning and memory) in several inbred mouse models demonstrate significant differences between strains for the behaviors examined (Langguth *et al.* 2018). For example, the C57BL/6J strain and (C57BL/6J × BTBR) F1 hybrid strain were seemingly susceptible to prenatal VDD, while the BALB/c and BTBR mice were less so. C57BL/6J offspring exhibited decreased preference for novel social interactions and the F1 offspring exhibiting hypolocomotive behavior when tested in an open field test (Langguth *et al.* 2018). Such behavioral deficits though were absent in the other two strains. The collective data suggest offspring sex and genotype can interact with prenatal VDD to influence later neurobehavioral outcomes, including cognitive and social impairments.

Neuro-affective disorders

Juvenile progeny of VDD Sprague–Dawley rat dams treated from mating until weaning showed heightened anxiety-like behaviors, as measured by significantly increased grooming frequency compared to other groups when tested in the elevated plus maze (EPM, measures anxiety-like and exploratory behaviors) (Pan *et al.* 2014). Interestingly, juvenile offspring of dams provided an excessive vitamin D diet (10.0 IU/g) also showed significantly increased grooming frequency during social behavior and learning tests (Pan *et al.* 2014). Effects of maternal VDD on anxiety-related behavior appear to be independent of the hypothalamic-pituitary-axis (HPA) with one study showing normal function in rats born to VDD dams (Eyles *et al.* 2006). Instead, the fetal mesencephalon and dopaminergic neurons might be affected by *Nurr1* and *p57Kip2* expression reduced in this brain region of this group (Cui *et al.* 2010).

Emerging zebrafish models

Initial evidence of a canonical role for VDR and the vitamin D endocrine system in calcium ion homeostasis and skeletal maintenance has been demonstrated for some teleost species (Eyles *et al.* 2005). It is likely that aquatic vertebrates also exhibit non-calcemic roles of vitamin D, including induction of xenobiotic metabolism, regulation of cell proliferation and differentiation, regulation of neurodevelopment and immune system function (Nagpal *et al.* 2005, Kollitz *et al.* 2016). Most teleost species express two distinct VDR paralogs (VDRα and VDRβ) (Howarth *et al.* 2008). These receptors exhibit similar functionality to mammalian VDRs, having high-affinity ligand binding and potent receptor transactivation efficacies with $1,25(OH)_2D$ and lithotomic acid as ligands (Kollitz *et al.* 2016).

Emerging zebrafish models of VDD during development pose as valuable tools to study the effects of VDD on neurobehavioral health. Small fish models offer unique advantages over traditional

rodent models, including low maintenance and husbandry costs, high fecundity and ease of developing genetic mutants with the added benefit of reduced animal welfare concerns (Planchart *et al.* 2016). In this regard, the zebrafish model has become a highly utilized animal model for investigating molecular mechanisms of neurodevelopment, cardiovascular disease and obesity.

With regards to neurodevelopment, zebrafish models can be used to assess important behavioral phenotypes due to their well-defined behavioral responses at larval and adult stages, skin transparency during embryonic and early larval developmental stages and a large number of genetic mutants available for testing (Norton 2013). More importantly, since zebrafish have external fertilization and development, a DOHaD zebrafish model of VDD will specifically allow for dissecting important effects of embryonic and early developmental VDD that are independent of maternal metabolism.

Metabolic health

Human studies of later life effects of VDD

In 2012, the WHO estimated that 2.8 million deaths were attributable to obesity and its metabolic sequelae every year (World Health Organization 2017). Although the etiology of obesity is often simplified as an issue of excess caloric intake, there is mounting evidence that *in utero* environment can determine offspring susceptibility to obesity and related metabolic complications in later life (Saffery & Novakovic 2014).

There is no universally accepted definition of the broad term 'metabolic health', however, a combination of assessment criteria including measurements of body weight/composition, blood pressure, serum lipid profile, insulin resistance (IR) and systemic inflammation are frequently used for clinical and research purposes (Phillips & Perry 2013). When using these criteria as terms in searching the existing literature, there exists only a paucity of data on the influence of maternal VDD on offspring metabolic health beyond the *neonatal/first year of life*. The findings are mixed but provide some evidence for a relationship between poor maternal vitamin D status and abnormal metabolic health outcomes such as excess adiposity and insulin resistance.

In the Southampton Women's Survey of 977 pregnant women and their offspring, lower pregnancy 25(OH)D concentrations were significantly linked to higher fat mass assessed at 6 years of age (Crozier *et al.* 2012). Similarly, findings from the Amsterdam Born Children and their Development (ABCD) study of 1882 mother–child pairs observed an inverse relationship between maternal 25(OH)D and offspring percent body fat at 5 years of age (Hrudey *et al.* 2015). This same study also showed inverse associations between maternal 25(OH)D and markers of IR in children whose mothers were overweight during pregnancy (Hrudey *et al.* 2015). Maternal VDD in another large birth cohort involving Indian children likewise predicted higher IR at 9.5 years old (Krishnaveni *et al.* 2011).

Not all cohort data support a connection between pregnancy vitamin D status and metabolic health. In a longitudinal prospective UK study, a weak inverse association was detected between circulating 25(OH)D concentrations during pregnancy and offspring C reactive protein measured in childhood and adolescence (Williams *et al.* 2013). However, no consistent associations were detected between pregnancy serum 25(OH)D concentrations and serum lipids, fasting glucose or fasting insulin at either time point (Williams *et al.* 2013). Neither the Danish D-Tect Case-Cohort Study or the 1988–89 Danish Cohort Study found associations between 25(OH)D concentrations at birth and risk of being overweight at 7 years of age (Jensen *et al.* 2017) or associations between maternal 25(OH)D and offspring cardio-metabolic risk factors (body weight, serum lipids, inflammatory markers and IR) in a 20-year follow-up (Rytter *et al.* 2016).

Metabolomic evidence from a randomized controlled trial

Recently, metabolomic data were used to identify downstream metabolites that are influenced by or interact with 25(OH)D (Blighe 2017). They used metabolomic data from 3-year olds enrolled in the Vitamin D Antenatal Asthma Reduction Trial (VDAART) (Litonjua *et al.* 2014). They identified three distinct subsets/clusters of biologically meaningful metabolic profiles that were distinguished by concentrations of inflammatory mediators (predominantly fatty acids and amines) and maternal vitamin D status postsupplementation. Individuals either had (1) high fatty acids, high amines and low maternal vitamin D status; (2) high amines, intermediate fatty acids and normal maternal vitamin D status or (3) low fatty acids and amines and normal maternal vitamin D status (Blighe 2017). Importantly, maternal vitamin D status had a significant influence on cluster membership. This finding suggests *in utero* vitamin D exposure may be an

important predictor of susceptibility to inflammation and other undesirable metabolic disorders later in life (Blighe 2017).

Important considerations

Maternal weight and fetal growth must be considered in the interpretation of offspring metabolic data collected later in life. Maternal obesity is an independent risk factor for the development of obesity and other metabolic complications in offspring later life (Gaillard 2015, Maffeis & Morandi 2017). Furthermore, pregnant women with excess adiposity are more likely to exhibit VDD as there is a well-established inverse association between body fat mass and serum 25(OH)D concentrations (Lagunova *et al.* 2009, Delle Monache *et al.* 2019). Thus, characterizing metabolic health effects of maternal obesity vs those of maternal VDD is confounded and appears to depend on the outcomes examined. The ABCD study found that only the offspring of overweight women exhibited an association between low maternal 25(OH)D (<29.9 nmol/L) and increased insulin resistance, and there were no interactive effects of pre-pregnancy BMI in the association between low maternal 25(OH)D and increased % body fat in offspring (Hrudey *et al.* 2015).

One theme dominating the literature on maternal VDD is its influence on fetal growth. Although, the specific effects of maternal VDD on fetal growth are dependent on the severity and timing of the deficiency, the preponderance of data show VDD is associated with decreased birth weight and higher risk for 'small for gestational age' (SGA) (Leffelaar *et al.* 2010, Burris *et al.* 2012, Schneuer *et al.* 2014, Eckhardt *et al.* 2015, Miliku *et al.* 2016, Bi *et al.* 2018). This influence complicates the interpretation of results examining the prenatal programming effects of maternal VDD since fetal growth restriction, regardless of its origin, and its subsequent 'catch-up' weight gain are also well known to be related to metabolic health complications (Hales & Ozanne 2003). Thus, the application of animal models can be quite useful in elucidating these complex relationships (Hales & Ozanne 2003).

Rodent models

Support for the role of maternal VDD in fetal programming of later metabolic disorders has been documented in several studies using rodent models subjected to *in utero* VDD (Reichetzeder *et al.* 2014). The majority of these investigations show that offspring of mothers with low serum 25(OH)D during pregnancy present with abnormal metabolic phenotypes later in life most commonly increased fat mass, insulin resistance, hypertension and/or altered fat metabolism.

In one of the earliest transgenerational mouse vitamin D fetal programming studies, compared with controls, 6-month-old F1 generation offspring of VDD dams displayed greater body and epididymal fat mass (Nascimento *et al.* 2013). These mice also had increased insulin secretion when given an oral glucose challenge and showed marked hepatic steatosis. An *in utero* VDD Sprague-Dawley rat model expanded these findings showing a positive correlation between serum inflammatory markers and HOMA-IR in adult (16-week-old) offspring, suggesting that IR might be a result of persistent inflammation (Zhang *et al.* 2014). Furthermore, the finding that progeny of VDD C57BL/6 dams exhibited impaired pancreatic development (smaller) and islet structure (smaller with diminished beta cell mass although overall morphology remained intact) and reduces insulin secretion, suggests that impaired insulin sensitivity in VDD offspring is due to alterations in structure and metabolism of the pancreas (Maia-Ceciliano *et al.* 2016). In support of this conclusion, VDD offspring exhibited a decrease in protein expression of PDK-1, an essential mediator of insulin-signaling in beta-cells (Maia-Ceciliano *et al.* 2016).

$1,25(OH)_2D$ is well known to inhibit the renin-angiotensin system through suppression of renin secretion in the kidney (Li *et al.* 2002) and in pancreatic islets (Cheng *et al.* 2011). However, there are limited data available on the effects of maternal VDD on kidney function. A few rodent studies show elevation in blood pressure in adult offspring of VDD dams (Nascimento *et al.* 2012, Meems *et al.* 2016). This increased blood pressure in progeny of VDD Swiss Webster dams was shown to be related to significant changes in kidney development (poor maturation of glomeruli) and decreased expression of the podocin protein, a key component of the renin-angiotensin system (Nascimento *et al.* 2012). Remarkably, both the F1 generation and F2 generation were negatively affected by maternal VDD (F0 generation). Alternatively, a Sprague–Dawley rat model demonstrated that increased susceptibility for hypertension in offspring of VDD parents is linked to impaired endothelial relaxation in the large vessels and that reduced Panx1 gene expression may contribute to the observed loss of endothelial relaxation (Meems *et al.* 2016).

Another condition related to maternal VDD and metabolic disturbances in offspring is nonalcoholic fatty liver disease (NAFLD) (Hyppönen & Boucher 2018). Since both vitamin D status and NAFLD are associated

with excess adiposity and IR, interest in examining their potential links has grown. This interest has extended into potential DOHaD effects. A recent study used a VDD Wistar rat model to explore this area. F1 generation adult (34 weeks old) female offspring exhibited severe hepatic steatosis, abnormal lipid metabolism, increased markers of inflammation and oxidative stress and downregulation of hepatic *Ppara* and *Ucp2* expression (Sharma *et al.* 2017). Interestingly, male F1 offspring were affected to a lesser extent with only mild hepatic steatosis but showed similar downregulation of *Ucp2* and the positive regulator of oxidative stress superoxide dismutase 1 (*Sod1*), demonstrating sex differences.

Adipogenesis and DOHaD effects

There is evidence that *in utero* adipogenic programming may be associated with obesity later in life (Desai & Ross 2011). In most mammals, including humans, adipose tissue forms throughout the lifespan (Rosen *et al.* 2000). Adipogenesis during fetal development is a complex, yet tightly regulated process involving the proliferation and differentiation of progenitor cells into preadipocytes (vs other cell types such myocytes), and eventually into mature adipocytes when stimulated (Desai *et al.* 2013). Perturbations to the intrauterine environment caused by suboptimal maternal nutrition (e.g. restricted energy and protein intakes) have been shown to lead to dramatic DOHaD effects on this process (Li *et al.* 2010). The specific consequences of maternal VDD, however, are largely unclear and contradictory, although the importance of VDR signaling in adipogenesis is undeniable as VDR-knockout mice exhibit drastic changes in adipose tissue development including reduced adiposity and resistance to diet-induced obesity (Narvaez *et al.* 2009). Moreover, $1,25(OH)_2D$ has been shown to influence several key adipogenic genes and transcription factors (Ding *et al.* 2012). Our lab recently completed a mouse study on the molecular mechanisms by which maternal VDD might influence adipose tissue in offspring (Belenchia *et al.* 2017). In that analysis, relative to controls, 19-week-old male mice born to VDD dams experienced rapid weight gain in the early weeks post weaning and acquired a higher proportion of body fat as depots associated with metabolic complications (visceral fat). Additionally, offspring of VDD dams also had higher expression of perigonadal adipose *Pparg*, a transcript with integral roles in adipogenesis and lipid storage.

Interestingly, a recent VDR-knockout study report did not support a fundamental role for vitamin D in adipogenesis (Schutkowski *et al.* 2018). While VDR knockouts represent a valuable genetic model of completely obliterated genomic vitamin D activity, these models may not recapitulate the consequences of diet-induced VDD, which better mimic human VDD with loss of both genomic and non-genomic effects, allowing also for potential physiological adaptations to low vitamin D provision (Narvaez *et al.* 2009, Kong *et al.* 2013, Narvaez *et al.* 2013). Therefore, caution should be exercised in comparing dietary and genetic models of VDD including systemic depletion, KO or disruption of any gene involved in vitamin D metabolism, transport or function.

Emerging zebrafish models

A putative relationship between vitamin D and obesity in zebrafish has recently been investigated using a *cyp2r1*$^{-/-}$ mutant line (Peng *et al.* 2017). *Cyp2r1* is a liver microsomal hydroxylase essential for the conversion of vitamin D into 25(OH)D. Human genetic variants in *CYP2R1* have been correlated with serum 25(OH)D concentrations in recent genome-wide association studies (Ahn *et al.* 2010, Wang *et al.* 2010). Deficits in this metabolic conversion would be expected to limit serum levels of $1,25(OH)_2D$ since 25(OH)D is the direct precursor. However, despite a >50% reduction in circulating 25(OH)D concentrations in mouse *Cyp2r1*$^{-/-}$ mutants, $1,25(OH)_2D$ levels in *Cyp2r1*$^{-/-}$ mutants were seemingly unaffected and mice were relatively healthy (Zhu *et al.* 2013). This finding strongly implicates additional contributors to this metabolic step in vitamin D activation. Additionally, there are likely localized and tissue-specific differences in 1-alpha-hydroxylase activities that may impart specified paracrine or autocrine functionalities like those observed in human brain pericytes and the epidermis which exhibit functionally active CYP2R1 enzyme activities (El-Atifi *et al.* 2015, Christakos *et al.* 2016).

In contrast to the mouse *Cyp2r1*$^{-/-}$ mutants, zebrafish *cyp2r1*$^{-/-}$ mutants exhibited an almost 70% reduction in circulating $1,25(OH)_2D$ that was completely rescued by 25(OH)D treatment (Peng *et al.* 2017). Zebrafish *cyp2r1*$^{-/-}$ mutants also exhibited an obesity-like phenotype with increased central adiposity (e.g. visceral fat). However, no significant differences in liver triglyceride concentrations, bone density or bone volume were observed (Peng *et al.* 2017), likely due to the incomplete depletion of $1,25(OH)_2D$. While these studies do suggest that vitamin D insufficiency may precede obesity, a causal mechanism has not been established. The ability of vitamin D to impact both preadipocytes and mesenchymal stem cells differentiation toward adipocytes may be one

putative mechanism; however, there are conflicting results on the pro or anti-adipogenic effects of vitamin D depending upon the model utilized (Abbas 2017). Differing effects of VDD on obesity between the mouse *Cyp2r1*$^{-/-}$ and zebrafish *cyp2r1*$^{-/-}$ mutant models highlight the value of assessing and comparing multiple animal models of VDD for the purpose of understanding human health.

Evidence for the role of epigenetic mechanisms

Epigenetic regulation of the genome through changes in DNA and histone modifications and noncoding RNA is an essential component of fetal development, and both the non-genomic and genomic actions of vitamin D can affect such responses. During development, dynamic changes in epigenetic markers such as DNA methylation, DNA hydroxymethylation, posttranslational covalent modifications (e.g. addition of methyl or acetyl groups to histone residues) and numerous types of short and long RNAs regulate the transcriptional activity of genes as cells acquire specific functions. Although select epigenetic marks are malleable throughout development, a subset of epigenetic states is programmed early on and stably maintained into adulthood. These epigenetic programs regulate essential cellular functions including cell metabolism, survival, proliferation and activity (Hemberger *et al.* 2009). Environmental dysregulation leading to the inability to establish or maintain these essential stable epigenetic programs has significant implications for long-term health outcomes (Walker & Ho 2012, Martinez *et al.* 2015, Chen *et al.* 2016, Faa *et al.* 2016).

The role of diet in modulating epigenetic state is well documented. Individual nutrients can act as donors of epigenetic markers, cofactors of epigenetic regulatory enzymes and signaling molecules of epigenetic regulation of transcription (Ideraabdullah & Zeisel 2018). Epigenetic dysregulation as a result of maternal restriction of individual macro- and micro-nutrients has been demonstrated (Ideraabdullah & Zeisel 2018). In some cases, this affects multiple generations (Wolff *et al.* 1998, Radford *et al.* 2014, Nowacka-Woszuk *et al.* 2018). Developing research shows that maternal vitamin D status during pregnancy may determine offspring epigenetic state although whether there are specific windows of susceptibility has not been examined. As illustrated in Fig. 2, VDD-induced epigenetic dysregulation during development represents a potential mechanistic link between maternal VDD and long-term offspring health.

Human studies

Human studies measuring the relationship between maternal vitamin D status and offspring epigenetic states have had differing results. A study performed in cohorts from Norway and the United Kingdom failed to find significant associations between maternal vitamin D status during the second trimester and cord blood DNA methylation at birth (Suderman *et al.* 2016). However, a more recent case/control study of a Midwestern US cohort, reported that maternal supplementation with vitamin D (3800 IU/day vs 400 IU/day) during pre- and post-natal fetal development (starting in the second trimester) resulted in numerous DNA methylation changes in infant leukocytes (Anderson *et al.* 2018). These changes localized to genes involved collagen metabolism, apoptosis, lung and bone development and immune function including loss of DNA methylation at *HLA-A*, an antigen of the major histocompatibility complex (Anderson *et al.* 2018). The differences in outcome between these two studies are possibly due to study design (supplemented vs basal serum vitamin D concentrations, geographical population, cell type assessed and cohort size) or differences in VDD prevalence within the cohort. While the Suderman *et al.* (2016) study reported mean serum 25(OH)D concentrations well within the currently recommended levels of sufficiency (73.5 ± 23.42 ng/mL and 68.3 ± 32.3 ng/mL), Anderson *et al.* (2018) reported much lower mean serum 25(OH)D concentration that decreased for control mothers (32.4 ng/mL–21.9 ng/mL postpartum) and subtly increased for supplemented mothers (31.4 ng/mL–36 ng/mL postpartum).

Association between maternal VDD and offspring epigenetic status at imprinted genes was also assessed recently in humans. Imprinted genes play vital roles in pre- and post-natal development and health (including growth, adiposity and brain development). Assessment of mother–infant dyads in the Newborn Epigenetics Study (NEST) study cohort found that maternal 25(OH)D status measured in the first or second trimester was inversely associated with birthweight z-scores and positively associated with 1-year-old weight-for-length and three-year-old BMI *z*-score (Neelon *et al.* 2018). However, no significant association was detected between maternal 25(OH)D concentrations and cord blood DNA methylation levels at imprinted genes *H19*, *IGF2*, *MEG3*, *MEG3- IG*, *MEST*, *NNAT*, *PEG3*, *PLAGL1* and *SGCE/PEG10* (Neelon *et al.* 2018).

These studies were limited to easily accessible biospecimens like maternal, infant or cord blood.

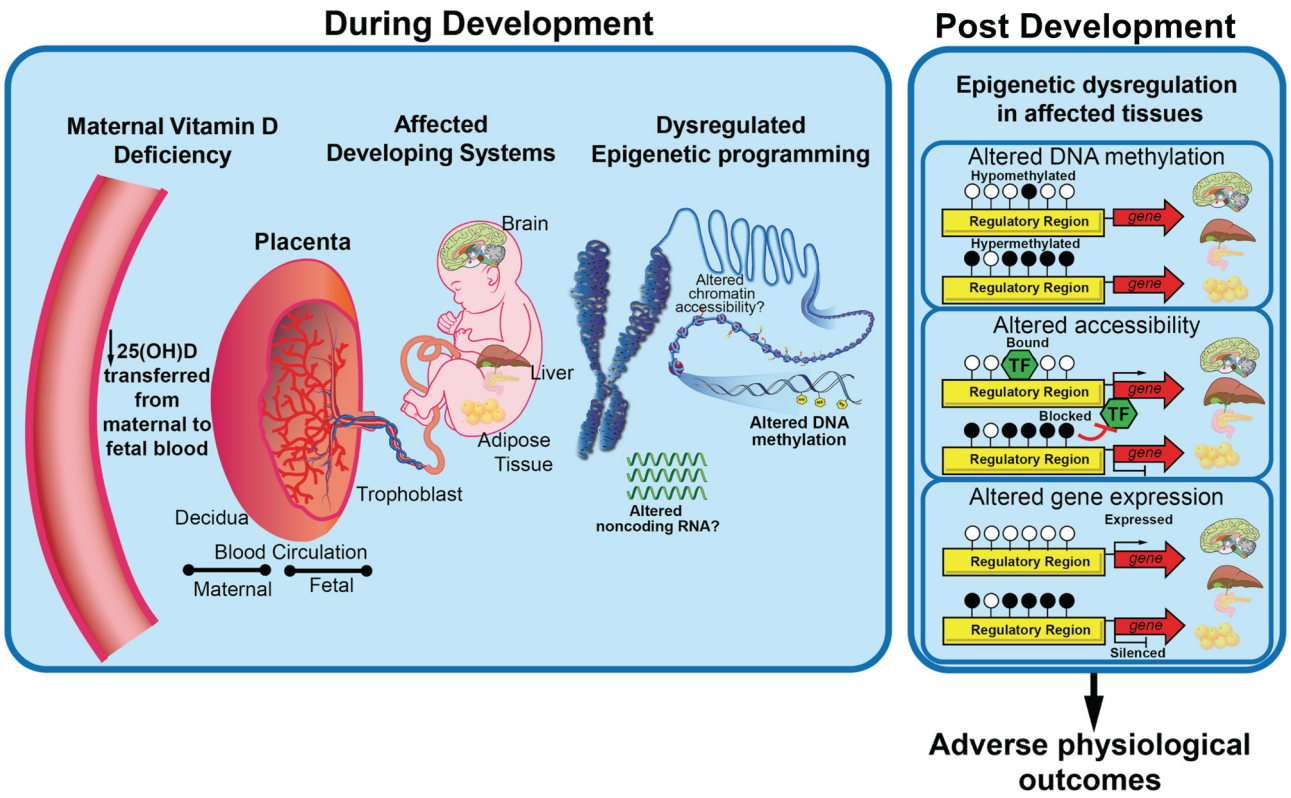

Figure 2

Model of *in utero* VDD-induced epigenetic effects on long-term health outcomes in offspring. Potential pathway of events connecting maternal vitamin D deficiency to offspring health outcomes via epigenetically regulated organ/tissue dysfunction. Decreased availability of maternal 25(OH)D leads to decreased 25(OH)D entering the placenta and thus decreased availability of the $1,25(OH)_2D$ required for genomic (VDR) and non-genomic signaling responses in the fetus. Consequently, fetal VDD potentially disrupts epigenetic programming during development of target organs/tissues such as brain, liver and adipose tissue. Dysregulated epigenetic programming leads to long term altered epigenetic states, which as shown, can disrupt genomic accessibility of regulatory machinery and downstream gene expression resulting in adverse long-term health outcomes in offspring, including neurobehavioral and metabolic disorders. A full colour version of this figure is available at https://doi.org/10.1530/JOE-18-0541.

Interpreting biological relevance of blood epigenetic changes is challenging due to wide variation in cell composition and often hampered by the lack of specific relevance to physiologically affected tissues. Animal models represent a valuable research tool, allowing for a controlled environment and precise dietary manipulation including assessment of discrete exposure windows and collection of tissues/cells from progressive developmental stages.

Rodent models

One of the earliest studies in rodents reported that progeny of VDD Sprague–Dawley dams exhibited a significant increase in global DNA methylation in adult liver (Zhang *et al.* 2014). This corresponded with changes in expression of DNA methyltransferases (*Dnmt1*, *Dnmt3a* and *Dnmt3b*) and glycemic dysregulation including lower glucose tolerance, lower insulin sensitivity and higher levels of hepatic markers of inflammation (Zhang *et al.* 2014). Further examination implicated the role of epigenetically regulated decreases in mRNA and protein levels of nuclear factor κB inhibitor α (IκBα, a key regulator of NFκB-mediated inflammation) (Zhang *et al.* 2014).

A later epigenome-wide DNA methylation study in Sprague–Dawley rats found that offspring of VDD dams exhibited differential methylation in adipose tissue at >800 loci linked to 305 genes (Wen *et al.* 2018). Differential expression was detected at 141 of the differentially methylated genes, including two validated lipid metabolism genes, *Vldlr* and *Hif1α*. These epigenetic and transcriptional changes were linked to obesity- and metabolic dysfunction-related phenotypes in the offspring (Wen *et al.* 2018). A separate epigenome-wide DNA methylation study also in Sprague–Dawley rats reported that progeny of VDD dams exhibited differential methylation at ten genes in the kidney including gain of methylation at Pannexin-1, *Panx1*, which is abundantly

expressed in heart, skeletal muscle and vasculature (Meems *et al.* 2016). No corresponding change in *Panx1* expression was detected in kidney, however, expression was altered in aorta but without any corresponding change in DNA methylation.

Our work recently showed that VDD in the mouse during gestation and lactation, followed by vitamin D sufficient diet at weaning, resulted in DNA methylation changes at imprinted loci across two generations (Xue *et al.* 2016). Furthermore, by comparing offspring from reciprocal crosses of inbred collaborative cross strains (CC001/Unc and CC011/Unc), we also showed that this effect is likely dependent on the maternal strain (Xue *et al.* 2016). For reciprocal crosses, Cross 1 mice were generated by mating CC001 dams to CC011 sires, while Cross 2 mice were generated by mating CC011 dams to CC001 sires. Thus, the maternal genomes and associated uterine environmental conditions differ between crosses, but the offspring are genetically identical (except at mitochondrial DNA and Y chromosome). First-generation offspring from Cross 1 exhibited loss of methylation at *H19/Igf2ICR* and *Grb10DMR* in liver and the latter was correlated with increased bodyweight. However, the genetically identical reciprocal cross (Cross 2) offspring showed no change in bodyweight or methylation at *H19/Igf2ICR* and *Grb10DMR*, but instead showed loss of methylation at *IG-DMR* in sperm (Xue *et al.* 2016). It will be important to determine whether the parent of origin-dependent outcomes are due to an imprinted effect or a maternal effect and whether bodyweight and adiposity changes are linked to subsequent metabolic dysfunction.

Ex vivo models

The impact of vitamin D status on epigenetic mechanisms beyond DNA methylation has been explored mainly in cell culture. $1,25(OH)_2D$ is proposed to interact with and modulate the activity of epigenetic regulatory proteins including chromatin remodeling complexes and histone-modifying enzymes (Fetahu *et al.* 2014). For example, when not bound to its preferred ligand, $1,25(OH)_2D$, VDR has been reported to associate with repressive chromatin remodelers including NCoR1, SMRT/NCoR2 and HDACs (Malinen *et al.* 2008). This would suggest that VDD might create an environment that is conducive to repressive epigenetic effects. On the other hand, supplementation in colon cancer cell lines led to increased expression of *JMJD3/KDM6B*, which demethylates repressive H3K27me2/3 marks (Pereira *et al.* 2011). However, since global H3K27me3 levels were unchanged (Pereira *et al.* 2012), functional impact on histone modifications is unclear. Vitamin D has also been proposed to mediate CTCF-dependent chromatin activity since supplementation in a human leukemic monocyte line (THP-1) caused transient genome-wide changes in chromatin accessibility at 8979 loci, 14% of which overlapped CTCF-binding sites (Seuter *et al.* 2016).

Conclusions

The current animal and human data provide robust evidence that VDD during development exerts important effects on later offspring neurobehavioral and metabolic health. Furthermore, these studies demonstrate the effectiveness of rodent models and potential for emerging zebrafish models as valuable tools poised to answer key mechanistic questions about developmental time points and in target tissues inaccessible in most human studies. To pinpoint how VDD affects individual organs such as the brain, development of conditional genetic models (e.g., VDR-Cre) in rodents and zebrafish will be useful. Epigenetic mechanisms present a promising link between VDD and offspring metabolic and neurobehavioral health outcomes (Fig. 2). Characterizing the impact of VDD-induced epigenetic changes in the genome is important for understanding and developing potential preventative/treatment measures to address VDD-induced effects. The mechanism by which maternal VDD alters offspring epigenetic status and physiological impact of such epigenetic modifications remains uncertain. Nonetheless, human and rodent studies strongly support the role of vitamin D as an effector of DNA methylation with potential dose-dependent effects (Zhu *et al.* 2016) and the ability to rescue methylation-dependent developmental phenotypes (Liu *et al.* 2017). Future studies are needed to elucidate windows of susceptibility, effective timing for intervention by supplementation and genetic population-specific differences in susceptibility. Furthermore, although we have alluded to the impact of VDD on offspring as a direct effect, the indirect role of maternal/intrauterine effects and adverse pregnancy outcomes are also important considerations.

In conclusion, VDD critically affects developmental programming of short- and long-term offspring metabolic and neurobehavioral health, potentially via epigenetic mechanisms. Whether these effects are due to canonical non-genomic or genomic actions of vitamin D remains unclear. Understanding causal mechanisms leading to adverse health in sons and daughters born to VDD

mothers is essential for early diagnoses and improving treatment during pregnancy to prevent later adverse DOHaD effects in at-risk offspring.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement
Manuscript sections were drafted by F.Y.I. (Abstract and Evidence for the role of epigenetic mechanisms and Discussion sections); C.A.P, A.M.B (Introduction and Metabolic health sections on human and rodent studies); CSR (Neurobehavioral health sections on human and rodent studies); S.W.K, M.K., D.M., M.B. and E.D.L. (Neurobehavioral health and Metabolic health sections on zebrafish studies, including generation of unpublished data). All authors contributed to revisions and have read and approved this manuscript for publication.

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