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Gut instincts: vitamin D/vitamin D receptor and microbiome in neurodevelopment disorders

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The gut microbiome regulates a relationship with the brain known as the gut–microbiota–brain (GMB) axis. This interaction is influenced by immune cells, microbial metabolites and neurotransmitters. Recent findings show gut dysbiosis is prevalent in autism spectrum disorder (ASD) as well as attention deficit hyperactivity disorder (ADHD). There are previously established negative correlations among vitamin D, vitamin D receptor (VDR) levels and severity of ASD as well as ADHD. Both vitamin D and VDR are known to regulate homeostasis in the brain and the intestinal microbiome. This review summarizes the growing relationship between vitamin D/VDR signalling and the GMB axis in ASD and ADHD. We focus on current publications and summarize the progress of GMB in neurodevelopmental disorders, describe effects and mechanisms of vitamin D/VDR in regulating the microbiome and synoptically highlight the potential applications of targeting vitamin D/VDR signalling in neurodevelopment disorders.

1. Introduction

The term 'microbiome' refers to the collective genomes of the microbial communities (bacteria, viruses and fungi) in all niches of the human body, whereas 'microbiota' refers to the microorganisms living in specific locations, such as the gut microbiota. There has been increasing emphasis on the role of the microbiota in physiology, suggesting that the microbiota can be considered as another 'human organ'. The gut microbiota is affected by intrinsic (i.e. genetics, age) and extrinsic (i.e. diet, medications) factors [1]. There is emerging evidence that this invisible 'organ' is a key driver of human health and disease [2].

The GMB axis describes the bidirectional relationship between the central nervous system (CNS) and gut microbiome, and this relationship is thought to be involved in neurodevelopmental disorders [3]. GMB functions are carried out through immune cell activity, metabolite synthesis and neurotransmitter production [3]. ASD and ADHD could be described as gut–brain disorders due to the potential role of gut microbiota [4]. The fifth edition of the *Diagnostic and Statistical Manual* (DSM-5) defines ASD diagnosis as reduced social-emotional reciprocity and nonverbal communication, whereas ADHD is characterized by hyperactivity and inattentiveness [5].

Vitamin D and VDR have novel functions beyond their classical roles in bone development. VDR activates innate immunity and affects intestinal development patterns. In the adult, vitamin D has regulatory roles in mucosal immunity, host defense and inflammation via VDR. This interaction involves host factors and the gut microbiome [6–11]. Vitamin D/VDR signalling is another pillar supporting the potential role of the GMB axis in the aetiology of ASD and ADHD [12,13]. The purpose of this review is to summarize the

progress of GMB in neurodevelopmental disorders, describe roles of vitamin D/VDR in regulating the microbiome, and discuss and highlight the potential role of vitamin D/VDR signalling in the gut–brain–microbiota in ASD and ADHD.

2. Gut microbiota in neurodevelopmental disorders

An adult gut is inhabited by approximately 10^{13} to 10^{14} microorganisms, which collectively exceed the number of human cells in the entire body [14]. Beginning at birth, the gut microbiota acts as an organ by influencing other organs through breakdown of nutrients, biosynthesis of metabolites and modulation of immune system [15]. The microbiota can influence the CNS directly or indirectly. Direct connections include its role in tryptophan metabolism resulting in production and release of neuroactive metabolites, such as serotonin, in the systemic circulation. Indirect connections include modulation of CNS inflammation, alteration of nutrient absorption and modification of metabolism of exogenous drugs [16]. Mice models have shown gut microbiota may change in neurological disorders, such as Parkinson's disease [17], Alzheimer's disease [18] and amyotrophic lateral sclerosis [19].

Gut microbiota alterations may be associated with cognitive as well as social deficits. In a cohort of 89 one-year-olds, a relative overabundance of the genus *Bacteroides* was associated with higher scores on Mullen's Early Learning Composite at age two [20]. Investigators examined if gut microbiota from infancy influenced neurodevelopment later (preschool age). In fecal samples collected between ages 3 and 6 months, abundance of the order *Clostridiales* was associated with poorer communication scores in the Ages and Stages Questionnaire 3 (β, –1.12; 95% CI, –2.23 to –0.01; $p = 0.05$), personal and social scores (β, –1.44; 95% CI, –2.47 to –0.40; $p = 0.01$) at age three [21].

The relationship between GI health and ASD individuals is growing. A longitudinal study of 124 children with ASD and 242 controls revealed that children with ASD had an increased incidence of constipation ($p = 0.003$) compared with controls [22]. In a cohort of 164 individuals with ASD, 49% exhibited common GI abnormalities such as constipation (26%) and diarrhoea (22%) [23]. The mechanism behind GI impairments has not been established. GI irregularities may be caused by microbial dysbiosis which is an imbalance of microbes in the gut microbiota that could alter the integrity of the intestinal barrier [24]. Srikantha *et al.* [3] predicted intestinal permeability caused by a reduction of barrier-forming tight junctions could be a potential biomarker in ASD pathology. However, the mechanism behind this hypothesis is unexplored.

ASD may be induced by maternal immune activation. Meta-analysis of over 40 000 ASD cases in 15 studies found a 1.13 OR (95% CI: 1.03–1.23) increase in ASD risk following maternal infection during pregnancy [25]. Notably, the effects of infection may persist following birth. When measured at age 2–5 years, 97 ASD-diagnosed children born to mothers with infection during pregnancy had the serum inflammatory cytokines IL-1β, IL-6, IL-12 and TNF-α elevated by 76%, 72%, 14% and 28%, respectively, compared with healthy controls, with higher levels correlated to worse disease symptoms [26]. The same cytokines are implicated in inflammatory bowel diseases [27]. IL-6 leads to expansion of CD4T-cells leading to chronic inflammation in the gut [27]. IL-1β induces production of inflammatory cytokines and promotes further expression of IL-6 by enterocytes [28]. Lastly, IL-12 is the chief cytokine for Th1/CD8T-cell differentiation [29]. Biologics against IL-12 (ustekinumab) and TNF-α (adalimumab) are routinely used to treat inflammatory bowel disease, but their usefulness in altering the course of ASD has not been investigated, probably due to high cost and immunosuppressive side effects [30].

In mice, maternal administration of the viral mimic polyriboinosinic-polyribocytidylic acid (poly(I:C)) induces infection. In these offspring, IL-1β, IL-6 and TNF-α are found elevated in the fetal brain and ASD symptoms result [31]. When vitamin D is co-administered with poly(I:C) in mice, ASD-related deficits in social interaction, stereotyped behaviour and emotional learning and memory were abolished. However, there was no change found in concentration of inflammatory cytokines in the brains of mothers or pups, indicating that vitamin D functions through a different pathway [32]. An important interaction that remains to be explored concerns the duelling inflammatory state brought on by dysbiosis and other conditions (e.g. maternal immune activation). For example, an increase in *Clostridium difficile*, a pathogenic microbe [33], in the infant gut has been associated with formula feeding [34]. While most colonization with *C. difficile* remains subclinical, an increase in *C. difficile* composition is associated with atopic conditions in childhood *C. difficile* levels persisted when measured months later. Indeed, breast milk feeding for at least six months is protective against ASD [35]. Vitamin D in breast milk [36] may contribute to gut microbiome growth during infancy. Future work may focus on comparing the relative effect of a spike in inflammation versus sustained dysbiosis because both have been shown to increase the incidence of ASD.

Some growing ideas to reduce GI irregularities and ASD severity including supplementation of probiotics or prebiotics and fecal microbiome transplant (FMT) have been examined in ASD clinical trials [37]. Probiotics are presumably thought to enhance GI health by reducing gut barrier permeability [38]. A probiotic (Vibosome containing *Lactobacillus* and *Bifidobacterium*) was administered to 13 ASD children (ages 3–12 years) to treat GI symptoms for a 19-week trial period. The Vibosome treatment showed significant improvement in GI complaints ($p = 0.02$) [39]. Another possible solution for ASD-GI comorbidities could be administration of vitamin D, because ASD individuals are often dietarily deficient [12]. The potential of vitamin D to improve behavioural ASD symptoms has been established. A clinical trial of vitamin D supplementation (2000 IU per day) in ASD children ($n = 42$; ages 2.5–8 years) for 12 months found that supplementation reduced behavioural irritability ($p = 0.01$) [40]. However, to our knowledge, no study has specifically examined the GI effects of vitamin D supplementation in ASD individuals. Prebiotic supplementation studies in ASD-GI comorbidities are growing. ASD children ($n = 30$) were given a prebiotic supplementation (B-GOS) to investigate the influence on stool and bowel movement as well as social behaviour scores in ASD individuals. The data were not reported, and researchers report no trend of GI discomfort reductions following B-GOS intervention [41]. A growing public interest in both pre- and probiotics led to a randomized clinical trial that investigated the effect of a probiotic containing *Bifidobacterium infantis* plus prebiotic bovine

colostrum product (BCP) mixture in ASD children ($n = 8$; aged 3.9–10.9 years old) with constipation, diarrhoea and/or irritable bowel syndrome. Participants were treated with BCP only and the combination mixture of *B. infantis* plus BCP for 12 weeks. Overall, 75% (6/8) reported greater GI improvement with BCP only treatment compared with 25% (2/8) improvement via combination treatment. A reduced frequency of diarrhoea (BCP: $p = 0.021$ versus combination: $p = 0.021$) and normal stool consistency (BCP: $p = 0.042$ versus combination: $p = 0.015$) was observed in ASD individuals [42]. An open-label clinical trial assessed if FMT from healthy controls ($n = 20$) to ASD-diagnosed children ($n = 18$) rectified constipation, diarrhoea, indigestion and abdominal pain in ASD individuals for 18 weeks. After daily maintenance doses for seven to eight weeks, the study found that 80% children with ASD had decreased GI symptoms ($p < 0.001$) and reduced ASD severity ($p = 0.002$) [43]. A follow-up of this cohort 2 years later showed that treatment subjects saw further improvement of GI and ASD symptoms [44]. The FMT treatment had a long-term effect compared with probiotic and prebiotic treatments. The solution for ASD-GI treatments will keep expanding.

Ming *et al.* hypothesized that altered microbiome composition and increased GI dysfunction may be present in ADHD children [45]. The link between ADHD and gut microbiota is still growing and the current results are varied. The gut microbiota of 14 male ADHD patients (mean age: 11.9 years) and 17 male controls (mean age: 13.1 years) were analysed via next generation 16S rDNA sequencing and examined for diversity and biomarkers. Microbial (α) diversity was significantly decreased ($p_{\text{Shannon}} = 0.036$) in ADHD patients compared with controls while β diversity varied between patients and controls ($p_{\text{ANOSIM}} = 0.033$, $p_{\text{ADONIS}} = 0.006$, $p_{\text{beta-disper}} = 0.002$). At the family level, Bacteroidaceae was overabundant in ADHD patients. The authors suggested the genus *Neisseria* and elevated levels of *Bacteroides spec*. could be associated with juvenile ADHD [46]. External validity is limited by the small sample size in the Prehn-Kristensen study. A different clinical study found that the genus *Bifidobacterium* was abundant ($p = 0.034$) in the gut of ADHD individuals ($n = 19$) compared with healthy controls ($n = 77$). Additionally, a predicted enzyme involved in the synthesis of a dopamine precursor (phenylalanine), cyclohexadienyl dehydratase (CDT) was significantly increased ($p = 0.038$) in ADHD patients compared with controls. *Bifidobacterium* abundance may contribute to the observed differences of CDT in a multiple regression analysis ($p < 0.001$). This finding suggests a hallmark of ADHD, diminished neural reward anticipation (a known functional target of dopamine), may be correlated with overabundance of *Bifidobacterium* in the gut which was positively associated with elevated CDT levels [47].

Studies regarding gut microbiome rebalance in ADHD are limited. A 10-week pilot study investigated the effects of a probiotic mixture (vitamins, minerals, amino acids and antioxidants) on fecal microbiome content in diagnosed ADHD children ($n = 17$; aged 7–12 years). There was no variability among treatment group and placebo in an ADHD scale (ADHD-IV-RS). The treatment group had significantly higher α diversity ($p = 0.005$) compared with controls, changes in Actinobacteria ($W = 6$, clr f statistic = 7.5), reduced *Bifidobacterium* (adj $p < 0.05$) and an inverse relationship between *Bifidobacterium* and ADHD-IV-RS ($p = 0.04$) [48]. These results are promising yet a salient bias is the small sample size. Additionally, the finding raises the question, could one probiotic be more influential in the mixture? Vitamin D as cholecalciferol (200 IU) was included in probiotic mixture. This finding supports the influence of *Bifidobacterium* involvement in ADHD as well as probiotics as a possible treatment.

ADHD is also associated with inflammation dysregulation. In comparison to studies regarding ASD, many fewer studies have been performed correlating maternal infection and ADHD. However, one large cohort study found maternal genitourinary infection was associated with an increase in risk for ADHD (OR = 1.29). Pre-eclampsia was also implicated (OR = 1.19), and both together conveyed highest risk (OR = 1.53) [49]. Comparing a cohort of children with diagnosed ADHD, children with mothers suffering infection displayed more severe ADHD symptoms than those with unstressed or healthy mothers [50]. However, the mechanism of this increased risk is not the same as in ASD, as studies have not identified a specific, definitive correlation between inflammation and ADHD [51–53]. Maternal smoking (pooled RR = 1.58) and obesity (OR = 1.62) are the most widely acknowledged external links to ADHD [54]. It is vital to note that genetics plays a profound role in the pathogenesis of ADHD, with heritability estimated at over 75% [55]. It is interesting to consider whether the gut microbiota of individuals who are predisposed to ADHD, but show no symptoms, may be protective. The ideal study would sample the microbiota of non-ADHD children of parents with ADHD, but does not exist. In fact, very few studies of ADHD include parents with ADHD, possibly because widespread recognition and pharmaceutical treatment of ADHD largely began in the last 25–30 years [56]. Fetal alcohol syndrome, caused by maternal alcohol use *in utero*, may produce an ADHD-like phenotype [57]. Neonates born to mothers who drank any alcohol had a 2.5-fold increase in risk of newborn infection and a 3.4-fold increase in risk if the mother drank heavily [58]. We were unable to find a study linking fetal alcohol syndrome and the microbiome. As adults with ADHD continue to have children, investigation of the protective effects of the gut microbiota on ADHD risk will become more possible.

3. Vitamin D/vitamin D receptor signalling in neurodevelopmental disorders

The human body intakes vitamin D as cholecalciferol through fortified dairy and oily fish or through the conversion of 7-dehydrocholesterol by ultraviolet light [59]. Once in the body, pro-vitamin D is twice hydroxylated into active 1,25-dihydroxy vitamin D ($1,25(OH)_2$, D_3), and binds to the VDR in the cytoplasm. Bound VDR then associates with the retinoid X receptor, and the entire complex enters the nucleus to function as a transcription factor. The greater than 900 DNA sequences modulated by the VDR complex are called vitamin D response elements (VDRE) [8]. Notably, vitamin D is known to upregulate the expression of its own receptor [60,61]. VDR functions as a transcription factor [62]. Target genes of VDR include anti-microbial peptide [17] cathelicidin precursor (also called LL-37) [63,64], β-defensin, [64] and the 1, $25(OH)_2D_3$-regulated VDR-specific, Cyp24 hydroxylase gene. Indeed, approximately 3% of the mouse and human genomes are regulated directly or indirectly by the vitamin D endocrine system, further supporting the possibility of widespread effects of vitamin D and VDR in disease mechanisms

[65–67]. In the brain, vitamin D/VDR signalling promotes neuroprotection by increasing intracellular levels of the antioxidants glutathione and superoxide dismutase [68]. Mice models have shown VDR regulates intestinal homeostasis and microbiota by maintaining butyrate-producing bacteria [69], inhibiting inflammation through the autophagy regulator gene ATG16L1 and increasing anti-microbial peptides [70], and regulating intestinal permeability [71]. Furthermore, human *Vdr* gene variation shapes gut microbiome and abundance of Parabacteroides affected by the VDR signalling in both human and mouse samples [72].

ASD has been negatively correlated with maternal serum vitamin D concentration through many phases of development. Meta-analysis of eight studies found that an increase in autism-related traits and diagnosed ASD was correlated with decreased maternal serum vitamin D concentrations. Reductions in cognitive ability were most associated with low concentration in early-mid pregnancy [73]. This association appears to weaken later in pregnancy; a cohort of 4229 Dutch mother–child pairs found that low vitamin D status at mid-gestation and at delivery was associated with ASD symptoms but low vitamin D at delivery alone was not [74]. A cohort of 468 Indian mothers found no correlation between ASD symptoms serum vitamin D measured at 30 ± 2 weeks gestation [75]. These data support the idea that the major role of vitamin D changes throughout pregnancy. vitamin D is required for calcium metabolism, and its role in bone development is greatest during calcification of the fetal skeleton during the 3rd trimester [76]. Maternal vitamin D is drained during pregnancy and rebounds slowly unless supplemented. Adequate vitamin D appears most critical early in pregnancy, which may explain the increased risk (14.4% versus 6.8%) of ASD recurrence in birth intervals of < 18 months versus greater than 4 years between siblings [77].

Although correlation of maternal vitamin D concentration with ASD may diminish through third trimester, the molecule regains foremost importance during the early years of life. In the infant, serum vitamin D has been negatively correlated with ASD diagnosis [78] and ASD severity, and vitamin D concentration is lower in ASD siblings compared with neurologically normal siblings [79]. A clinical trial found that 85 children with ASD had an increase ($p = 0.041$) in *fok1*, a VDR polymorphism, compared with 82 healthy controls. ASD individuals had decreased serum vitamin D levels which support the notion that VDR activity is strongly tied to serum vitamin D levels in ASD patients [80]. Vitamin D supplementation significantly improves ASD symptoms in deficient patients [78,81]. Comprehensive meta-analyses support findings of individual researchers across ethnicities and nationalities [82]. Thus, the correlation between low serum vitamin D and ASD is established, and further studies are best directed toward describing GMB axis.

The observed effect of maternal serum vitamin D concentration is varied in ADHD. In a cohort study, which stratified maternal serum vitamin D into high (greater than 50.7 nmol l^{-1}) and low (less than 38.4 nmol l^{-1}) groups, the high concentration group showed a reduced incidence of hyperactivity–impulsivity symptoms (IRR = 0.63, 95% CI = 0.39–0.99) and total ADHD-like symptoms (IRR = 0.60, 95% CI = 0.37–0.95) when observed at age 4 [83]. A cohort of 1650 mother–child pairs found an 11% decrease in total ADHD-like symptoms for each 10 ng ml^{-1} increase in serum vitamin D at age 4–5 years [84]. In a different experiment, researchers measured the serum VDR levels of 80 children (40 ADHD diagnosed and 40 healthy controls) ranging from 6–12 years old. Serum VDR levels were significantly decreased (pless than 0.001) in ADHD children compared with controls (1.69 ± 0.22 ng ml^{-1} versus 2.08 ± 0.42 ng ml^{-1}, respectively) [85]. On the other hand, a longitudinal study of 965 pairs found no association between serum vitamin D and diagnosed ADHD when offspring were followed from birth to 21 years of age [86], and a comparison of cord blood from 202 ADHD-diagnosed patients and healthy controls found no correlation of vitamin D concentration [87]. The tentative consensus is that maternal serum vitamin D is associated with ADHD-like behavioural issues at young ages but not with the clinical diagnosis of ADHD.

A stronger correlation exists between low serum vitamin D in the growing child and ADHD. Meta-analysis of available studies showed that concentration decreases of 6.75 ng ml^{-1} from average has a 2.57 OR (95% CI = 1.09–6.04). Similarly, prospective studies show that low perinatal vitamin D concentrations increase risk of diagnosis later in life (RR: 1.40; 95% CI = 1.09–1.81). This meta-analysis must be interpreted with caution, as removal of one study abolishes the correlation [88]. Considering the risk of ASD and ADHD observed with vitamin D deficiency, vitamin D may join folate as recommended supplementation in women preparing for pregnancy. In a different experiment, researchers measured the serum VDR levels of 80 children (40 ADHD diagnosed and 40 healthy controls) ranging from 6 to 12 years old. Serum VDR levels were significantly decreased ($p < 0.001$) in ADHD children compared with controls (1.69 ± 0.22 ng ml^{-1} versus 2.08 ± 0.42 ng ml^{-1}, respectively). The results for these experiments suggest ADHD may have an effect on VDR levels.

4. Gut microbiota and neurotransmitters in autism spectrum disorder and attention deficit hyperactivity disorder

Gut microbiota controls neurobehaviour via modulating brain insulin sensitivity and metabolism of tryptophan, the precursor of serotonin [89]. Increased influx of tryptophan into the brain by HFD could be related to increased blood insulin levels. The neurotransmitter serotonin is low in the brain of ASD individuals [90]. Positron emission tomography scans of autistic children (average age 6.6 years) and their non-autistic siblings (average age 9.9 years) revealed asymmetric changes in serotonin production in the frontal cortex and thalamus of the autistic children [91]. Serotonin synthesis is limited by the enzymes tryptophan hydroxylase 1 (TPH1) in the periphery and TPH2 in the brain and enteric nervous system. The balance of TPH1/2 is under transcriptional control by a VDRE. Vitamin D upregulates transcription of TPH2 and downregulates transcription of TPH1, suggesting that vitamin D deficiency may contribute to lower serotonin levels in the brain [90]. In vitro, 24 h culture of glioblastoma, HCT-116 and HEK-293 cells with vitamin D produced dose-dependent upregulation of TPH2 transcription [92]. In rats, vitamin D supplementation after birth caused a dose-dependent increase in TPH2 expression in the prefrontal cortex [93]. Lastly, vitamin D supplementation in rats represses the transcription of serotonin transporter and monoamine oxidase mRNA and therefore

raises serotonin levels in the brain by modulating both production and breakdown [94].

The BALB/c mice containing a loss-of-function mutation in TPH2 showed a 20% decrease in TPH2 mRNA and 28% fewer TPH2 immunolabelled neurons compared with TPH2 wild-type C57BL/6 J mice [95]. Russo *et al* [96] found that BALB/c mice quantitatively exhibited reduced social behaviour and increased anxious behaviour compared with C57BL/6 J mice. Intriguingly, this study found that in either strain, TPH2 activity was not significantly correlated to the changes in sociability or anxiety. Finally, complete TPH2 knockout in mice generates a psychologic phenotype characteristic of ASD [97]. To our knowledge, no *in vivo* experiment linking maternal vitamin D and offspring TPH1/2 expression has been attempted.

TPH2 is also responsible for producing serotonin in the enteric nervous system (ENS) in the gut. Serotonergic neurons are the first to develop in the ENS where they direct the patterning of future neurons and neurotransmitter secretors [98]. TPH2 knockout mice show intestinal dysmotility. Serotonin dysregulation, secondary to vitamin D deficiency, has been linked to Inflammatory bowel syndrome [41] and inflammatory bowel disease [99,100]. It is possible that serotonin is the common mediator in the changes seen in each of these conditions. Overall, the effect of vitamin D in the neurotransmitter axis of ASD is underexplored, and a secondary process via the microbiome remains plausible.

A hypothesis in the axis of ADHD is alteration of dopamine (DA) and norepinephrine function. DA functions in emotional response, reward, motivation, motor activity and attention, while norepinephrine is a an adrenergic neurotransmitter activating the sympathetic nervous system [101]. Decreased dopamine function may be caused by decreased dopamine release, lower density of dopaminergic neurons or lower levels by each neuron, or overly rapid clearance at the site of action. *In vitro*, adding norepinephrine to culture of rat mesencephalic cells increased the differentiation of dopaminergic neurons [102].

Following release into the synaptic cleft, dopamine activity is terminated via breakdown by monoamine oxidase [103] or via reuptake into the presynapse by the dopamine transporter (DAT) or into synaptic vesicles by vesicular monoamine transporter 2 (VMAT2) [104]. The main described pathway of ADHD involves overabundance of DAT resulting in diminished duration and intensity of DA action [105]. The ADHD medication methylphenidate increases DA activity by binding and inhibiting DAT, while mixed amphetamine salts mainly inhibit VMAT2. Understanding of ADHD in the context of the GMB axis and VDR is limited but growing. In rats, maternal vitamin D deficiency was associated with increased DAT density in the nucleus accumbens of female, but not male, offspring [106]. A study of 96 children with ADHD found that vitamin D supplementation (50 000IU/week) for eight weeks improved ADHD symptoms as assessed by the Conners Parent Rating Scale [107,108]. Vitamin D supplementation produced an increase in dopamine, but not serotonin, in children with ADHD [108].

Norepinephrine is a second neurotransmitter implicated in ADHD pathogenesis. Analogous to the perturbation seen with DA, overactivity of the norepinephrine transporter (NET) causes rapid reuptake of NE into the presynaptic cytoplasm [109]. An alternative ADHD treatment, amphetamine, increases the activity of dopamine and norepinephrine in the brain by displacing them from synaptic vesicles and into the synaptic clefts [110]. Although the simplicity of dopamine as the chief neurotransmitter in reward and motivation in ADHD has been challenged, the dopamine/NE theory remains an acceptable mechanism because of the effectiveness of amphetamine medication [111,112]. Studies have indicated that up to two-thirds of individuals with ADHD have a comorbid mental disorder, such as mood or anxiety disorder, which may be used as a starting point to study ADHD [113].

In ADHD, alterations in neurodevelopment are evident *in utero*. Rats born to vitamin D-deficient mothers display grossly increased lateral ventricle volume and altered appearance of the dopaminergic substantia nigra [114]. VDR activation drives the expression of tyrosine hydroxylase, the rate limiting step in dopamine production [115]. In rats, this activation takes effect *in utero* between E12 and E15 which supports the correlation of maternal vitamin D deficiency in ADHD [116]. DAT overexpression is still believed to be the primary axis, but the effect of low serum vitamin D is certainly strong enough to potentiate or exacerbate the problem. Future work in the neurotransmission axis of ADHD may need to be creative and novel in the incorporation of genetics into experimental conditions.

5. Microbial metabolite in autism spectrum disorder and attention deficit hyperactivity disorder

In humans, metabolites such as short-chain fatty acids (SCFA) are produced via bacterial fermentation in the colon [117], in contrast with mice where fermentation of dietary carbohydrate takes place in the cecum [118]. SCFA consists of 2–6 carbon chains which positively alter the gut microbiome by enhancing anti-inflammatory processes and regulating the enteric neuroendocrine system to promote gut homeostasis [4]. Adequate production of SCFAs has shown positive effects in various diseases including obesity, diabetes, inflammatory bowel diseases as well as psychiatric and neurologic disorders, which has become an interesting aspect of GMB interactions [119]. Metabolome profiling in ASD and ADHD cases is ongoing via clinical trials and mouse models.

Propionate is the SCFAs most produced by ASD prevalent microorganisms [120,121]. SCFA may exert influence on the CNS by binding to free fatty acid receptors [107] in the brain. Propionate bound to the receptor FFAR3 on human brain entholieum inhibited pathways associated with non-specific microbial infections via a CD14-dependent mechanism, suppressed expression of LRP-1 and protected the BBB from oxidative stress via NRF2 signalling [122]. This study was done in post-mortem brains. The influence of SCFAs on a normal functioning brain is unknown. By contrast, butyrate levels in the brain are not naturally high enough to modulate histone deacetylase inhibition in the gut [123].

In order to understand gut microbiome contributions in developing ASD, researchers transplanted microbiota from ASD human donors to germ-free mice and found ASD microbiota may induce hallmark autistic behaviours. Mice colonized with microbiota from ASD human donors had a different microbial composition: a significant decrease in *Bacteroidetes*, *Bacteroides* and *Parabacteroides*, with an increase in *Akkermansia*, *Sutterella* and *Lachnospiraceae*. The brains of mice colonized

with ASD-associated microbiota display alternative splicing of ASD-relevant genes. Metabolome profiles of mice harbouring ASD microbiota ($n = 20$; 4–7 mice per donor) show distinct metabolites in the colon may modulate ASD behaviour. The metabolites taurine and 5-aminovaleric acid (5AV) ($p = 0.0243$) were significantly reduced in mice harbouring ASD microbiota compared with control germ-free mice. Metabolome profile differences between mice models may result from microbial metabolism [124]. This study suggests ASD causes alterations in distinct bacterial phylum, which may lead to the production of certain SCFAs. Taurine is essential for brain development [125], whereas 5AV is described as an anticonvulsant in mice [126]. Clinical trials regarding endogenous SCFA levels in ASD and ADHD are still being developed.

Multiple clinical trials found variation in fecal SCFA within ASD individuals. A clinical trial comparing the levels of fecal SCFAs between ASD children ($n = 23$) and neurotypical children ($n = 31$) aged 11–12 years old found ASD children had higher levels of total SCFAs (136.6 ± 8.7 versus 111.1 ± 6.6 mmol kg^{-1}) compared with neurotypical controls. Specifically, ASD individuals had higher concentrations of acetate, propionate, butyrate, isobutyrate, valerate and isovalerate compared with neurotypical children. Researchers concluded higher concentrations of fecal SCFAs in ASD may not be disastrous to the health of ASD participants [127]. In fact, the high concentration in this cohort was not due to different diets. Additionally, a different clinical assessment of fecal SCFAs in ASD individuals found ASD individuals ($n = 23$) had significantly higher levels of isopropanol ($p = 0.022$) in stool compared with healthy controls ($n = 21$) individuals aged 4–17 years old. High levels of isopropanol were hypothesized to cause GI disturbances like abdominal pain [128]. The microbes *Clostridium beijerinckii* and *C. aurantibutyricum* convert acetone to isopropanol [129,130] yet none of the listed microbes where detected in the feces of ASD or neurotypical children [128]. Isopropanol is rapidly absorbed throught the GI tract [131] yet isoproponal poisioning irritates mucosal surfaces and causes GI impairment such as abdomal pain [132]. Isopropanol is also an organic solvent that preserves fecal SCFA [133]. A 2019 study analysed the relationship between gut microbiome and fecal SCFAs in Chinese autistic and neurotypical children. The presence of SCFAs was altered in ASD individuals; acetic and butyrate levels decreased while valeric acid was increased in the ASD group [134]. A recent study compared fecal SCFA levels between an ASD cohort ($n = 26$) and healthy control ($n = 24$) and found significantly reduced levels of acetate, propionate and butyrate in ASD individuals [135].

Regardless of the variability of SCFA in the previous studies, propionic acidaemia (PA) at birth is suggested to increase ASD risk. PA is a propionate deficiency caused by reduced propionyl-CoA carboxylase (PCC) activity in the liver and other tissues. Interestingly, PA and ASD share most of their core symptoms and multiple case studies report ASD as a comorbidity to PA [136–138]. However, only a few ASD cases were associated with PA: PA has been reported in a 7-year-old girl with ASD [139], five ASD patients [137] and four patients with abnormal PCC and ASD [138]. Overall, the relationship between SCFA and ASD phenotypes is still growing. Differentiation in SCFA concentration suggests the importance to investigate other factors that alter SCFA concentration within ASD.

The SCFA levels associated with ADHD pathogenesis is largely unknown due to difficulty in identifying definite biomarkers. A pilot study investigated microbial differences in the microbiome between ADHD and neurotypical adolescent boys. The investigators found a significant difference between control and ADHD microbial composition. They also found a relative overabundance of *Bifidobacterium* predicts ADHD by upregulating synthesis of phenylalanine, a precursor of dopamine, and decreases neural reward anticipation [47]. A potential biomarker includes intermediate products of tryptophan such as kynurenine, kynurenic acid (KA) and xanthurenic acid (XA) [6]. These metabolites may influence the immune system and neurotransmission in ADHD via inflammatory pathways [140]. VDR deficiency could enhance kynurenine metabolite levels, which may be implicated in ADHD pathology, yet the results are inconclusive. A Norwegian study compared serum levels of kynurenines in 133 adult ADHD patients versus adult controls (18–40 years) and found the ADHD group did not have lower levels of tryptophan, kynurenic acid or xanthurenic acid [141]. These findings contradict a Roman study testing serum kynurenine metabolite in ADHD children ($n = 102$), who exhibited increased kynurenine (+48.6%) and reduced serum KA (−11.2%) and XA levels (−12.5%) compared with healthy controls ($n = 62$) [142]. Limitations in both studies include age, location and serum level measures, which showed kynurenine metabolite activity throughout the body instead of the CNS; both studies only analysed serum levels in ADHD patients. Assessment of intestinal VDR in ADHD microbiome may highlight VDR influence in ADHD metabolites. Unlike ASD, the complexity of ADHD is hard to recapitulate in a mouse model. One study proposed a that mice lacking *Fez1*, a gene in the nervous system, which leads to hyperactivity and impulsivity phenotypes [143]. This mouse model has common ADHD phenotypes, yet some areas are unclear. The authors did not assess the gut microbiota of *Fez1-KO* mice. Furthermore, ADHD studies in metabolites are limited. It would be novel to identify the types and levels of metabolites in ADHD individuals.

Our research has shown that loss of intestinal epithelial VDR leads to an increase in butyrate-producing bacteria in intestinal inflammation [70]. It may be further implicated in the GMB axis of neurologic disorders. Deletion of intestinal epithelial VDR increased kynurenine, a pathway associated with inflammatory neurological disorder in a mouse model [144]. Our recent study has also shown that the mice with VDR deletion in immune cells displayed significant downregulation of quinolinate and tocopherol pathway-derived metabolites and increase in nicotinamide. Quinolinate acts as a neurotoxin, pro-inflammatory mediator and prooxidant molecule. These changes indicate a potential role of VDR in neurophysiology. The role of vitamin D/VDR in gut–brain axis needs further investigation in future research [144].

6. Concluding remarks

ASD is characterized by a multitude of social deficits while ADHD is characterized by inattentiveness, impulsivity and hyperactivity [5]. However, changes in social and behavioural impairments overtime create a predicament in identifying definite biomarkers for both disorders. Gut microbiome disorders are observed in ASD and ADHD. Thus, microbial composition may be an effective biomarker for ASD and ADHD. Our studies and others have demonstrated that VDR regulates the gut microbiome by inhibiting inflammation, maintaining

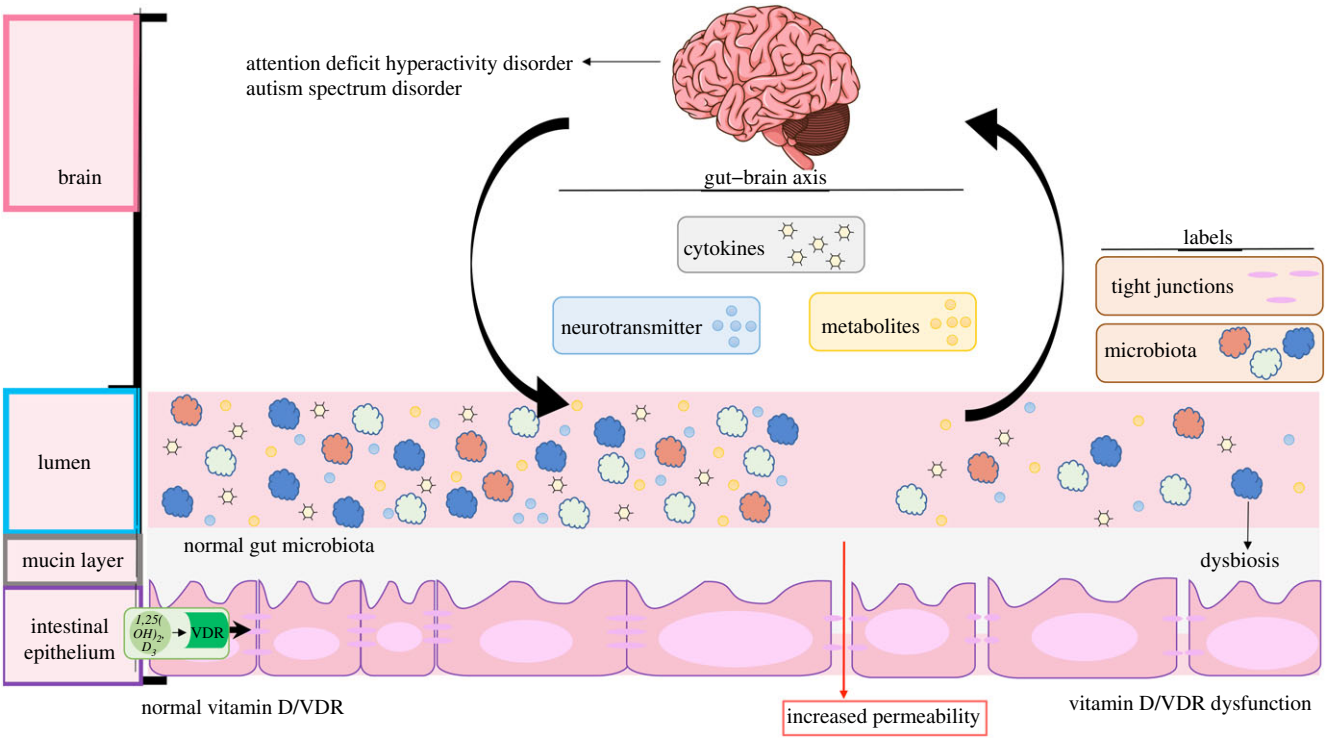

Figure 1. A working model of the potential roles of vitamin D/VDR signalling in ASD and ADHD via the GMB. Vitamin D intake improved GI deficits in ASD individuals yet the mechanisms in vitamin D/VDR signalling are unexplored. Susceptibility to ASD is correlated with polymorphisms in the *VDR* gene as well as low vitamin D in the serum. VDR may decrease microbial dysbiosis, enhance tight junction proteins as well as increase serotonin production, alleviate pro-inflammatory cytokines and increase commensal SCFA production via the GMB.

barrier functions and promoting microbial homeostasis [70–72]. Susceptibility to ASD is correlated with polymorphisms in the *VDR* gene as well as low vitamin D in the serum. It is still unclear if reduction of vitamin D/VDR signalling in the intestinal lumen contributes to the low microbial diversity seen in the gut of ASD and ADHD individuals. We speculate that VDR may modify gut microbiota in ASD and ADHD through GMB axis, such as cytokines, neurotransmitters and SCFAs (figure 1).

Gut microbial patterns in ASD individuals show decreased microbial diversity and some GI irregularities. Vitamin D supplementation reduced irritability in ASD individuals, yet the influence on GI dysfunction and microbial composition is limited. Additionally, the influence of vitamin D supplements via intestinal VDR should be explored to understand how VDR exerts influence in ASD. Immune activity in genetic ASD resembles immune activity in inflammatory bowel disease yet the influence of VDR in ASD immune activity is lacking. VDR may alter neurotransmitter activity in ASD via transcriptional regulation of tryptophan metabolism, the precursor of serotonin, yet the implications of VDR in serotonin activity are limited. Additionally, metabolites enhanced by VDR loss are unexplored in ASD cases. Fecal SCFAs concentrations are altered in ASD individuals yet inconsistencies among studies, suggest that factors, such as diet, age, location and/or cohort size may contribute to the observed differences. Characterization of abnormal SCFAs within ASD warrants further investigation.

There are indirect relationships linking VDR and ADHD via GMB axis. Activation of VDR drives the expression of a rate limiting step in dopamine production, tyrosine hydroxylase. VDR deficiency enhances tryptophan metabolites which are pronounced in the serum of some ADHD individuals. The gut microbiota in ADHD revealed an overabundance of *Bifidobacterium* which acts as a functional target for dopamine. Its influence on the GI barrier is unexplored.

Understanding of gut microbiota involvement in ASD and ADHD is growing. It is highly unlikely that the breadth of effects of vitamin D/VDR dysregulation is limited to just these two disorders. The interplay between brain development, gut microbiota and the VDR may be implicated in other CNS diseases.

Data accessibility. This article has no additional data.

Competing interests. We declare we have no competing interests.

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