REVIEW

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)₂D) 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)₂D via the 1- α -hydroxylase CYP27B1. However, extrarenal expression of CYP27B1 also generates 1,25(OH)₂D 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)₂D. 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)₂D, although it is increasingly being recognized that other organs can convert 25(OH)D to 1,25(OH)₂D. Once formed, 1,25(OH)₂D 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 [$1,25(\text{OH})_2\text{D}$], the primary bioactive form, does not readily cross the placenta, umbilical cord concentrations of its precursor, $25(\text{OH})\text{D}$, 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 $25(\text{OH})\text{D}$ 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 $1,25(\text{OH})_2\text{D}$ from maternal $25(\text{OH})\text{D}$ via 1- α -hydroxylase (Ganguly *et al.* 2018). Likewise, both decidua and trophoblast also express VDR (Liu & Hewison 2012). Placental production of $1,25(\text{OH})_2\text{D}$ 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 calcitrophic and noncalcitrophic functions (Maalouf 2008). It plays a major role in calcium ion homeostasis by regulating calcium transport and bone mineralization. Noncalcitrophic functions of vitamin D occur *via* vitamin D receptor (VDR) activity in many tissues across the body. $1,25(\text{OH})_2\text{D}$ 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 calcitrophic 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-calcitrophic 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). $1,25(\text{OH})_2\text{D}$ 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* (*FokI*) or *rs731236* (*TaqI*) 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* *TaqI* 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 *FokI* 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 (VDR α and VDR β) (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) $_2$ D and lithocholic 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, Schnerer *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 (Reichetzedler *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 as 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- α -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-Woszek *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 κ B inhibitor α (I κ B α , a key regulator of NF κ B-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 *Hif1a*. 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. $1,25(\text{OH})_2\text{D}$ 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, $1,25(\text{OH})_2\text{D}$, 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 H3K27me_{2/3} 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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References

- Abbas MA 2017 Physiological functions of vitamin D in adipose tissue. *Journal of Steroid Biochemistry and Molecular Biology* **165** 369–381. (<https://doi.org/10.1016/j.jsmb.2016.08.004>)
- Adams JS & Hewison M 2012 Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. *Archives of Biochemistry and Biophysics* **523** 95–102. (<https://doi.org/10.1016/j.abb.2012.02.016>)
- Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, Gallicchio L, Jacobs EJ, Ascherio A, Helzlsouer K, Jacobs KB, *et al.* 2010 Genome-wide association study of circulating vitamin D levels. *Human Molecular Genetics* **19** 2739–2745. (<https://doi.org/10.1093/hmg/ddq155>)
- Anderson CM, Gillespie SL, Thiele DK, Ralph JL & Ohm JE 2018 Effects of maternal vitamin D supplementation on the maternal and infant epigenome. *Breastfeeding Medicine* **13** 371–380. (<https://doi.org/10.1089/bfm.2017.0231>)
- Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene) 2009 Genome-wide association study identifies new multiple sclerosis susceptibility loci on chromosomes 12 and 20. *Nature Genetics* **41** 824–828. (<https://doi.org/10.1038/ng.396>)
- Belenchia AM, Johnson SA, Ellersieck MR, Rosenfeld CS & Peterson CA 2017 In utero vitamin D deficiency predisposes offspring to long-term adverse adipose tissue effects. *Journal of Endocrinology* **234** 301–313. (<https://doi.org/10.1530/JOE-17-0015>)
- Beninger RJ 1983 The role of dopamine in locomotor activity and learning. *Brain Research* **287** 173–196. ([https://doi.org/10.1016/0165-0173\(83\)90038-3](https://doi.org/10.1016/0165-0173(83)90038-3))
- Berridge MJ 2018 Vitamin D deficiency: infertility and neurodevelopmental diseases (attention deficit hyperactivity disorder, autism, and schizophrenia) *American Journal of Physiology: Cell Physiology* **314** C135–C151. (<https://doi.org/10.1152/ajpcell.00188.2017>)
- Bi WG, Nuyt AM, Weiler H, Leduc L, Santamaria C & Wei SQ 2018 Association between vitamin D supplementation during pregnancy and offspring growth, morbidity, and mortality: A systematic review and meta-analysis. *JAMA Pediatrics* **172** 635–645. (<https://doi.org/10.1001/jamapediatrics.2018.0302>)
- Blighe K, Chawes BL, Kelly RS, Mirzakhani H, McGeachie M, Litonjua AA, Weiss ST & Lasky-Su JA 2017 Vitamin D prenatal programming of childhood metabolomics profiles at age 3 y. *American Journal of Clinical Nutrition* **106** 1092–1099. (<https://doi.org/10.3945/ajcn.117.158220>)
- Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW & Roberts JM 2007 Maternal vitamin D deficiency increases the risk of preeclampsia. *Journal of Clinical Endocrinology and Metabolism* **92** 3517–3522. (<https://doi.org/10.1210/jc.2007-0718>)
- Brannon PM 2012 Vitamin D and adverse pregnancy outcomes: beyond bone health and growth. *Proceedings of the Nutrition Society* **71** 205–212. (<https://doi.org/10.1017/S0029665111003399>)
- Burris HH, Rifas-Shiman SL, Camargo CAJ, Litonjua AA, Huh SY, Rich-Edwards JW & Gillman MW 2012 Plasma 25-hydroxyvitamin D during pregnancy and small-for-gestational age in black and white infants. *Annals of Epidemiology* **22** 581–586. (<https://doi.org/10.1016/j.annepidem.2012.04.015>)
- Cannell JJ 2017 Vitamin D and autism, what's new? *Reviews in Endocrine and Metabolic Disorders* **18** 183–193. (<https://doi.org/10.1007/s11154-017-9409-0>)
- Chango A & Pogribny IP 2015 Considering maternal dietary modulators for epigenetic regulation and programming of the fetal epigenome. *Nutrients* **7** 2748–2770. (<https://doi.org/10.3390/nu7042748>)
- Chen T, Liu HX, Yan HY, Wu DM & Ping J 2016 Developmental origins of inflammatory and immune diseases. *Molecular Human Reproduction* **22** 858–865. (<https://doi.org/10.1093/molehr/gaw036>)
- Cheng Q, Li YC, Boucher BJ & Leung PS 2011 A novel role for vitamin D: modulation of expression and function of the local renin-angiotensin system in mouse pancreatic islets. *Diabetologia* **54** 2077–2081. (<https://doi.org/10.1007/s00125-011-2100-1>)
- Christakos S, Dhawan P, Verstuyf A, Verlinden L & Carmeliet G 2016 Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiological Reviews* **96** 365–408. (<https://doi.org/10.1152/physrev.00014.2015>)
- Churchill GA, Airey DC, Allayee H, Angel JM, Attie AD, Beatty J, Beavis WD, Belknap JK, Bennett B, Berrettini W, *et al.* 2004 The Collaborative Cross, a community resource for the genetic analysis of complex traits. *Nature Genetics* **36** 1133–1137. (<https://doi.org/10.1038/ng1104-1133>)
- Cox MB, Ban M, Bowden NA, Baker A, Scott RJ & Lechner-Scott J 2012 Potential association of vitamin D receptor polymorphism Taq1 with multiple sclerosis. *Multiple Sclerosis Journal* **18** 16–22. (<https://doi.org/10.1177/1352458511415562>)
- Crozier SR, Harvey NC, Inskip HM, Godfrey KM, Cooper C, Robinson SM & SWS Study Group 2012 Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. *American Journal of Clinical Nutrition* **96** 57–63. (<https://doi.org/10.3945/ajcn.112.037473>)
- Cui X, Pelekanos M, Burne TH, McGrath JJ & Eyles DW 2010 Maternal vitamin D deficiency alters the expression of genes involved in dopamine specification in the developing rat mesencephalon. *Neuroscience Letters* **486** 220–223. (<https://doi.org/10.1016/j.neulet.2010.09.057>)

- Cui X, Gooch H, Petty A, McGrath JJ & Eyles D 2017 Vitamin D and the brain: genomic and non-genomic actions. *Molecular and Cellular Endocrinology* **453** 131–143. (<https://doi.org/10.1016/j.mce.2017.05.035>)
- Delle Monache S, Di Fulvio P, Iannetti E, Valerii L, Capone L, Nespoli MG, Bologna M & Angelucci A 2019 Body mass index represents a good predictor of vitamin D status in women independently from age. *Clinical Nutrition* **38** 829–834. (<https://doi.org/10.1016/j.clnu.2018.02.024>)
- Desai M & Ross MG 2011 Fetal programming of adipose tissue: effects of intrauterine growth restriction and maternal obesity/high-fat diet. *Seminars in Reproductive Medicine* **29** 237–245. (<https://doi.org/10.1055/s-0031-1275517>)
- Desai M, Beall M & Ross MG 2013 Developmental origins of obesity: programmed adipogenesis. *Current Diabetes Reports* **13** 27–33. (<https://doi.org/10.1007/s11892-012-0344-x>)
- Ding C, Gao D, Wilding J, Trayhurn P & Bing C 2012 Vitamin D signalling in adipose tissue. *British Journal of Nutrition* **108** 1915–1923. (<https://doi.org/10.1017/S0007114512003285>)
- Eckhardt CL, Gernand AD, Roth DE & Bodnar LM 2015 Maternal vitamin D status and infant anthropometry in a US multi-centre cohort study. *Annals of Human Biology* **42** 215–222. (<https://doi.org/10.3109/03014460.2014.954616>)
- El-Ansary A, Cannell JJ, Bjorklund G, Bhat RS, Dbass AI AM, Alfawaz HA, Chirumbolo S & Al-Ayadhi L 2018 In the search for reliable biomarkers for the early diagnosis of autism spectrum disorder: the role of vitamin D. *Metabolic Brain Disease* **33** 917–931. (<https://doi.org/10.1007/s11011-018-0199-1>)
- El-Atifi M, Dreyfus M, Berger F & Wion D 2015 Expression of CYP2R1 and VDR in human brain pericytes: the neurovascular vitamin D autocrine/paracrine model. *NeuroReport* **26** 245–248. (<https://doi.org/10.1097/WNR.0000000000000328>)
- Eyles DW, Smith S, Kinobe R, Hewison M & McGrath JJ 2005 Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *Journal of Chemical Neuroanatomy* **29** 21–30. (<https://doi.org/10.1016/j.jchemneu.2004.08.006>)
- Eyles DW, Rogers F, Buller K, McGrath JJ, Ko P, French K & Burne THJ 2006 Developmental vitamin D (DVD) deficiency in the rat alters adult behaviour independently of HPA function. *Psychoneuroendocrinology* **31** 958–964. (<https://doi.org/10.1016/j.psyneuen.2006.05.006>)
- Eyles D, Burne T & McGrath J 2011 Vitamin D in fetal brain development. *Seminars in Cell and Developmental Biology* **22** 629–636. (<https://doi.org/10.1016/j.semcdb.2011.05.004>)
- Eyles DW, Burne TH & McGrath JJ 2013 Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Frontiers in Neuroendocrinology* **34** 47–64. (<https://doi.org/10.1016/j.yfrne.2012.07.001>)
- Faa G, Manchia M, Pintus R, Gerosa C, Marcalis MA & Fanos V 2016 Fetal programming of neuropsychiatric disorders. *Birth Defects Research. Part C, Embryo Today* **108** 207–223. (<https://doi.org/10.1002/bdrc.21139>)
- Fernandes de Abreu DA, Nivet E, Baril N, Khrestchatsky M, Roman F & Feron F 2010 Developmental vitamin D deficiency alters learning in C57Bl/6j mice. *Behavioural Brain Research* **208** 603–608. (<https://doi.org/10.1016/j.bbr.2010.01.005>)
- Fetahu IS, Höbaus J & Kállay E 2014 Vitamin D and the epigenome. *Frontiers in Physiology* **5** 164. (<https://doi.org/10.3389/fphys.2014.00164>)
- Fiscaletti M, Stewart P & Munns CF 2017 The importance of vitamin D in maternal and child health: a global perspective. *Public Health Reviews* **38** 19. (<https://doi.org/10.1186/s40985-017-0066-3>)
- Fleischman AR & Cole J 1980 Maternal and fetal serum 1,25-dihydroxyvitamin D levels at term. *Jurnalul Pediatruilui* **97** 640–642. ([https://doi.org/10.1016/S0022-3476\(80\)80030-8](https://doi.org/10.1016/S0022-3476(80)80030-8))
- Fu L, Chen YH, Chen X, Xu S, Yu Z & Xu DX 2017 Vitamin D deficiency impairs neurobehavioral development in male mice. *Physiology and Behavior* **179** 333–339. (<https://doi.org/10.1016/j.physbeh.2017.07.017>)
- Fudge NJ & Kovacs CS 2010 Pregnancy up-regulates intestinal calcium absorption and skeletal mineralization independently of the vitamin D receptor. *Endocrinology* **151** 886–895. (<https://doi.org/10.1210/en.2009-1010>)
- Gaillard R 2015 Maternal obesity during pregnancy and cardiovascular development and disease in the offspring. *European Journal of Epidemiology* **30** 1141–1152. (<https://doi.org/10.1007/s10654-015-0085-7>)
- Ganguly A, Tamblyn JA, Finn-Sell S, Chan SY, Westwood M, Gupta J, Kilby MD, Gross SR & Hewison M 2018 Vitamin D, the placenta and early pregnancy: effects on trophoblast function. *Journal of Endocrinology* **236** R93–R103. (<https://doi.org/10.1530/JOE-17-0491>)
- García-Martín E, Agúndez JAG, Martínez C, Benito-León J, Millán-Pascual J, Calleja P, Díaz-Sánchez M, Pisa D, Turpín-Fenoll L, Alonso-Navarro H, *et al.* 2013 Vitamin D3 receptor (VDR) gene rs2228570 (FokI) and rs731236 (TaqI) variants are not associated with the risk for multiple sclerosis: results of a new study and a meta-analysis. *PLoS ONE* **8** e65487. (<https://doi.org/10.1371/journal.pone.0065487>)
- Glazier JD, Mawer EB & Sibley CP 1995 Calbindin-D9K gene expression in rat chorioallantoic placenta is not regulated by 1,25-dihydroxyvitamin D3. *Pediatric Research* **37** 720–725. (<https://doi.org/10.1203/00006450-199506000-00008>)
- Gray TK, Lowe W & Lester GE 1981 Vitamin D and pregnancy: the maternal-fetal metabolism of vitamin D. *Endocrine Reviews* **2** 264–274. (<https://doi.org/10.1210/edrv-2-3-264>)
- Gur EB, Gur MS, Ince O, Kasap E, Genc M, Tatar S, Bugday S, Turan GA & Guclu S 2016 Vitamin D deficiency in pregnancy may affect fetal thymus development. *Ginekologia Polska* **87** 378–383. (<https://doi.org/10.5603/GP.2016.0008>)
- Hales CN & Ozanne SE 2003 The dangerous road of catch-up growth. *Journal of Physiology* **547** 5–10. (<https://doi.org/10.1113/jphysiol.2002.024406>)
- Hawes JE, Tesic D, Whitehouse AJ, Zosky GR, Smith JT & Wyrwoll CS 2015 Maternal vitamin D deficiency alters fetal brain development in the BALB/c mouse. *Behavioural Brain Research* **286** 192–200. (<https://doi.org/10.1016/j.bbr.2015.03.008>)
- Heaney RP & Skillman TG 1971 Calcium metabolism in normal human pregnancy. *Journal of Clinical Endocrinology and Metabolism* **33** 661–670. (<https://doi.org/10.1210/jcem-33-4-661>)
- Hemmerger M, Dean W & Reik W 2009 Epigenetic dynamics of stem cells and cell lineage commitment: digging Waddington's canal. *Nature Reviews Molecular Cell Biology* **10** 526–537. (<https://doi.org/10.1038/nrm2727>)
- Hillman LS & Haddad JG 1974 Human perinatal vitamin D metabolism. I. 25-Hydroxyvitamin D in maternal and cord blood. *Journal of Pediatrics* **84** 742–749. ([https://doi.org/10.1016/S0022-3476\(74\)80024-7](https://doi.org/10.1016/S0022-3476(74)80024-7))
- Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM & Endocrine Society 2011 Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* **96** 1911–1930. (<https://doi.org/10.1210/jc.2011-0385>)
- Hossein-nezhad A & Holick MF 2013 Vitamin D for health: a global perspective. *Mayo Clinic Proceedings* **88** 720–755. (<https://doi.org/10.1016/j.mayocp.2013.05.011>)
- Howarth DL, Law SHW, Barnes B, Hall JM, Hinton DE, Moore L, Maglich JM, Moore JT & Kullman SW 2008 Paralogous vitamin D receptors in teleosts: transition of nuclear receptor function. *Endocrinology* **149** 2411–2422. (<https://doi.org/10.1210/en.2007-1256>)
- Brudey EJ, Reynolds RM, Oostvogels AJM, Brouwer IA & Vrijkotte TGM 2015 The association between maternal 25-hydroxyvitamin D

- concentration during gestation and early childhood cardio-metabolic outcomes: is there interaction with pre-pregnancy BMI? *PLoS ONE* **10** e0133313. (<https://doi.org/10.1371/journal.pone.0133313>)
- Hyppönen E & Boucher BJ 2018 Adiposity, vitamin D requirements, and clinical implications for obesity-related metabolic abnormalities. *Nutrition Reviews* **76** 678–692. (<https://doi.org/10.1093/nutrit/nuy034>)
- Ideraabdullah FY & Zeisel SH 2018 Dietary modulation of the epigenome. *Physiological Reviews* **98** 667–695. (<https://doi.org/10.1152/physrev.00010.2017>)
- Jensen CB, Lundqvist M, Sorensen TIA & Heitmann BL 2017 Neonatal vitamin D levels in relation to risk of overweight at 7 years in the Danish D-Tect case-cohort study. *Obesity Facts* **10** 273–283. (<https://doi.org/10.1159/000471881>)
- Karamali M, Beihaghi E, Mohammadi AA & Asemi Z 2015 Effects of high-dose vitamin D supplementation on metabolic status and pregnancy outcomes in pregnant women at risk for pre-eclampsia. *Hormone and Metabolic* **47** 867–872. (<https://doi.org/10.1055/s-0035-1548835>)
- Karamali M, Asemi Z, Ahmadi-Dastjerdi M & Esmailzadeh A 2016 Calcium plus vitamin D supplementation affects pregnancy outcomes in gestational diabetes: randomized, double-blind, placebo-controlled trial. *Public Health Nutrition* **19** 156–163. (<https://doi.org/10.1017/S1368980015000609>)
- Kesby JP, Cui X, Ko P, McGrath JJ, Burne THJ & Eyles DW 2009 Developmental vitamin D deficiency alters dopamine turnover in neonatal rat forebrain. *Neuroscience Letters* **461** 155–158. (<https://doi.org/10.1016/j.neulet.2009.05.070>)
- Kollitz EM, Zhang G, Hawkins MB, Whitfield GK, Reif DM & Kullman SW 2016 Evolutionary and functional diversification of the vitamin D receptor-lithocholic acid partnership. *PLoS ONE* **11** e0168278. (<https://doi.org/10.1371/journal.pone.0168278>)
- Kong J, Chen Y, Zhu G, Zhao Q & Li YC 2013 1,25-Dihydroxyvitamin D3 upregulates leptin expression in mouse adipose tissue. *Journal of Endocrinology* **216** 265–271. (<https://doi.org/10.1530/JOE-12-0344>)
- Kovacs CS, Woodland ML, Fudge NJ & Friel JK 2005 The vitamin D receptor is not required for fetal mineral homeostasis or for the regulation of placental calcium transfer in mice. *American Journal of Physiology: Endocrinology and Metabolism* **289** E133–E144. (<https://doi.org/10.1152/ajpendo.00354.2004>)
- Krishnaveni GV, Veena SR, Winder NR, Hill JC, Noonan K, Boucher BJ, Karat SC & Fall CH 2011 Maternal vitamin D status during pregnancy and body composition and cardiovascular risk markers in Indian children: the Mysore Parthenon Study. *American Journal of Clinical Nutrition* **93** 628–635. (<https://doi.org/10.3945/ajcn.110.003921>)
- Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S & Moan J 2009 The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Research* **29** 3713–3720. (<https://doi.org/10.14341/2071-8713-4886>)
- Langguth M, Fassin M, Alexander S, Turner KM & Burne THJ 2018 No effect of prenatal vitamin D deficiency on autism-relevant behaviours in multiple inbred strains of mice. *Behavioural Brain Research* **348** 42–52. (<https://doi.org/10.1016/j.bbr.2018.04.004>)
- Leffelaar ER, Vrijkotte TGM & van Eijsden M 2010 Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. *British Journal of Nutrition* **104** 108–117. (<https://doi.org/10.1017/S000711451000022X>)
- Li YC, Kong J, Wei M, Chen ZF, Liu SQ & Cao LP 2002 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *Journal of Clinical Investigation* **110** 229–238. (<https://doi.org/10.1172/JCI15219>)
- Li CCY, Maloney CA, Cropley JE & Suter CM 2010 Epigenetic programming by maternal nutrition: shaping future generations. *Epigenomics* **2** 539–549. (<https://doi.org/10.2217/epi.10.33>)
- Lim S-J & Kim SH 2014 Vitamin D in cancer: effects of pharmaceutical drugs on the vitamin D pharmacokinetics. *Journal of Pharmaceutical Investigation* **44** 317–328. (<https://doi.org/10.1007/s40005-014-0147-y>)
- Litonjua AA, Lange NE, Carey VJ, Brown S, Laranjo N, Harshfield BJ, O'Connor GT, Sandel M, Strunk RC, Bacharier LB, *et al.* 2014 The vitamin D Antenatal Asthma Reduction Trial (VDAART): rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children. *Contemporary Clinical Trials* **38** 37–50. (<https://doi.org/10.1016/j.cct.2014.02.006>)
- Liu NQ & Hewison M 2012 Vitamin D, the placenta and pregnancy. *Archives of Biochemistry and Biophysics* **523** 37–47. (<https://doi.org/10.1016/j.abb.2011.11.018>)
- Liu C, Chen Z, Li W, Huang L & Zhang Y 2017 Vitamin D enhances alveolar development in antenatal lipopolysaccharide-treated rats through the suppression of interferon- γ production. *Frontiers in Immunology* **8** 1923. (<https://doi.org/10.3389/fimmu.2017.01923>)
- Maalouf NM 2018 The non-calcitropic actions of vitamin D: recent clinical developments. *Current Opinion in Nephrology and Hypertension* **17** 408–415. (<https://doi.org/10.1097/MNH.0b013e3283040c99>)
- Maffei C & Morandi A 2017 Effect of maternal obesity on foetal growth and metabolic health of the offspring. *Obesity Facts* **10** 112–117. (<https://doi.org/10.1159/000456668>)
- Maia-Ceciliano TC, Barreto-Vianna AR, Barbosa-da-Silva S, Aguilu MB, Faria TS & Mandarim-de-Lacerda CA 2016 Maternal vitamin D-restricted diet has consequences in the formation of pancreatic islet/insulin-signaling in the adult offspring of mice. *Endocrine* **54** 60–69. (<https://doi.org/10.1007/s12020-016-0973-y>)
- Malinen M, Saramäki A, Ropponen A, Degenhardt T, Vaisänen S & Carlberg C 2008 Distinct HDACs regulate the transcriptional response of human cyclin-dependent kinase inhibitor genes to Trichostatin A and 1 α ,25-dihydroxyvitamin D3. *Nucleic Acids Research* **36** 121–132. (<https://doi.org/10.1093/nar/gkm913>)
- Marshall I, Mehta R & Petrova A 2013 Vitamin D in the maternal-fetal-neonatal interface: clinical implications and requirements for supplementation. *Journal of Maternal-Fetal and Neonatal Medicine* **26** 633–638. (<https://doi.org/10.3109/14767058.2012.746306>)
- Martinez SR, Gay MS & Zhang L 2015 Epigenetic mechanisms in heart development and disease. *Drug Discovery Today* **20** 799–811. (<https://doi.org/10.1016/j.drudis.2014.12.018>)
- McAree T, Jacobs B, Manickavasagar T, Sivalokanathan S, Brennan L, Bassett P, Rainbow S & Blair M 2013 Vitamin D deficiency in pregnancy - still a public health issue. *Maternal and Child Nutrition* **9** 23–30. (<https://doi.org/10.1111/mcn.12014>)
- McGrath J 1999 Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophrenia Research* **40** 173–177. ([https://doi.org/10.1016/S0920-9964\(99\)00052-3](https://doi.org/10.1016/S0920-9964(99)00052-3))
- Meems LMG, Mahmud H, Buikema H, Tost J, Michel S, Takens J, Verkaik-Schakel RN, Vreeswijk-Baudoin I, Mateo-Leach IV, van der Harst P, *et al.* 2016 Parental vitamin D deficiency during pregnancy is associated with increased blood pressure in offspring via Panx1 hypermethylation. *American Journal of Physiology: Heart and Circulatory Physiology* **311** H1459–H1469. (<https://doi.org/10.1152/ajpheart.00141.2016>)
- Miliku K, Vinkhuyzen A, Blanken LM, McGrath JJ, Eyles DW, Burne TH, Hofman A, Tiemeier H, Steegers EA, Gaillard R, *et al.* 2016 Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes. *American Journal of Clinical Nutrition* **103** 1514–1522. (<https://doi.org/10.3945/ajcn.115.123752>)
- Mirzaei F, Michels KB, Munger K, O'Reilly E, Chitnis T, Forman MR, Giovannucci E, Rosner B & Ascherio A 2011 Gestational vitamin D and the risk of multiple sclerosis in offspring. *Annals of Neurology* **70** 30–40. (<https://doi.org/10.1002/ana.22456>)
- Morales E, Julvez J, Torrent M, Ballester F, Rodríguez-Bernal CL, Andiaarena A, Vegas O, Castilla AM, Rodríguez-Dehli C, Tardón A, *et al.* 2015 Vitamin D in pregnancy and attention deficit hyperactivity

- disorder-like symptoms in childhood. *Epidemiology* **26** 458–465. (<https://doi.org/10.1097/EDE.0000000000000292>)
- Munger KL, Aivo J, Hongell K, Soilu-Hänninen M, Surcel HM & Ascherio A 2016 Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the Finnish maternity cohort. *JAMA Neurology* **73** 515–519. (<https://doi.org/10.1001/jamaneurol.2015.4800>)
- Nagpal S, Na S & Rathnachalam R 2005 Noncalcemic actions of vitamin D receptor ligands. *Endocrine Reviews* **26** 662–687. (<https://doi.org/10.1210/er.2004-0002>)
- Narvaez CJ, Matthews D, Broun E, Chan M & Welsh J 2009 Lean phenotype and resistance to diet-induced obesity in vitamin D receptor knockout mice correlates with induction of uncoupling protein-1 in white adipose tissue. *Endocrinology* **150** 651–661. (<https://doi.org/10.1210/en.2008-1118>)
- Narvaez CJ, Simmons KM, Brunton J, Salinero A, Chittur SV & Welsh JE 2013 Induction of STEAP4 correlates with 1,25-dihydroxyvitamin D3 stimulation of adipogenesis in mesenchymal progenitor cells derived from human adipose tissue. *Journal of Cellular Physiology* **228** 2024–2036. (<https://doi.org/10.1002/jcp.24371>)
- Nascimento FAM, Ceciliano TC, Aguila MB & Mandarim-de-Lacerda CA 2012 Maternal vitamin D deficiency delays glomerular maturity in F1 and F2 offspring. *PLoS ONE* **7** e41740. (<https://doi.org/10.1371/journal.pone.0041740>)
- Nascimento FAM, Ceciliano TC, Aguila MB & Mandarim-de-Lacerda CA 2013 Transgenerational effects on the liver and pancreas resulting from maternal vitamin D restriction in mice. *Journal of Nutritional Science and Vitaminology* **59** 367–374. (<https://doi.org/10.3177/jnsv.59.367>)
- Neelon SEB, White AJ, Vidal AC, Schildkraut JM, Murtha AP, Murphy SK, Kullman SW & Hoyo C 2018 Maternal vitamin D, DNA methylation at imprint regulatory regions and offspring weight at birth, 1 year and 3 years. *International Journal of Obesity* **42** 587–593. (<https://doi.org/10.1038/ijo.2017.160>)
- Norton WHJ 2013 Toward developmental models of psychiatric disorders in zebrafish. *Frontiers in Neural Circuits* **7** 79. (<https://doi.org/10.3389/fncir.2013.00079>)
- Nowacka-Woszek J, Szczerbal I, Malinowska AM & Chmurzynska A 2018 Transgenerational effects of prenatal restricted diet on gene expression and histone modifications in the rat. *PLoS ONE* **13** e0193464. (<https://doi.org/10.1371/journal.pone.0193464>)
- Nowicki M, Tran S, Chatterjee D & Gerlai R 2015 Inhibition of phosphorylated tyrosine hydroxylase attenuates ethanol-induced hyperactivity in adult zebrafish (*Danio rerio*) *Pharmacology, Biochemistry, and Behavior* **138** 32–39. (<https://doi.org/10.1016/j.pbb.2015.09.008>)
- Orton SM, Morris AP, Herrera BM, Ramagopalan SV, Lincoln MR, Chao MJ, Vieth R, Sadovnick AD & Ebers GC 2008 Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis. *American Journal of Clinical Nutrition* **88** 441–447. (<https://doi.org/10.1093/ajcn/88.2.441>)
- Orton SM, Ramagopalan SV, Para AE, Lincoln MR, Handunnetthi L, Chao MJ, Morahan J, Morrison KM, Sadovnick AD & Ebers GC 2011 Vitamin D metabolic pathway genes and risk of multiple sclerosis in Canadians. *Journal of the Neurological Sciences* **305** 116–120. (<https://doi.org/10.1016/j.jns.2011.02.032>)
- Pan P, Jin DHS, Chatterjee-Chakraborty M, Halievski K, Lawson D, Remedios D, Smetka C, Pinto V, Parra E & Fleming AS 2014 The effects of vitamin D₃ during pregnancy and lactation on offspring physiology and behavior in sprague-dawley rats. *Developmental Psychobiology* **56** 12–22. (<https://doi.org/10.1002/dev.21086>)
- Park H, Wood MR, Malysheva OV, Jones S, Mehta S, Brannon PM & Caudill MA 2017 Placental vitamin D metabolism and its associations with circulating vitamin D metabolites in pregnant women. *American Journal of Clinical Nutrition* **106** 1439–1448. (<https://doi.org/10.3945/ajcn.117.153429>)
- Peng X, Shang G, Wang W, Chen X, Lou Q, Zhai G, Li D, Du Z, Ye Y, Jin X, *et al.* 2017 Fatty acid oxidation in zebrafish adipose tissue is promoted by 1 α ,25(OH)₂D₃. *Cell Reports* **19** 1444–1455. (<https://doi.org/10.1016/j.celrep.2017.04.066>)
- Pereira F, Barbáchano A, Silva J, Bonilla F, Campbell MJ, Munoz A & Larriba MJ 2011 KDM6B/JMJD3 histone demethylase is induced by vitamin D and modulates its effects in colon cancer cells. *Human Molecular Genetics* **20** 4655–4665. (<https://doi.org/10.1093/hmg/ddr399>)
- Pereira F, Barbáchano A, Singh PK, Campbell MJ, Munoz A & Larriba MJ 2012 Vitamin D has wide regulatory effects on histone demethylase genes. *Cell Cycle* **11** 1081–1089. (<https://doi.org/10.4161/cc.11.6.19508>)
- Pertile RAN, Cui X & Eyles DW 2016 Vitamin D signaling and the differentiation of developing dopamine systems. *Neuroscience* **333** 193–203. (<https://doi.org/10.1016/j.neuroscience.2016.07.020>)
- Phillips CM & Perry IJ 2013 Does inflammation determine metabolic health status in obese and nonobese adults? *Journal of Clinical Endocrinology and Metabolism* **98** E1610–E1619. (<https://doi.org/10.1210/jc.2013-2038>)
- Planchart A, Mattingly CJ, Allen D, Ceger P, Casey W, Hinton D, Kanungo J, Kullman SW, Tal T, Bondesson M, *et al.* 2016 Advancing toxicology research using in vivo high throughput toxicology with small fish models. *ALTEX* **33** 435–452. (<https://doi.org/10.14573/altex.1601281>)
- Radford EJ, Ito M, Shi H, Corish JA, Yamazawa K, Isganaitis E, Seisenberger S, Hore TA, Reik W, Erkek S, *et al.* 2014 In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. *Science* **345** 1255903–1255903. (<https://doi.org/10.1126/science.1255903>)
- Reichetzeder C, Chen H, Foller M, Slowinski T, Li J, Chen YP, Lang F & Hochoer B 2014 Maternal vitamin D deficiency and fetal programming – lessons learned from humans and mice. *Kidney and Blood Pressure Research* **39** 315–329. (<https://doi.org/10.1159/000355809>)
- Rosen ED, Walkey CJ, Puigserver P & Spiegelman BM 2000 Transcriptional regulation of adipogenesis. *Genes and Development* **14** 1293–1307.
- Ross AC 2011 The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutrition* **14** 938–939. (<https://doi.org/10.1017/S1368980011000565>)
- Rytter D, Bech BH, Halldorsson TI, Henriksen TB, Grandström C, Cohen A & Olsen SF 2016 Maternal vitamin D status at Week 30 of gestation and offspring cardio-metabolic health at 20 years: A prospective cohort study over two decades. *PLoS ONE* **11** e0164758. (<https://doi.org/10.1371/journal.pone.0164758>)
- Saffery R & Novakovic B 2014 Epigenetics as the mediator of fetal programming of adult onset disease: what is the evidence? *Acta Obstetrica et Gynecologica Scandinavica* **93** 1090–1098. (<https://doi.org/10.1111/aogs.12431>)
- Schmidt RJ, Hansen RL, Hartiala J, Allayee H, Sconberg JL, Schmidt LC, Volk HE & Tassone F 2015 Selected vitamin D metabolic gene variants and risk for autism spectrum disorder in the CHARGE study. *Early Human Development* **91** 483–489. (<https://doi.org/10.1016/j.earlhumdev.2015.05.008>)
- Schutkowski A, Max D, Bönn M, Brandsch C, Grundmann SM, Hirche F, Staeger MS, Stangl GI 2018 Vitamin D does not play a functional role in adipose tissue development in rodent models. *Molecular Nutrition and Food Research* **62** [epub]. (<https://doi.org/10.1002/mnfr.201700726>)
- Schneuer FJ, Roberts CL, Guilbert C, Simpson JM, Algert CS, Khambalia AZ, Tasevski V, Ashton AW, Morris JM & Nassar N 2014 Effects of maternal serum 25-hydroxyvitamin D concentrations in the first trimester on subsequent pregnancy outcomes in an Australian population. *American Journal of Clinical Nutrition* **99** 287–295. (<https://doi.org/10.3945/ajcn.113.065672>)

- Senti J, Thiele DK & Anderson CM 2012 Maternal vitamin D status as a critical determinant in gestational diabetes. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* **41** 328–338. (<https://doi.org/10.1111/j.1552-6909.2012.01366.x>)
- Seuter S, Neme A & Carlberg C 2016 Epigenome-wide effects of vitamin D and their impact on the transcriptome of human monocytes involve CTCF. *Nucleic Acids Research* **44** 4090–4104. (<https://doi.org/10.1093/nar/gkv1519>)
- Sharma SS, Jangale NM, Harsulkar AM, Gokhale MK & Joshi BN 2017 Chronic maternal calcium and 25-hydroxyvitamin D deficiency in Wistar rats programs abnormal hepatic gene expression leading to hepatic steatosis in female offspring. *Journal of Nutritional Biochemistry* **43** 36–46. (<https://doi.org/10.1016/j.jnutbio.2017.01.008>)
- Stednitz SJ, Freshner B, Shelton S, Shen T, Black D & Gahtan E 2015 Selective toxicity of L-DOPA to dopamine transporter-expressing neurons and locomotor behavior in zebrafish larvae. *Neurotoxicology and Teratology* **52** 51–56. (<https://doi.org/10.1016/j.ntt.2015.11.001>)
- Suderman M, Stene LC, Bohlin J, Page CM, Holvik K, Parr CL, Magnus MC, Håberg SE, Joubert BR, Wu MC, *et al.* 2016 25-Hydroxyvitamin D in pregnancy and genome wide cord blood DNA methylation in two pregnancy cohorts (MoBa and ALSPAC). *Journal of Steroid Biochemistry and Molecular Biology* **159** 102–109. (<https://doi.org/10.1016/j.jsbmb.2016.03.005>)
- Takeshima M, Miyazaki I, Murakami S, Kita T & Asanuma M 2016 L-Theanine protects against excess dopamine-induced neurotoxicity in the presence of astrocytes. *Journal of Clinical Biochemistry and Nutrition* **59** 93–99. (<https://doi.org/10.3164/jcbrn.16-15>)
- Townsend K, Evans KN, Campbell MJ, Colston KW, Adams JS & Hewison M 2005 Biological actions of extra-renal 25-hydroxyvitamin D-1 α -hydroxylase and implications for chemoprevention and treatment. *Journal of Steroid Biochemistry and Molecular Biology* **97** 103–109. (<https://doi.org/10.1016/j.jsbmb.2005.06.004>)
- Van Cromphaut SJ, Rummens K, Stockmans I, Van Herck E, Dijcks FA, Ederveen AG, Carmeliet P, Verhaeghe J, Bouillon R & Carmeliet G 2003 Intestinal calcium transporter genes are upregulated by estrogens and the reproductive cycle through vitamin D receptor-independent mechanisms. *Journal of Bone and Mineral Research* **18** 1725–1736. (<https://doi.org/10.1359/jbmr.2003.18.10.1725>)
- Vinkhuyzen AAE, Eyles DW, Burne THJ, Blanken LME, Kruithof CJ, Verhulst F, Jaddoe VW, Tiemeier H & McGrath JJ 2018 Gestational vitamin D deficiency and autism-related traits: the Generation R Study. *Molecular Psychiatry* **23** 240–246. (<https://doi.org/10.1038/mp.2016.213>)
- Vuolo L, Di Somma C, Faggiano A & Colao A 2012 Vitamin D and cancer. *Frontiers in Endocrinology* **3** 58. (<https://doi.org/10.3389/fendo.2012.00058>)
- Walker CL & Ho SM 2012 Developmental reprogramming of cancer susceptibility. *Nature Reviews. Cancer* **12** 479–486. (<https://doi.org/10.1038/nrc3220>)
- Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL, *et al.* 2010 Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet* **376** 180–188. ([https://doi.org/10.1016/S0140-6736\(10\)60588-0](https://doi.org/10.1016/S0140-6736(10)60588-0))
- Wen J, Hong Q, Wang X, Zhu L, Wu T, Xu P, Fu Z, You L, Wang X, Ji C, *et al.* 2018 The effect of maternal vitamin D deficiency during pregnancy on body fat and adipogenesis in rat offspring. *Scientific Reports* **8** 365. (<https://doi.org/10.1038/s41598-017-18770-4>)
- Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM & Hart PH 2012 Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics* **129** 485–493. (<https://doi.org/10.1542/peds.2011-2644>)
- Williams DM, Fraser A, Fraser WD, Hyppönen E, Davey Smith G, Deanfield J, Hingorani A, Sattar N & Lawlor DA 2013 Associations of maternal 25-hydroxyvitamin D in pregnancy with offspring cardiovascular risk factors in childhood and adolescence: findings from the Avon Longitudinal Study of Parents and Children. *Heart* **99** 1849–1856. (<https://doi.org/10.1136/heartjnl-2013-303678>)
- Wolff GL, Kodell RL, Moore SR & Cooney CA 1998 Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. *FASEB Journal* **12** 949–957. (<https://doi.org/10.1096/fasebj.12.11.949>)
- World Health Organization 2017 10 facts on obesity. Geneva, Switzerland: WHO. (available at: <https://www.who.int/features/factfiles/obesity/en/>)
- Xue J, Schoenrock SA, Valdar W, Tarantino LM & Ideraabdullah FY 2016 Maternal vitamin D depletion alters DNA methylation at imprinted loci in multiple generations. *Clinical Epigenetics* **8** 107. (<https://doi.org/10.1186/s13148-016-0276-4>)
- Yates NJ, Tesic D, Feindel KW, Smith JT, Clarke MW, Wale C, Crew RC, Wharfe MD, Whitehouse AJO & Wyrwoll CS 2018 Vitamin D is crucial for maternal care and offspring social behaviour in rats. *Journal of Endocrinology* **237** 73–85. (<https://doi.org/10.1530/JOE-18-0008>)
- Zhang H, Chu X, Huang Y, Li G, Wang Y, Li Y & Sun C 2014 Maternal vitamin D deficiency during pregnancy results in insulin resistance in rat offspring, which is associated with inflammation and IkappaB α methylation. *Diabetologia* **57** 2165–2172. (<https://doi.org/10.1007/s00125-014-3316-7>)
- Zhu JG, Ochalek JT, Kaufmann M, Jones G & DeLuca HF 2013 CYP2R1 is a major, but not exclusive, contributor to 25-hydroxyvitamin D production in vivo. *PNAS* **110** 15650–15655. (<https://doi.org/10.1073/pnas.1315006110>)
- Zhu H, Bhagatwala J, Huang Y, Pollock NK, Parikh S, Raed A, Gutin B, Harshfield GA & Dong Y 2016 Race/Ethnicity-specific association of vitamin D and global DNA methylation: Cross-sectional and interventional findings. *PLoS ONE* **11** e0152849. (<https://doi.org/10.1371/journal.pone.0152849>)
- Zumaraga MP, Medina PJ, Recto JM, Abrahan L, Azurin E, Tanchoco CC, Jimeno CA & Palmes-Saloma C 2017 Targeted next generation sequencing of the entire vitamin D receptor gene reveals polymorphisms correlated with vitamin D deficiency among older Filipino women with and without fragility fracture. *Journal of Nutritional Biochemistry* **41** 98–108. (<https://doi.org/10.1016/j.jnutbio.2016.12.003>)

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