Over the past few decades, the prevalence of neurodevelopmental disorders has increased. Several genetic risk factors, including rare and common genetic variants, chromosomal anomalies, and gene defects, have been found through heritability studies. However, there are pre-natal, peri-natal, and post-natal environmental risk factors. Among these factors, disturbed regulation of the neuroactive metabolites has been linked to various neurodevelopmental and neuropsychiatric disorders, including Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), depression, and schizophrenia. As a growing body of research links vitamin D to a range of physiological metabolic processes, the American authors investigated the metabolic impact of vitamin D on early childhood communication abilities that reflect a child's neurodevelopment.

Vitamin D is a fat-soluble vitamin, produced mainly from skin exposure to UVB radiation. The human body metabolizes vitamin D into a series of steroid-like hormones, which regulate a variety of physiological processes, such as bone growth, immune response, brain development, and function. During neurodevelopment, different vitamin D actions were proposed, such as the modulation of autoimmune response, the production of pro-inflammatory cytokines and antioxidants, and the synthesis of neurotransmitters serotonin and dopamine. Vitamin D was shown to activate tryptophan hydroxylase 2, which preferentially converts tryptophan to serotonin over kynurenine. Also, a gestational vitamin D deficiency was found to increase the risk of ASD development, while a reduced ASD incidence was linked with maternal vitamin D supplementation.

In this study, child communication status was measured by the ASQ-communication score (ASQ-comm score), which has been reported to identify 95% of children at risk for ASD based on the Modified Checklist for Autism in Toddlers (M-CHAT). Multiple studies have reported that delayed communication skills in ASD, ADHD, and dyslexia are linked to the disordered metabolism of lipids and fatty acids, which is known to affect brain growth and cognitive development. The studies have also found a strong association between ASD and blood hyper-serotoninemia or overproduction of quinolinic, xanthurenic, and kynurenic acid, linked to enhanced kynurenine and glutamatergic activity.

The same group of authors has previously shown that plasma metabolites associated with the ASQ-comm score at three years of age represent accurate predictors of ASD diagnosis later in life. They have also identified strong associations between tryptophan metabolites and ASQ-comm score in plasma and stool metabolome of children in the Vitamin D Antenatal Asthma Reduction Trial.

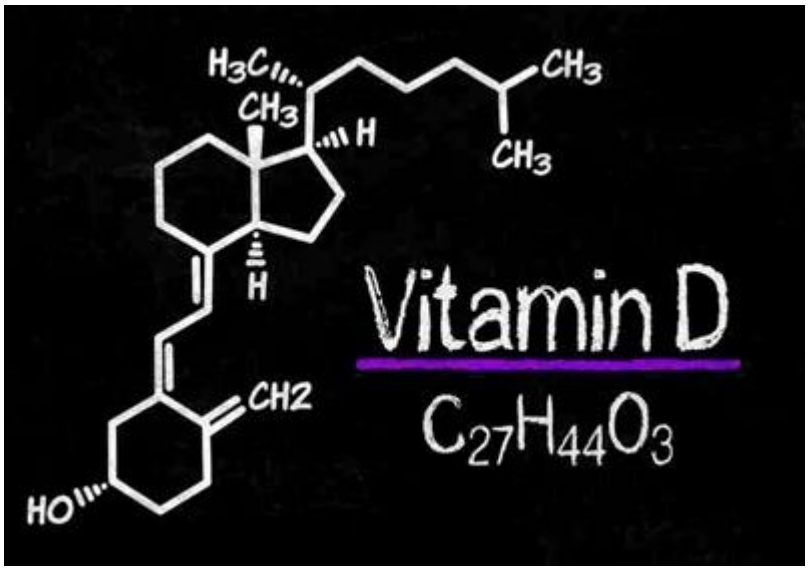
About the study

The authors analyzed the metabolomic profiles of 381 children within the Vitamin D Antenatal Asthma Reduction Trial to investigate the metabolic processes associated with the vitamin D functions linked with neurodevelopment. During pregnancy, their mothers were randomly assigned to receive a daily supplement of 4000 IU of vitamin D3 or a placebo at 10-18 gestational weeks. All women also received a daily multivitamin containing 400 IU of vitamin D3. A supplementation took place until delivery. Offspring were evaluated quarterly through questionnaires and yearly through in-person visits. During the year visit, children's blood samples were collected for plasma metabolomic profiling and serum vitamin D level measurements. Serum vitamin levels were also measured in mothers at 32–38 weeks of gestation and one year after delivery.

During the annual follow-up visit at three years of age, developmental predictors were collected through the Ages and Stages Questionnaire (ASQ). The ASQ is a parent-completed, developmental screening test that evaluates a child's communication, personal-social, problem-solving, fine motor, and gross motor skills. The study was particularly focused on child communication status measured by the ASQ-comm score, which reflects a child's proficiency in different aspects of communication.

Scientists integrated the metabolomic profiles, clinical characteristics (asthma and recurrent wheezing), and communication status of children through a unique network

framework. They applied the LIONESS (Linear Interpolation to Obtain Network Estimates for Single Samples) method, which analyzes individual network relationships connected to individual phenotypes and disease status. To determine the metabolic pathways underlying the Vitamin D Interaction (VDI) network, they performed the Metabolic Set Enrichment Analysis (MSEA) using the Kyoto Encyclopedia of Genes and Genomes (KEGG).



Results

All metabolites were ranked based on the number of their connections, or “degree”, in the Vitamin D Interaction network. The results showed that low levels of vitamin D were associated with changes in the metabolic networks of tryptophan metabolism, linoleic acid metabolism, and unsaturated fatty acid biosynthesis. Within the tryptophan pathway, MSEA analysis indicated serotonin, quinolinate, xanthurenate, tryptophan, and kynurenine as leading metabolites, suggesting that vitamin D may alter metabolic interactions between serotonin and other members of the tryptophan metabolism pathway, including xanthurenate, L-tryptophan, N-formylanthranilic acid, and quinolinate. MSEA-leading metabolites in linoleic acid metabolism included linoleate, dihomolinolenate, and arachidonate. MSEA-leading metabolites annotated for unsaturated fatty acid biosynthesis included docosahexaenoate, stearate, and palmitate.

As these metabolites are major constituents of membrane phospholipids, these findings support recent theories about dysregulation of phospholipid metabolism in patients affected by neurodevelopmental disorders, including ASD and ADHD.

To investigate whether differences within these pathways underlie epidemiological differences among the children within the Vitamin D Antenatal Asthma Reduction Trial, the authors identified five main clusters of the children with different clinical, physiological, and metabolic characteristics.

Vitamin D levels were higher in clusters 3 and 5. Cluster 5 had significantly higher vitamin D levels at three years of age than all other clusters. Vitamin D levels in clusters 3 and 5 at three years of age correlated with maternal vitamin D levels in cord blood and one year after birth. Children in cluster 4 had significantly lower vitamin D levels. Vitamin D levels in cluster 4 at three years of age also correlated with maternal vitamin D levels in cord blood. Except for cluster 4, cluster 2 also had the lowest maternal vitamin D levels in late pregnancy.

This cluster analysis showed significant associations between the vitamin D levels of children and their mothers during and after pregnancy, confirming that maternal vitamin D imbalance may be related to vitamin D imbalance in the offspring in early childhood. According to the authors, this effect could be due to biological factors or breastfeeding habits.

The analysis of the ASQ-communication scores across clusters revealed that children in clusters 3 and 5 with higher vitamin D levels exhibited higher communication scores, with cluster 3 reaching statistical significance. Children in cluster 4 with lower vitamin D levels showed significantly lower communication scores. This cluster (assigned as the low-communication cluster) represented children with delayed communication development. These results support a potential neuroprotective role of vitamin D in early communication development.

As the VDAART cohort was initially established to examine the impact of vitamin D on asthma and allergies, the scientists investigated potential connections between the Vitamin D Interaction network and asthma incidence. The children in cluster 2, whose mothers had the lowest vitamin D levels during late pregnancy, had a higher incidence of asthma and maternal asthma. At age three, 70% of children in cluster 2 had vitamin D concentrations below the deficiency threshold of 20 ng/ml. The researchers concluded that cluster 2 (assigned as the asthma cluster) reflects a different phenotype associated with vitamin D deficiency. This can be interpreted within the context of the immunomodulatory and anti-

inflammatory effects of vitamin D. In support of this opinion, children in cluster 3 with higher vitamin D levels had a lower incidence of asthma. The authors emphasized that several pathways highlighted by this network analysis, such as serotonin and fatty acid metabolism, have been previously implicated in asthma and asthma phenotypes.

Conclusion

This study showed that vitamin D operates through several metabolic pathways, altering interactions within the tryptophan metabolism, lipid metabolism, and unsaturated fatty acid metabolism pathways. The results also supported a potential neuroprotective role of vitamin D in early communication development. As language and communication deficits represent a characterizing feature of various neurodevelopmental disorders, especially ASD, this work offers new insights into the potential of vitamin D as a treatment for ASD and other neurodevelopmental disorders. The authors concluded that further clinical and translational assessments will be crucial for establishing a causative link between vitamin D and ASD.

Journal Reference

De Marzio M, Lasky Su J, Chu SH et al. The metabolic role of vitamin D in children's neurodevelopment: a network study. Scientific Reports 2024; 14: 16929. (Open Access) https://doi.org/10.1038/s41598-024-67835-8