Review Article

Prenatal Vitamin D deficiency and Prenatal Ethanol Exposure as Modifiable Risk Factors for Neurodevelopmental Disorders

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ABSTRACT

There is a high prevalence of both vitamin D deficiency and exposure to low levels of ethanol consumption in pregnant women. However, there are a paucity of studies that have addressed the impact of both of these exposures on the offspring's vulnerability to neuropsychological disorders later in life. Maternal vitamin D deficiency has been implicated in adverse offspring health outcomes such as neurodevelopmental disorders including schizophrenia and autism. Ethanol consumption during pregnancy has deleterious effects on the developing foetus ranging from subtle physical deficits to severe behavioural abnormalities and are encompassed under a broad umbrella term, Foetal Alcohol Spectrum Disorders (FASD). High levels of ethanol exposure show distinct effects, whereas the consequences of moderate exposures have been less well studied. We propose that vitamin D signalling may be essential for compensatory mechanisms that take place to protect the brain from secondary exposures, such as from ethanol, which may result in greater disease susceptibility. In this review we provide an overview of the effects of each of these risk factors and discuss whether the combination of these exposures have the potential for an increased risk of neurodevelopmental disorders.

REVIEW METHODOLOGY

The literature survey was conducted during September 2017-October 2018 using a combination of methods comprising of key word search (MeSH terms vitamin D deficiency and combined with "prenatal ethanol exposure", "foetal alcohol spectrum disorder", "neurodevelopmental disorders") and author search of PubMed and science citation index reference database. We also searched the references and citations from recent research and review articles as they also formed an important part of the literature review.

INTRODUCTION

There is a wide range of modifiable non-genetic risk factors that could potentially influence neurodevelopment, such as medications, chemicals, physical agents, social and cultural influences as well as maternal lifestyle. These include (but are not limited to) maternal nutritional status during pregnancy, use of alcohol, tobacco, or illicit drugs during pregnancy, lower socioeconomic status, preterm birth, low birth weight, the physical environment, and prenatal or childhood exposure to certain environmental contaminants [1-7]. However, these risk factors may serve as proxy markers for

disease rather than causes of higher risk. For example, season is a proxy variable for various exposures, including influenza, other infections, pesticides, sunlight exposure and vitamin D levels [8]. Seasonality of birth or conception has been associated with increased risk of neuropsychiatric disorders such as schizophrenia and Autism Spectrum Disorders (ASD) in several studies [9-11]. A meta-analysis found that ASD is more common among the offspring in which the first and second trimester coincided with the winter and spring months [12]. Recent studies suggest that maternal diet can program offspring growth and metabolic pathways, altering lifelong susceptibility to diabetes and obesity. If maternal psychosocial experience has similar programming effects on the developing offspring, one might expect a comparable contribution to neurodevelopmental disorders, including affective disorders, schizophrenia, ASD and eating disorders.

Due to their early onset, prevalence and chronicity, some of these disorders, such as ASD and pervasive developmental disorders are important causes of disability worldwide, although there is a lack of evidence from much of the world's population [13]. Moreover, epidemiological studies on schizophrenia have revealed that its incidence is dependent upon developmental environment, sex, ethnicity and migrant status [14-16]. Prenatal Vitamin D (PVD) deficiency and Prenatal Ethanol Exposure (PEE) are modifiable risk factors, which have been individually studied in the literature and have been associated with neurodevelopmental disorders, such as ASD or ADHD [17-23]. Vitamin D deficiency is common in Australian adults, with recent population-based studies indicating that 35% of Australians over 25 years of age have suboptimal levels of vitamin D [24]. Although there is a debate about the optimal levels of circulating vitamin D, [25](OH)D, we have followed the guidelines that suggest serum concentrations are defined as follows; sufficient (>75 nM), insufficient (50-74 nM), mild deficiency (25-49 nM) and severe deficiency (<25 nM) [24].

In addition, Australian women of childbearing age have reported alcohol consumption to be as high as 85%. Moreover, with over 50% of pregnancies unplanned [25], this may allow at least a four-week gap during which pregnancy might be unknown and alcohol consumption may occur, suggesting PEE is a common exposure that may occur concurrently with maternal vitamin D deficiency. However, to our knowledge there are no studies that have measured the co-occurrence of PVD and PEE, and no direct causality between PVD and PEE has been identified.

Animal models have been a valuable tool used to test the effects separately of PVD deficiency and PEE, with findings in mice demonstrating that PVD deficiency (mice fed a vitamin D deficient diet resulting in 25(OH)D <10nM) has an impact on brain structure, behaviour and gene expression. Some of these alterations include decreased lateral ventricle volume [26], age-dependent decline in hippocampal volume [27], strain-dependent hyperlocomotion, increased exploration [28], altered response inhibition [29] and disrupted transcription of genes important for neural development [30,31]. Similarly, previous studies using moderate levels of PEE in mice (exposed to a 10% ethanol solution during the first 8 days of gestation, with a blood alcohol level of 120 mg/dl) have shown subtle alterations in brain morphology, adult behaviour and regulation of gene expression. For example, some of the changes seen due to PEE included enlarged ventricles and hippocampus [32], altered locomotion, learning and memory [33] and dysregulation of genes important for glutamatergic signalling [34]. Therefore, the overall aim of this review was to provide an overview of the individual effects of PVD deficiency and PEE on brain function and behaviour from preclinical and clinical data, to establish whether the combination of these exposures have the potential for an increased risk of neurodevelopmental disorders.

Prenatal vitamin D deficiency as a risk factor for neurodevelopmental disorders

The active form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH2)D3), is a secosteroid hormone, synthesized through several intermediate stages from vitamin D (cholecalciferol). Cholecalciferol is synthesised in the skin via exposure to UBV radiation via photolysis of the prohormone 7-dehydrocholesterol [35] or obtained from the diet, typically found in oily, deep sea fish and in lower levels in other foods such as eggs [36,37]. Cholecalciferol is hydroxylated in the liver to 25(OH)D3, which is then converted to the active form 1,25(OH2)D3, catalysed by the cytochrome p450 1α-hydroxylase (CYP27B1). The half-life of 1,25(OH2)D3 is relatively short (approx. 15h), and its production by CYP27B1

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is influenced by blood calcium and parathyroid hormone levels [38,39]. For this reason, 25(OH)D3 (pro-hormone) is considered a more reliable indicator of vitamin D levels.

Vitamin D is important for calcium (Ca2+) homeostasis, bone metabolism and various other physiological functions, but also exerts potent effects on neural cells and can impact brain development and function. For example, the distribution of the vitamin D receptor (VDR) and CYP27B1 has been mapped in human brain [40]. In line with its receptor's presence in developing brain tissue, vitamin D increases the expression of neurotrophic factors including nerve growth factor (NGF) [41], glial-derived neurotrophic factor (GDNF) [42] and neurotrophic factor 3 [43], while causing down-regulation of neurotrophic factor 4 [43].

Consistent with its regulation of neurotrophic factors, there is some evidence that vitamin D is a neuroprotective agent. Vitamin D may protect against excitotoxicity induced by glutamate [44], and has been shown to have an inhibitory effect on Ca2+ influx via down-regulation of the expression of mRNA for pore-forming subunits of L-type voltage-gated Ca2+ channels (L-VGCCs) [45]. It can also upregulate the expression of calbindin and parvalbumin in motor neurons, which are Ca2+ binding proteins that limit excitotoxicity by chelating intracellular Ca2+ [46]. The optimal level of vitamin D status, as measured by 25(OH)D3 has not yet been established. People with circulating 25(OH)D3 < 25nmol/L are considered vitamin D deficient, and those with < 50 nmol/L are considered vitamin D insufficient [47]. Epidemiological data on women of childbearing age indicated that vitamin D deficiency was prevalent in 4% of fair-skinned women and in 42% of dark-skinned women residing throughout the United States [48], which has raised concerns regarding the impact this may have on foetal development during pregnancy. Multiple factors affect the available levels of vitamin D in the body. For example, the concentration of melanin in the skin is the major endogenous factor, as it absorbs ultraviolet B radiation, thereby inhibiting the photolysis reaction that yields vitamin D in its active form [49]. This means that dark-skinned individuals with high melanin concentrations are more prone to vitamin D deficiency than those with fair skin. In addition, exogenous factors that influence vitamin D status are mostly related to sunlight exposure (for example, season) [50]. Winter is associated with reduced skin exposure due to the cold as well as a reduction in sunlight intensity, which both contribute to a reduction in vitamin D synthesis [51-53]. Additionally, it is important to take into account that the decrease in sunlight intensity rises accordingly with the distance from the equator; consequently, people living at high latitudes are more likely to become vitamin D deficient during the winter months [54].

The prevalence of maternal vitamin D deficiency is common and increasing [55] and has been implicated in adverse offspring health outcomes such as ASD, schizophrenia and other neurodevelopmental disorders [23,56,57]. Pregnancy may be a time of particular vulnerability for sub-optimal vitamin D levels, due to dietary and lifestyle changes resulting from pregnancy. For example, a population based, case-control study, which used neonatal dried blood samples to measure the concentration of 25(OH)D3, found that neonates in the lower three quintiles (compared to those in the fourth quintile- 40.5-50.9 nM) had a two-fold elevated risk of schizophrenia [58]. Another study, which used maternal mid-gestation sera examined the association between 25(OH)D3 and ASD found that mid-gestational vitamin D deficiency increased the risk of ASD by more than twofold compared to the vitamin D sufficient group 23.

Prenatal ethanol exposure as a risk factor for neurodevelopmental disorders

The deleterious effects of prenatal alcohol consumption were first established in 1973 and are referred to as Foetal Alcohol Syndrome (FAS) [59]. FAS is characterized by three main clinical features, including growth restriction, craniofacial abnormalities in addition to structural and/or functional deficits in the brain [60,61]. It is the most severe form of alcohol related disorders within the non-diagnostic umbrella term Foetal Alcohol Spectrum Disorders (FASD). Although the severity can vary among individuals, it is mostly associated with the level of exposure, in which heavy drinking patterns are more likely to cause FAS. Moderate and light drinking are commonly responsible for milder forms of FASD, which lack the presence of dysmorphic features typical of FAS but exhibit neurobehavioural and cognitive impairment 62. For example, several studies have reported FASD children to be hyperactive, irritable and experience difficulties in tasks of vigilance, reaction time and information processing. Life-long impairments

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can include impulsivity, hyperactivity, social ineptness, poor judgement and learning disabilities [63-66].

FAS is the least common effect of prenatal alcohol exposure among the FASD umbrella, with a prevalence of 5% in children of typically alcoholic mothers [62,67]. A major focus of prenatal alcohol research has been on levels of alcohol within the moderate to high range. Fewer studies have investigated the impact of relatively low concentrations of alcohol exposure in utero on behaviour and cognitive performance in the offspring, with studies reporting conflicting findings. A large longitudinal study in pregnant women revealed that mothers who consumed light levels of alcohol (2-6 standard drinks per week) in the first three months of pregnancy had children with significantly lower total and internalizing behaviour scores over fourteen years, representing more positive behaviour than non-drinkers at three months' gestation [68]. This study also revealed that children of light to moderate drinkers (2-10 standard drinks per week) were at a clinically meaningful lower risk of total, internalising and externalising behavioural problems than the children of women who did not drink.

Although these results support other studies with similar findings, which suggest that low levels of alcohol exposure were not associated with developmental risks [69], they are in opposition to others, which report that even low levels of alcohol were adversely related with child behaviour [70,71]. A prospective, population-based study found that consumption of >1 drink per week during the first trimester of pregnancy was independently associated with clinically significant mental health problems in girls at 47 months, and persisted at 81 months [70]. Another longitudinal study monitored maternal alcohol and drug use during pregnancy and followed up with families six years later. Using the Achenbach Child Behaviour Checklist (CBCL) to assess child behaviour, results showed that children with any prenatal alcohol exposure were more likely to have higher CBCL scores on externalizing (aggressive and delinquent) and internalizing (anxious/depressed and withdrawn) syndrome scales as well as on the total problem score. Furthermore, there were significant differences found between no and low-exposure groups for aggressive and externalizing behaviours at age 6 to 7, which persisted after controlling for other factors associated with adverse behavioural outcomes, thereby suggesting that the adverse effects of prenatal alcohol exposure are evident even at low levels of exposure [71].

Multiple studies in humans have reported that one of the side effects from chronic alcohol exposure is vitamin D deficiency, as the toxic effects of alcohol impairs vitamin D/calcium homeostasis and results in decreased bone mineral density [72-74]. Moreover, alcohol metabolism is taxing on the liver, which also metabolises vitamin D to its active form. However, to the best of our knowledge there are no studies looking at the reverse situation, metabolism of alcohol in vitamin D deficient patients.

Secondary insults to prenatal vitamin D deficiency

Human epidemiological studies are important to understand the prevalence of environmental risk factors, such as PVD deficiency and PEE, and the possible association with neurodevelopmental disorders. However, animal models are essential in studying how genetic and environmental risk factors impact on brain development, and how the neurobiology underlying specific behaviours under controlled conditions, while limiting confounding factors that are commonly encountered in human studies.

Gene expression

Vitamin D can regulate the expression of genes involved in important neurodevelopmental processes, including cell proliferation, apoptosis, neuronal migration and dopamine signalling [75-77]. A study using BALB/c mice reported altered neural gene expression as a result of PVD deficiency. Transcripts involved in dopamine regulation, FoxP2 and tyrosine hydroxylase (Th), were reduced in PVD-deficient foetuses, while neuroproliferation markers Bdnf and Tgf-a1 were increased, thereby highlighting the crucial role of vitamin D for normal brain development 31. Similarly, PEE has been shown to dysregulate expression of genes important in numerous signalling cascades critical for normal embryogenesis, including the Sonic hedgehod, Wnt and Notch pathways [78-82]. PEE can also disrupt the regulation of neurotransmitter signalling including glutamatergic, dopaminergic and GABAergic transmission [83-87]. Focusing on moderate dose of exposure in mice, previous studies have found subtle gene expression changes at embryonic stages [88], further alterations in adolescent offspring [32], and long-lasting changes in adults [34].

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In the case of PEE, rodents have been widely used to investigate its effects on brain function and behaviour [69,89]. However, there is no standard FASD rodent model because researchers alter experimental parameters such as dose, pattern and timing of exposure and route of administration, which influence outcomes and mirrors the diverse manifestations of FASD in humans. C57BL/6J mice exhibit a propensity to voluntarily consume alcohol [90] which has a practical advantage in that it minimizes confounding effects of maternal stress caused by ethanol injections. A previously established mouse model utilised ad libitum ethanol exposure (moderate levels of 10% v/v) during the first eight days of gestation (GD 0-8), which is equivalent to the first 3–4 weeks of a human pregnancy, thereby mimicking the period of time during which mothers are unaware of pregnancy [67,91]. Using this procedure, adult coat colour changes were detected in C57Bl/6 mice carrying the epigenetically regulated allele, Agouti viable yellow (Avy). Given that adult coat colour is linked to the Avy allele, changes in this phenotype show that moderate prenatal alcohol exposure (GD 0–8) could alter Avy expression and DNA methylation. This study showed, for the first time, that moderate prenatal alcohol exposure could affect the adult phenotype by modifying the epigenotype of the early embryo.

At a molecular level, studies using high dose ethanol exposures have encountered alterations in glutamatergic signalling as well as in synaptic plasticity in hippocampal tissue, showing dysregulation of vesicular glutamate transporter 1 (Vglut1), complexin 1, various N-methyl-d-aspartate (NMDA) receptor subunits and excitatory amino acid transporters 1 and 3 (EAAT1 and 3) [84-86]. Moreover, a recent model using moderate levels of exposure early in gestation revealed a disruption in the developmental silencing of solute carrier family 17 member (Slc17a6), which encodes for vesicular glutamate transporter 2 (Vglut2) in the adult hippocampus, suggesting a long-term effect on glutamatergic signalling. Additionally, epigenetic analyses have shown complex patterns of DNA methylation and post-translational histone modifications at the promoter and an upstream region of Slc17a6, including dynamic epigenetic marks that are altered by transcriptional activity as well as fixed DNA methylation mark that possibly confers epigenetic memory of prenatal ethanol exposure.

PEE has also been found to affect other neurotransmitter systems, including the dopaminergic system [92]. PEE has been associated with a reduction in spontaneous activity in dopamine (DA) neurons, decreased DA uptake and receptor binding sites, decreased DA metabolite homovanilic acid (HVA) in DA neurons and decreased D1 receptors in the hypothalamus and striatum [92-97], as well reduced dendritic growth in DA neurons [98] and changes in DA receptor function [99], which highlights the potent extent to which ethanol can affect neurodevelopment.

Neuroanatomy

Altered neuroanatomy has been previously reported for PVD-deficient rats and mice. However, results have often been in opposite directions. For example, PVD-deficient rats were found to have increased ventricle size and decreased cortical thickness at birth [100]. A study in mice found a decrease in lateral ventricle volume in both males and females at embryonic age (E18) using ex-vivo MRI 26. Another study using in-vivo MRI on PVD-deficient male mice at two different time points (P210 and P490) showed that PVD-deficient mice had smaller ventricles, while whole brain and hippocampal volumes were unaffected at P210. In control mice, the volume of the hippocampus did not differ significantly between the two ages. However, PVD-deficient mice experienced a significant 20% decline in hippocampal volume from P210 to P490, indicating that age-related neuroanatomical changes may be potentiated in PVD-deficient mice [27]. Another study using PVD deficiency in BALB/c mice focused on foetal development and found structural changes in the foetus [31]. For example, stereological analysis showed a reduction in foetal crown-rump length and head size, as well as in lateral ventricle volume of PVD-deficient samples at E17.5.

PEE leads to varying levels of cortical dysfunction, including defects in neuronal migration, changes in apoptosis or cell death, alterations in cortical thickness, callosal connectivity, and selective reduction of GABA neurons [101-106]. Other studies have identified non-cortical damage to the developing nervous system from PEE. For example, Livy and colleagues described abnormal development in the hippocampus, cerebellum, and CC following prenatal ethanol exposure in a rat model of FASD [107-109]. A recent study reported alterations to developmental cortical thinning across functionally diverse

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regions of cortex, and altered development of extra neocortical structures, with correlative behavioural deficits in early adulthood, which are consistent with documented human patterns of birth defects present at early developmental stages [110]. Based on its crucial role in learning and memory, the hippocampus has been the focus of numerous prenatal alcohol exposure studies. Human data has shown a reduction in hippocampal volume and Magneic Resonance Imaging (MRI)-behavioural evaluations have suggested links between alterations in hippocampal volume and memory deficits [65,111]. Likewise, decreased hippocampal volume has been reported in rats [107,112] along with alterations in hippocampal-dependent learning and memory [85,113]. Neuroanatomical analyses at of mice at GD17 have shown disproportionate reductions in the olfactory bulbs, hippocampus and cerebellum, as well as an increase in ventricular volumes [112]. In another study [114], a decrease in cerebellar volume and an increase in septal volume was found in mice exposed to ethanol at GD7-10, while a reduction in hippocampal volume and enlarged pituitaries was observed in animals exposed to ethanol at GD12-16. A more recent MRI study on adult mice exposed to moderate PEE (GD0-8) reported a small decrease in total brain volume, and after normalizing for total brain volume, the hippocampus and lateral ventricles of PEE mice were enlarged, while the olfactory bulb was reduced and no changes were found in cerebellar volume [32].

Behaviour

Behavioural studies in outbred rats using PVD deficiency have shown transient spontaneous hyperlocomotion in adult Sprague-Dawley rats [115]. Others have found that PVD deficiency is associated with subtle changes in learning and memory functions as adults. In particular, a significantly impaired latent inhibition was found, however both memory acquisition and retrieval were unaffected [116]. Furthermore, PVD deficiency was associated with enhanced sensitivity to the locomotor effects of psychomimetic drugs, in particular those that disrupt glutamatergic and dopaminergic signalling [117-120].

A model of PVD deficiency was also established in two mouse strains, C57Bl/6J and 129/SyJ. After a comprehensive behavioural screen, it was found that 129/SvJ DVD-deficient mice exhibited spontaneous hyperlocomotion in the open field, and 129/SvJ and C57BL/6J PVD-deficient mice were hyper-explorative on the hole-board test [30]. There was no effect of maternal diet on parameters assessed by the SmithKline Beecham, Harwell, Imperial College, Royal London Hospital, phenotype assessment (SHIRPA) primary screen, a procedure is used for the standardised assessment of mouse phenotype, or on tests of sensorimotor gating, social behaviour, anxiety or depression. Some behavioural findings, such as hyperlocomotion, are consistent across rats and mice, but there were a number of behavioural differences reported in PVD-deficient mice that were not observed in rats, such as increased exploration (found in mice [121], not in rats [116,122], while behavioural response to psychomimetics was altered in rats [119] but not displayed in C57BL/6J or 129/Svj mice [26]. Additionally, findings were also dependant on the background mouse strain, as there were discrepancies between C57BL/6J and 129/Svj. Although the behaviour of PVD-deficient BALB/c mice has not been characterized, adult vitamin D deficiency studies have shown that the behavioural profile of BALB/c mice is significantly different to that of C57BL/6J, showing altered behaviour in anxiety-related tasks, as well as altered responses to heat, shock and sound [123].

Taken together, temporary depletion of vitamin D during gestation in mice results in subtle alterations in the offspring, suggesting that it is a plausible risk factor for neurodevelopmental disorders. However, no direct causal relationship between vitamin D and brain disorders has been found. It has now been established that the majority of neurodevelopmental disorders, including ASD, ADHD and schizophrenia are a result of a combination of genetic and/or environmental factors. Therefore, it is possible that sub-optimal vitamin D levels reduce the neuroprotective capacity leading to increased vulnerability to insults from secondary exposures, such as detrimental environmental exposures, injury or disease [124,125]. The summation of these factors may result in greater risk of neurodevelopmental disorders.

With respect to PEE, social and cognitive domains have been studied across various animal models. The specific experimental design (dose, timing and mode of exposure) greatly influences outcome measures, therefore, mixed findings have been reported. Communication in mice is often assessed via ultrasonic vocalizations (USVs) emitted by pups when separated from the dam and litter [126]. A study in which dams were exposed to

ethanol for the first and second trimester reported a reduction in USVs in PEE juvenile offspring [127], while a model of chronic exposure (GD1-P10) showed no effect of ethanol. Furthermore, in the sociability domain, some have reported reduced play/fight encounters, shorter gap-crossings [127], impaired prosocial interaction and increased avoidance [128] and increased wrestling behaviour in ethanol-exposed adult males, while little to no effect has been found in females. Moreover, there are little to no reports on these behaviours at juvenile stages, during which neurodevelopmental disorders as ASD usually become prominent in children.

Given that learning and memory deficits have been a prominent phenotype in children with FAS, this domain has been heavily studied in rodent models utilising several methods. High levels of exposure have found deficits in the Morris Water Maze (MWM) in rats [129,130], and similarly, chronic ethanol exposure in mice has been shown to induce deficits in the Barnes Maze test [90]; nevertheless, moderate levels of exposure have been reported to have either no effect in rats [131], while another study in mice showed an enhanced performance in ethanol-exposed males in the MWM [33].

DISCUSSION: TIMING OF EXPOSURES

The duration of vitamin D deficiency has been explored in previous studies, intending to identify a 'critical window' during which the absence of vitamin D exerts its most potent effects. In rats, offspring from dams that were vitamin D deplete until birth had increased lateral ventricle volume at birth [100], while if the vitamin D deficiency period was prolonged until weaning, the ventricle enlargement phenotype persisted into adulthood [132]. However, prolonged vitamin D deficiency resulted in hypocalcaemia, which confounded the interpretation of postnatal findings.

With regards to PEE, timing of exposure has also been shown to have a significant impact on the results observed at gene, protein and behavioural levels. Of particular relevance to moderate PEE, the equivalent to the first 3 – 4 weeks of a human pregnancy is a period of time during which most Australian women have yet to confirm their pregnancies [133]. CNS development is characterized by vulnerable periods during which exposure to teratogens may result in abnormalities specific to the ontogenic events occurring at the time of exposure [134]. Ethanol appears to interfere with all neurodevelopmental stages [135]. The first trimester in humans (GD1-11 in mice) is considered the first critical period of development, during which organogenesis begins and the neural tube and crest are formed [134]. Moreover, during the second week of gestation in mice (first month in humans), specific areas of the CNS begin to form with neurogenesis and migration of cells in the forebrain, midbrain, and hindbrain [134]. Mice exposed to acute doses of ethanol during GD 7 or 8 exhibit the craniofacial anomalies associated with FAS, as well as forebrain deficiencies including hypoplasia or aplasia of the corpus callosum, and deficiency in the hippocampus and the anterior cingulated cortex [136]. Previous studies using moderate levels of PEE have shown more subtle changes in behaviour [33], brain structure [32], craniofacial morphology [91], and transcriptional and epigenetic in various postnatal tissues [32,34,67,91] Another study evaluated the effects of PEE shortly after the termination of ethanol exposure (GD9) to assess whether the alterations observed at postnatal stages were present from the time of exposure, or if there was a latency in their onset. Findings at GD9 did not reveal changes of large effect at this stage [88], which suggests that there is a delayed onset of PEE-induced alterations.

While there is no current data showing that PVD deficiency amplifies the effects of PEE, there is preclinical evidence that vitamin D deficiency can exacerbate other second hit exposures. For example, and as a proof of concept, a study using a model of stroke in rats showed that vitamin D-deficient rats had a larger infarct volume in comparison to controls, which then correlated with greater post-stroke impairments in sensorimotor behavioural tests [124]. Molecular analyses revealed that compared to controls, vitamin D-deficient rats had significantly lower levels of Insulin-like Growth Factor-1 (IGF-1) in plasma, brain and liver. IGF-1 is a neuroprotectant normally elevated post-injury to rescue the tissue. Therefore, it is possible that a reduction of IGF-1 occurred as a result of vitamin D deficiency, which then contributed to the greater infarct volume observed in vitamin D-deficient rats [124]. Another study focusing on Parkinson's Disease (PD) provided further evidence for the neuroprotective properties of vitamin D. The impact of vitamin D supplementation (1200 IU daily for one year) was examined on a number of PD-related outcomes. Patients that belonged to the Placebo group showed a stable

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worsening of PD outcomes, while those in the vitamin D supplement group presented no change in PD outcomes throughout the year of treatment, which suggests that low levels of vitamin D exacerbate the progression of disease. It has also been suggested that low vitamin D can aggravate the vulnerability to psychosocial stressors [137]. Jiang et al. [138] documented an up-regulation of both VDR and 1,25(OH)2D in the hippocampus of rats as a result of chronic mild stress. This suggests that vitamin D signalling may be essential for compensatory mechanisms that take place to protect the brain from insults such as stress, and that the combination of both vitamin D deficiency and a secondary exposure may result in greater disease susceptibility.

CONCLUSION

Currently, there is limited evidence in the literature investigating the interaction of PVD and PEE during the embryonic and postnatal period. However, taking into account the high prevalence of both PVD deficiency and moderate PEE, particularly in women of childbearing age, in addition to evidence showing that each of these factors have subtle, although long-lasting, effects on rodent offspring behaviour and glutamatergic and dopaminergic signalling, the likelihood of deleterious effects of the combined effects of these exposures in offspring seems likely, and future studies are warranted. This would provide valuable information regarding the timing and interaction of these two risk factors, highlighting crucial cellular processes that may be vulnerable to subtle exposures and enhancing the understanding of whether their combination may increase the risk for neurodevelopmental disorders in the offspring. We speculate that the effects of this combination of factors may span across the offspring's life, showing more distinct alterations at early postnatal stages, and would be subsequently influenced by the postnatal environment. Furthermore, this would aid the recommendation of optimal vitamin D levels for pregnant women and would reinforce the importance of abstinence from alcohol during pregnancy.

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REFERENCES

1. Adnan T Bhutta, Mario A Cleves, Patrick H Casey, Mary M Cradock, Anand KJS.(2002). Cognitive and Behavioral Outcomes of School-Aged Children Who Were Born Preterm: A Meta-analysis. JAMA. 288: 728-737.
2. Karen Markussen Linnet, Søren Dalsgaard, Carsten Obel, Kirsten Wisborg, Tine Brink Henriksen, et al.(2003). Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. Am J Psychiatry. 160: 1028-1040.
3. Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Behrman RE, Butler AS, editors. Preterm Birth: Causes, Consequences, and Prevention. 2007. National Academies Press.
4. Thompson KN, Phillips LJ, Komesaroff P, Yuen HP, Wood SJ, et al.(2007). Stress and HPA-axis functioning in young people at ultra high risk for psychosis. J Psychiatr Res. 41: 561-569.
5. Herrmann M, King K, Weitzman M.(2008). Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. Curr Opin Pediatr. 20: 184-190.
6. Aarnoudse-Moens CSH, et al.(2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 124: 717.
7. Perera F, Herbstman J.(2011). Prenatal environmental exposures, epigenetics, and disease. Reprod Toxicol. 31: 363-373.
8. Lyall K, Schmidt I, Hertz-Picciotto.(2014). Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int J Epidemiol. 43: 443-464.
9. Kolevzon A, Mark Weiser, Raz Gross, Gad Lubin, Haim Y Knobler, et al.(2006). Effects of season of birth on autism spectrum disorders: Fact or fiction? Am J Psychiatry. 163: 1288-U3.
10. Hebert KJ, Miller LL, Joinson CJ. (2010). Association of autistic spectrum disorder with season of birth and conception in a UK cohort. Autism Res. 3: 185-190.

11. Zerbo O, Iosif A, Delwiche L, Walker C, Hertz-Picciotto I.(2011). Month of Conception and Risk of Autism. Epidemiol. 22: 469-475.
12. Gardener H, Spiegelman D, Buka SL. (2009). Prenatal risk factors for autism: comprehensive meta-analysis. BJ Psych Int. 195: 7-14.
13. Elsabbagh M, Divan G, Yun-Joo K, Shin Kim Y, Kauchali S, et al. (2012). Global prevalence of autism and other pervasive developmental disorders. Autism Res. 5: 160-179.
14. Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, et al. (1999). Effects of family history and place and season of birth on the risk of schizophrenia. N Engl J Med. 340: 603-608.
15. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, et al. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Medicine. 2: 13.
16. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, et al. (2007). High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. J Nutr. 137: 447-452.
17. Banerjee TD, Middleton F, Faraone SV. (2007). Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatr. 96: 1269-1274.
18. Cannell JJ. (2008). Autism and vitamin D. Med Hypotheses. 70: 750-759.
19. Eliasen M, Tolstrup JS, Nybo Andersen AM, Grønbaek M, Olsen J, et al. (2010). Prenatal alcohol exposure and autistic spectrum disorders--a population-based prospective study of 80,552 children and their mothers. Int J Epidemiol. 39: 1074-1081.
20. Mukherjee R, Layton M, Yacoub E, Turk J. (2011). Autism and autistic traits in people exposed to heavy prenatal alcohol: data from a clinical series of 21 individuals and nested case control study. Advances in Mental Health and Intellectual Disabilities. 5: 42-49.
21. Whitehouse AJO, Holt BJ, Serralha M, Holt PG, Hart PH, et al. (2013). Maternal vitamin D levels and the autism phenotype among offspring. J Autism Dev Disord. 43: 1495-1504.
22. Rojas-Mayorquín AE, Padilla-Velarde E, Ortuño-Sahagún D. (2016). Prenatal alcohol exposure in rodents as a promising model for the study of ADHD molecular basis. Front Neurosci. 10: 565.
23. Vinkhuyzen AAE, , Eyles DW, Burne THJ, Blanken LME, Kruithof CJ, et al. (2017). Gestational vitamin D deficiency and autism spectrum disorder. BJPsych Open. 3: 85-90.
24. Daly RM, Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, et al. (2012). Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. Clin Endocrinol (Oxf). 77: 26-35.
25. Giglia RC, Binns CW. (2007). Patterns of alcohol intake of pregnant and lactating women in Perth, Australia. Drug Alcohol Rev. 26: 493-500.
26. Harms LR, Cowin G, Eyles DW, Kurniawan ND, McGrath JJ, et al. (2012). Neuroanatomy and psychomimetic-induced locomotion in C57BL/6J and 129/X1SvJ mice exposed to developmental vitamin D deficiency. Behav Brain Res. 230: 125-131.
27. Harms LR, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH. (2010). Developmental vitamin D deficiency alters learning in C57Bl/6J mice. Behav Brain Res. 208: 603-608.
28. Harms LR, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH, et al. (2008). Developmental vitamin D deficiency alters adult behaviour in 129/SvJ and C57BL/6J mice. Behav Brain Res. 187: 343-350.
29. Harms LR, Turner KM, Eyles DW, Young JW, McGrath JJ, et al. (2012). Attentional processing in C57BL/6J mice exposed to developmental vitamin D deficiency. PLoS One. 7: e35896.
30. Harms LR. (2011). Brain development and behaviour in developmentally vitamin D-deficient mice. The University of Queensland, Queensland Brain Institute.
31. Hawes JE, Tesic D, Whitehouse AJ, Zosky GR, Smith JT, et al. (2015). Maternal vitamin D deficiency alters fetal brain development in the BALB/c mouse. Behav Brain Res. 286: 192-200.

32. Marjonen H, Sierra A, Nyman A, Rogojin V, Gröhn O, et al. (2015). Early maternal alcohol consumption alters hippocampal DNA methylation, gene expression and volume in a mouse model. PLoS One. 10.
33. Sanchez Vega MC, Chong S, Burne TH. (2013). Early gestational exposure to moderate concentrations of ethanol alters adult behaviour in C57BL/6J mice. Behav Brain Res. 252: 326-33.
34. Zhang CR, Ho MF, Vega MCS, Burne TH2, Chong S, et al. (2015). Prenatal ethanol exposure alters adult hippocampal VGLUT2 expression with concomitant changes in promoter DNA methylation, H3K4 trimethylation and miR-467b-5p levels. Epigenetics Chromatin. 8: 40.
35. Holick MF. (1987). Photosynthesis of vitamin D in the skin: Effect of environmental and life-style variables. Federation Proceedings. 46: 1876-1882.
36. Mattila P, Lehikoinen K, Kiiskinen T, V Piironen V. (1999). Cholecalciferol and 25-hydroxycholecalciferol content of chicken egg yolk as affected by the cholecalciferol content of feed. J Agric Food Chem. 47: 4089-4092.
37. Ostermeyer U, Schmidt T. (2006). Vitamin D and provitamin D in fish: determination by HPLC with electrochemical detection. Eur Food Res Technol. 222: 403.
38. Deluca H. (2004). Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr. 80: 1689S-1696S.
39. Holick MF. (2006). Resurrection of vitamin D deficiency and rickets. J Clin Investig. 116: 2062-2072.
40. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. (2005). Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. J Chem Neuroanat. 29: 21-30.
41. Saporito MS, Brown ER, Hartpence KC, Wilcox HM, Vaught JL, et al. (1994). Chronic 1,25-Dihydroxyvitamin D-3-mediated induction of nerve growth-factor messenger-RNA and protein in L929 fibroblasts and in adult-rat brain. Brain Res, 1994. 633: 189-196.
42. Naveilhan P, Neveu I, Wion D, Brachet P. (1996). 1,25-dihydroxyvitamin D-3, an inducer of glial cell line-derived neurotrophic factor. Neuroreport. 7: 2171-2175.
43. Neveu I, Naveilhan P, Baudet C, Brachet P, M Metsis. (1994). 1,25-Dihydroxyvitamin D-3, regulates Nt-3, Nt-4 but not Bdnf messenger-Rna in astrocytes. Neuroreport. 6: 124-126.
44. Ibi M, Sawada H, Nakanishi M, Kume T, Katsuki H, et al. (2001). Protective effects of 1 alpha,25-(OH)(2)D-3 against the neurotoxicity of glutamate and reactive oxygen species in mesencephalic culture. Neuropharmacol. 40: 761-771.
45. Brewer LD, Thibault V, Chen KC, Langub MC, Landfield PW, et al. (2001). Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. J Neurosci. 21: 98-108.
46. Alexianu ME, Robbins E, Carswell S, Appel SH. (1998). 1 alpha,25 dihydroxyvitamin D-3-dependent up-regulation of calcium-binding proteins in motoneuron cells. J Neurosci Res. 51: 58-66.
47. Ross AC. Vitamin D The 2011 report on dietary reference intakes for calcium and vitamin D. Public Health Nutr. 14: 938-939.
48. Nesby O, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, et al. (2002). Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr,. 76: 187-192.
49. Holick MF. (1995). Environmental factors that tnfluence the cutaneous production of vitamin D. Am J Clin Nutr. 61: S638-S645.
50. 50. Wu W, Beilhartz G, Roy Y, Richard CL, Curtin M, et al. (2010). Nuclear translocation of the 1,25D(3)-MARRS (membrane associated rapid response to steroids) receptor protein and NF kappa B in differentiating NB4 leukemia cells. Exp Cell Res. 316: 1101-1108.
51. Webb AR, Kline L, Holick MF. (1988). Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab. 67: 373-378.
52. Marks R. (1999). Sunscreens and vitamin D levels. J Am Acad Dermatol. 40: 497-497.

53. Marks R, McCarthy WH. (1990). Skin cancer: increasing incidence and public awareness. Med J Aust. 153: 505.
54. Holick MF. (2003). Vitamin D: A millenium perspective. Journal Cell Biochem. 88: 296-307.
55. Looker AC, Gunter EW. (1998). Hypovitaminosis D in medical inpatients. N Engl J Med. 339: 344-345; author reply 345-6.
56. Tare M, Parkington H, Morley R. (2006). Vitamin D in pregnancy and offspring health, in Early Life Origins of Health and Disease, E.M. Wintour and J. Owens, Editors. Springer US. p. 195-203.
57. Ginde AA, Liu MC, Camargo CA Jr. (2009). Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med. 169: 626-632.
58. McGrath JJ, Eyles DW, Pedersen CB, Anderson C, Ko P, et al. (2010). Neonatal vitamin D status and risk of schizophrenia a population-based case-control study. Arch Gen Psychiatry. 67: 889-894.
59. Jones KL, Smith DW. (1973). Recognition of Fetal Alcohol Syndrome in Early Infancy. Lancet. 2: 999-1001.
60. Abel EL. (1984). Prenatal effects of alcohol. J Alcohol Drug Depend. 14: 1-10.
61. Sokol RJ, Delaney-Black V, Nordstrom B. (2003). Fetal alcohol spectrum disorder. JAMA. 290: 2996-2999.
62. Abel EL, Kruger ML, Friedl J. (1998). How do physicians define "light", "moderate", and "heavy" drinking? Alcohol Clin Exp Res. 22: 979-984.
63. Nanson JL, Hiscock M. (1990). Attention Deficits in Children Exposed to Alcohol Prenatally. Alcohol Clin Exp Res. 14: 656-661.
64. Brown RT, Coles CD, Smith IE, Platzman KA, Silverstein J, et al. (1991). Effects of Prenatal Alcohol Exposure at School Age .2. Attention and Behavior. Neurotoxicol Teratol. 13: 369-376.
65. Coles CD, Goldstein FC, Lynch ME, Chen X, Kable JA, et al. (2011). Memory and brain volume in adults prenatally exposed to alcohol. Brain and Cognition. 75: 67-77.
66. Mattson SN, Crocker N, Nguyen TT. (2011). Fetal Alcohol Spectrum Disorders: Neuropsychological and behavioral features. Neuropsychol Rev. 21: 81-101.
67. Kaminen-Ahola N, Ahola A, Maga M, Mallitt KA, Fahey P, et al. (2010). Maternal ethanol consumption alters the epigenotype and the phenotype of offspring in a mouse model. PLoS Genet. 6: e1000811.
68. Robinson M, Oddy WH, McLean NJ, Jacoby P, Pennell CE, et al. (2010). Low–moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study. BJOG. 117: 1139-1152.
69. Kelly SJ, Goodlett CR, Hannigan JH. (2009). Animal models of Fetal Alcohol Spectrum Disorders: Impact of the social environment. Dev Disabil Res Rev. 15: 200-208.
70. Sayal K, et al. (2007). Prenatal alcohol exposure and gender differences in childhood mental health problems: A longitudinal population-based study. Pediatrics. 119: e426-e434.
71. Sood B, Heron J, Golding J, Emond A. (2001). Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. Pediatrics. 108: E34.
72. Laitinen K, Valimaki M. (1991). Alcohol and bone. Calcif Tissue Int. 49: S70-73.
73. Mercer KE, Wynne RA, Lazarenko OP, Lumpkin CK, Hogue WR, et al. (2012). Vitamin D supplementation protects against bone loss associated with chronic alcohol administration in female mice. J Pharmacol Exp Ther. 343: 401-412.
74. Sampson HW. (1997). Alcohol, osteoporosis, and bone regulating hormones. Alcohol Clin Exp Res. 21: 400-403.
75. Ko P, Burkert R, McGrath J, Eyles D. (2004). Maternal vitamin D3 deprivation and the regulation of apoptosis and cell cycle during rat brain development. Brain Res Dev Brain Res. 153: 61-68.
76. Cui X, et al. (2010). Maternal vitamin D deficiency alters the expression of genes involved in dopamine specification in the developing rat mesencephalon. Neurosci Lett. 486: 220-223.
77. Kesby JP, Pelekanos M, Burne THJ, McGrath JJ, Eyles DW. (2009). Developmental vitamin D deficiency alters dopamine turnover in neonatal rat forebrain. Neurosci Lett. 461: 155-158.
78. Ahlgren SC, Thakur V, Bronner-Fraser M. (2002). Sonic hedgehog rescues cranial neural crest from cell death induced by ethanol exposure. Proc Natl Acad Sci U S A. 99: 10476-10481.

79. Li YX, Hai-Tao Yang, Marzena Zdanowicz, Jason K Sicklick, Yi Qi, et al. (2007). Fetal alcohol exposure impairs hedgehog cholesterol modification and signaling. Lab Invest. 87: 231-240.
80. Vangipuram SD, Lyman WD. (2012). Ethanol affects differentiation-related pathways and suppresses wnt signaling protein expression in human neural stem cells. Alcohol Clin Exp Res. 36: 788-797.
81. Serrano M, Mingda Han, Pilar Brinez, Kersti K Linask. (2010). Fetal alcohol syndrome: cardiac birth defects in mice and prevention with folate. Am J Clin Exp Obstet Gynecol. 203: 75.e7-75.e15.
82. Tong M, Jason Ziplow, William Cy Chen, Quynh-Giao Nguyen, Charles Kim, et al. (2013). Motor function deficits following chronic prenatal ethanol exposure are linked to impairments in insulin/igf, notch and wnt signaling in the cerebellum. Diabetes Metab J. 4: 238.
83. Sathyan P, Golden HB, Miranda RC. (2007). Competing interactions between micro-RNAs determine neural progenitor survival and proliferation after ethanol exposure: evidence from an ex vivo model of the fetal cerebral cortical neuroepithelium. J Neurosci. 27: 8546.
84. Naassila M, Daoust M. (2002). Effect of prenatal and postnatal ethanol exposure on the developmental profile of mRNAs encoding NMDA receptor subunits in rat hippocampus. J Neurochem. 80: 850-860.
85. Zink M, Thomas Ferbert, Stefanie T Frank, Patricia Seufert, Peter J Gebicke-Haerter, et al. (2011). Perinatal exposure to alcohol disturbs spatial learning and glutamate transmission-related gene expression in the adult hippocampus. Eur J Neurosci. 34: 457-68.
86. Zink M, Gülsemin Araç, Stefanie Th Frank, Peter Gass, Peter J Gebicke-Härter, et al. (2009). Perinatal exposure to alcohol reduces the expression of complexins I and II. Neurotoxicol Teratol. 31: 400-405.
87. Valenzuela CF, Puglia MP, Zucca S. (2011). Focus on: neurotransmitter systems. Alcohol Res Health. 34: 106-120.
88. Yamada L. (2017). A study of the consequences of early gestational ethanol and/or nicotine exposure in the mouse. 2017, The University of Queensland, School of Medicine.
89. Wilson SE, Cudd TA. (2011). Focus on: The use of animal models for the study of Fetal Alcohol Spectrum Disorders. Alcohol Res Health. 34: 92-98.
90. Kleiber ML, Wright E, Singh SM. (2011). Maternal voluntary drinking in C57BL/6J mice: Advancing a model for fetal alcohol spectrum disorders. Behav Brain Res. 223: 376-387.
91. Kaminen-Ahola N, Arttu Ahola, Traute Flatscher-Bader, Sarah J Wilkins, Greg J Anderson, et al. (2010). Postnatal growth restriction and gene expression changes in a mouse model of fetal alcohol syndrome. Birth Defects Res A Clin Mol Teratol. 88: 818-826.
92. Druse MJ, Tajuddin N, Kuo A, Connerty M. (1990). Effects of in utero ethanol exposure on the developing dopaminergic system in rats. J Neurosci Res. 27: 233-240.
93. Detering N, Collins RM Jr, Hawkins RL, Ozand PT, Karahasan A. (1980). Comparative effects of ethanol and malnutrition on the development of catecholamine neurons: Changes in neurotransmitter levels. J Neurochem. 34: 1587-1593.
94. Rathbun W, Druse MJ. (1985). Dopamine, serotonin, and acid metabolites in brain regions from the developing offspring of ethanol-treated rats. J Neurochem. 44: 57-62.
95. Cooper D, Rudeen K. (1988). Alterations in regional catecholamine content and turnover in the male rat brain in response to in utero ethanol exposure. Alcohol Clin Exp Res. 12: 282-285.
96. Shen RY, Hannigan JH, Kapatos G. (1999). Prenatal ethanol reduces the activity of adult midbrain dopamine neurons. Alcohol Clin Exp Res. 23: 1801-1807.
97. Zhou FC, Youssef Sari, Teresa Powrozek, Charles R Goodlett, Ting-Kai Li. (2003). Moderate alcohol exposure compromises neural tube midline development in prenatal brain. Dev Brain Res. 144: 43-55.
98. Shetty AK, Burrows RC, Phillips DE. (1993). Alterations in neuronal development in the substantia nigra pars compacta following in utero ethanol exposure: Immunohistochemical and Golgi studies. Neurosci. 52: 311-322.
99. Shen RY, Hannigan J, Chiodo L. (1995). The effects of chronic amphetamine treatment on prenatal ethanol-induced changes in dopamine receptor function:

Electrophysiological findings. J Pharmacol Exp Ther. 274: 1054-1060.

100. Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F, et al. (2003). Vitamin D3 and brain development. Neurosci. 118: 641-653.

101. Cao G, Zhen Gu, Yongxin Ren, Lei Shu, Chunxiang Tao, et al. (2009). Parathyroid hormone contributes to regulating milk calcium content and modulates neonatal bone formation cooperatively with calcium. Endocrinol. 150: 561-569.

102. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, et al. (1999). Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 283: 70-74.

103. Miller MW. (1986). Effects of alcohol on the generation and migration of cerebral cortical neurons. Science. 233: 1308-1311.

104. O'Leary-Moore SK, Scott E Parnell, Robert J Lipinski, Kathleen K Sulik. (2011). Magnetic resonance-based imaging in animal models of Fetal Alcohol Spectrum Disorder. Neuropsychol Rev. 21: 167-185.

105. Smiley JF, Mariko Saito, Cynthia Bleiwas, Kurt Masiello, Babak Ardekani, et al. (2015). Selective reduction of cerebral cortex GABA neurons in a late gestation model of fetal alcohol spectrum disorder. Alcohol (Fayetteville, N.Y.). 49: 571-580.

106. Sampson PD, Bookstein FJ, Barr HM, Streissguth AP. (1994). Prenatal alcohol exposure, birthweight, and measures of child size from birth to age 14 years. Am J Public Health. 84: 1421-1428.

107. Livy DJ, E Kathryn Miller, Susan E Maier, James R West. (2003). Fetal alcohol exposure and temporal vulnerability: effects of binge-like alcohol exposure on the developing rat hippocampus. Neurotoxicol Teratol. 25: 447-458.

108. Livy DJ, Elberger AJ. (2008). Alcohol exposure during the first two trimesters-equivalent alters the development of corpus callosum projection neurons in the rat. Alcohol. 42: 285-293.

109. Maier SE, West JR. (2001). Regional differences in cell loss associated with binge-like alcohol exposure during the first two trimesters equivalent in the rat. Alcohol. 23: 49-57.

110. Abbott CW, Olga O, Joseph Kanaan, Kara M, Kelly J. (2016). The impact of prenatal ethanol exposure on neuroanatomical and behavioral development in mice. Alcohol Clin Exp Res. 40: 122-133.

111. Willoughby KA, Erin D Sheard, Kelly Nash, Joanne Rovet. (2008). Effects of prenatal alcohol exposure on hippocampal volume, verbal learning, and verbal and spatial recall in late childhood. J Int Neuropsychol Soc. 14: 1022-1033.

112. Parnell SE, Shonagh K, Elizabeth A, Deborah B, Brice W, et al. (2009). Magnetic resonance microscopy defines ethanol-induced brain abnormalities in prenatal mice: Effects of acute insult on gestational day 8. Alcohol Clin Exp Res. 33: 1001-1011.

113. Wozniak DF, Richard E Hartman, Maureen P Boyle, Sherri K Vogt, Ashley R Brooks, et al. (2004). Apoptotic neuro degeneration induced by ethanol in neonatal mice is associated with profound learning/memory deficits in juveniles followed by progressive functional recovery in adults. Neurobiol Dis. 17: 403-414.

114. Parnell SE, Hunter E Holloway, Lorinda K Baker, Martin A Styner, Kathleen K. Sulik. (2014). Dysmorphogenic effects of first trimester-equivalent ethanol exposure in mice: A magnetic resonance microscopy-based study. Alcohol Clin Exp Res. 38: 2008-2014.

115. Burne TH, Jonathon O'Loan, John J McGrath, Darryl W Eyles. (2006). Hyperlocomotion associated with transient prenatal vitamin D deficiency is ameliorated by acute restraint. Behav Brain Res. 174: 119-124.

116. Becker A, Darryl W Eyles, John J McGrath, Gisela Greck. (2005). Transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats. Behav Brain Res. 161: 306-312.

117. Kesby JP, Burne Thomas HJ, McGrath John J, Eyles,Darryl W. (2006). Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: An animal model of schizophrenia. Biol Psychiatry. 60: 591-596.

118. Kesby JP, Xiaoying Cui, Jonathan O'Loan, John J McGrath, Thomas HJ Burne, et al. (2010). Developmental vitamin D deficiency alters dopamine-mediated behaviors and dopamine transporter function in adult female rats. Psychopharmacology. 208: 159-168.

119. Kesby JP, Jonathan C O'Loan, Suzanne Alexander, Chao Deng, Xu-Feng Huang, et al. (2012). Developmental vitamin D deficiency alters MK-801-induced behaviours in adult offspring. Psychopharmacology. 220: 455-463.

120. Kesby JP, Karly M Turner, Suzanne Alexander, Darryl W Eyles, John J McGrath, et al. (2017). Developmental vitamin D deficiency alters multiple neurotransmitter systems in the neonatal rat brain. Int J Dev Neurosci. 62: 1-7.

121. Harms LR, Darryl W Eyles, John J McGrath, Alan Mackay-Sim, Thomas HJ Burne. (2008). Developmental vitamin D deficiency alters adult behaviour in 129/SvJ and C57BL/6J mice. Behav Brain Res. 187: 343-350.

122. Burne TH, Axel Becker, Jillanne Brown, Darryl W Eyles, Alan Mackay-Sim, et al. (2004). Transient prenatal Vitamin D deficiency is associated with hyperlocomotion in adult rats. Behav Brain Res. 154: 549-55.

123. Groves NJ, James P Kesby, Darryl W Eyles, John J McGrath, Alan Mackay-Sim, et al. (2013). Adult vitamin D deficiency leads to behavioural and brain neurochemical alterations in C57BL/6J and BALB/c mice. Behav Brain Res. 241: 120-131.

124. Balden R, Selvamani A, Sohrabji F. (2012). Vitamin D deficiency exacerbates experimental stroke injury and dysregulates ischemia-induced inflammation in adult rats. Endocrinol. 153: 2420-2435.

125. Suzuki M, Masayuki Yoshioka, Masaya Hashimoto, Maiko Murakami, Miki Noya, et al. (2013). Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. Am J Clin Nutr. 97: 1004.

126. Scattoni ML, Crawley J, Ricceri L. (2009). Ultrasonic vocalizations: a tool for behavioural phenotyping of mouse models of neurodevelopmental disorders. Neurosci Biobehav Rev. 33: 508-515.

127. Wellmann KA, Finney George, Fares Brnouti, Sandra M Mooney. (2015). Docosahexaenoic acid partially ameliorates deficits in social behavior and ultrasonic vocalizations caused by prenatal ethanol exposure. Behav Brain Res. 286: 201-211.

128. Hellemans KGC, Pamela Verma, Esther Yoon, Wayne Z Yu, Allan H Young, et al. (2010). Prenatal alcohol exposure and chronic mild stress differentially alter depressive- and anxiety-like behaviors in male and female offspring. Alcohol Clin Exp Res. 34: 633-645.

129. Savage DD, Matthew Becher, Alejandro J de la Torre, Robert J Sutherland. (2002). Dose-dependent effects of prenatal ethanol exposure on synaptic plasticity and learning in mature offspring. Alcohol Clin Exp Res. 26: 1752.

130. Mattson SN, Goodman AM, Caine C, Delis DC, Riley EP. (1999). Executive functioning in children with heavy prenatal alcohol exposure. Alcohol Clin Exp Res. 23: 1808.

131. Cullen CL, Thomas HJB, Nickolas AL, Karen MM. (2013). Low dose prenatal ethanol exposure induces anxiety-like behaviour and alters dendritic morphology in the basolateral amygdala of rat offspring. PLoS One. 8: e54924.

132. Féron F, Burne THJ, Brown J, Smith E, McGrathet JJ, et al. (2005). Developmental Vitamin D 3 deficiency alters the adult rat brain. Brain Res Bull. 65: 141-148.

133. Callinan S, Room R. (2012). Alcohol consumption during pregnancy: results from the 2010 national drug strategy household survey. Found Alc Res Educ.

134. Rice D, Barone S Jr. (2000). Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 3: 511-533.

135. Guerri C. (1998). Neuroanatomical and neurophysiological mechanisms involved in central nervous system dysfunctions induced by prenatal alcohol exposure. Alcohol Clin Exp Res. 22: 304-312.

136. Marino MD, Aksenov MY, Kelly SJ. (2004). Vitamin E protects against alcohol-induced cell loss and oxidative stress in the neonatal rat hippocampus. Int J Dev Neurosci. 22: 363-377.

137. Cui XY, Natalie J Groves, Thomas Hj Burne, Darryl W Eyles, John J McGrath. (2013). Low vitamin D concentration

exacerbates adult brain dysfunction. Am J Clin Nutr. 97: 907-908.

138. Jiang P, Wen-Yuan Zhang, Huan-De Li, Hua-Lin Cai, Yi-Ping Liu, et al. (2013). Stress and vitamin D: Altered vitamin D metabolism in both the hippocampus and myocardium of chronic unpredictable mild stress exposed rats. Psychoneuroendocrinology. 38: 2091-2098.