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The Effect of Vitamin D Deficiency on Neurobehavioral Outcomes and Approaches in Children: A Systematic Review

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ABSTRACT

Neurobehavioral disorders are common amongst children around the world, especially in low- and middle-income countries (LMICs). Almost 81 million children under the age of five in these countries have developmental, cognitive, emotional, and social disorders. Vitamin D may affect neurobehavioral outcomes in children through its role in brain development. The present study is a systematic review conducted by searching the databases of Elsevier, PubMed, Springer, Wiley and with the keywords Childhood, Vitamin D, Cognitive function and neurobehavioral outcomes, and studies between 2012 -2020 were reviewed. Out of a total of 968 articles, 20 articles were finally selected based on the inclusion and exclusion criteria for further review, the results of which showed a relation amongst serum levels of vitamin D and neurobehavioral outcomes in children, however, no relation was observed in some articles. More extensive research is needed to further understand the role of vitamin D, as well as the relationamong vitamin D and other factors involved in neurobehavioral approaches and disorders.

KEYWORDS

Cognitive Development, Behavioral Development, Vitamin D, Neuro-behavioral Outcomes.

Introduction

Neurobehavioral disorders are usual among children around the world, andmostly in low- and middle-income countries (LMICs). Almost 81 million children under the age of 5 in these countries have developmental, cognitive, emotional, and social disorders, 44% of whom live in Black Africa. Factors involved in developmental disorders include infection, malnutrition, and micronutrient deficiencies. Vitamin D deficiency is one of the important public health concerns affecting approximately one billion people worldwide[1-5]. This vitamin is fat-soluble and plays an important role in bone health by maintaining homeostasis of calcium. In addition to skeletal systems, normal levels of D (OH) 25 (the main circulating form of vitamin D) is essential for maintaining immunity, reproduction, the cardiovascular system, and the nervous and muscular systems. Vitamin D in humans is synthesized in the skin and in exposure to sunlight (UV-B)[6]. This vitamin may be important for the development of the brain, mostly in the childhood when the brain is growing rapidly and it is also sensitive to deficiencies of nutrients[1]. Vitamin D may have neurobehavioral effectson the development of brain. The receptors and metabolites of this vitamin in cerebrospinal fluid and parts of the brain, including the hippocampus and cortex, may play a major role in brain development. Vitamin D deficiency also causes structural and functional changes in the rodent brain, which is associated with impaired behavior, learning, and motor and cognitive functions. Vitamin D also appears to have an effecton neuroprotection through its anti-inflammatory properties in the brain [7]. This vitamin has aconsiderable role in regulating the growth, differentiation, and arborization of neurons by affecting neurotrophic factors [6, 8-10]. However, studies on the efficacy of vitamin D status on neurobehavioral disorders in children have demonstrated conflicting results. For instance, in a study by Gale et al., no relationship was seenamongst maternal vitamin D status and IQ, mental health, and cardiovascular system of the children[11, 12], but Whitehouse et al. Showed that maternal vitamin D deficiency during gestation is significantly relatedto speech disorders in children [13]. The aim of the presentstudy was to provide a systematic review of published research evidence regarding the efficacy of vitamin D on neurobehavioral outcomes and approachesin children.

Materials and Methods

The present study is a systematic review conducted by searching the databases of Elsevier, PubMed, Springer, Wiley and with the keywords Childhood, Vitamin D, Cognitive function and neurobehavioral outcomes. These words were often used separately and in some cases as a combination of two words. Inclusion criteria were full-text articles on the relation between vitamin D deficiency and neurobehavioral approaches in children considering the limitation of the year of publication (after 2012) and articles published in English and exclusion criteria of the study included

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articles without full text, articles published before 2012, and review articles. In the analysis phase, the information collected from the studies included the author (s), year, objective, method of work, and research results. No interpretation was used during the data collection and the main phrases of the articles, that were used by the author (s), were used.

Results

At the initialstage, 968 titles were selected. At this stage, the title and, if necessary, the abstract of the articles was reviewed, and then 94 studies were selected. In the second stage, the full texts of these articles werestudied and 36 studies were removed due to duplication. Out of the remaining 58 articles, 38 articles were excluded from the study based on inclusion/exclusion criteria, and finally, full texts of 20 articles published in English on the relation between vitamin D deficiency and neurobehavioral outcomes in children were reviewed. The reviewed studies were published between 2012-2020.

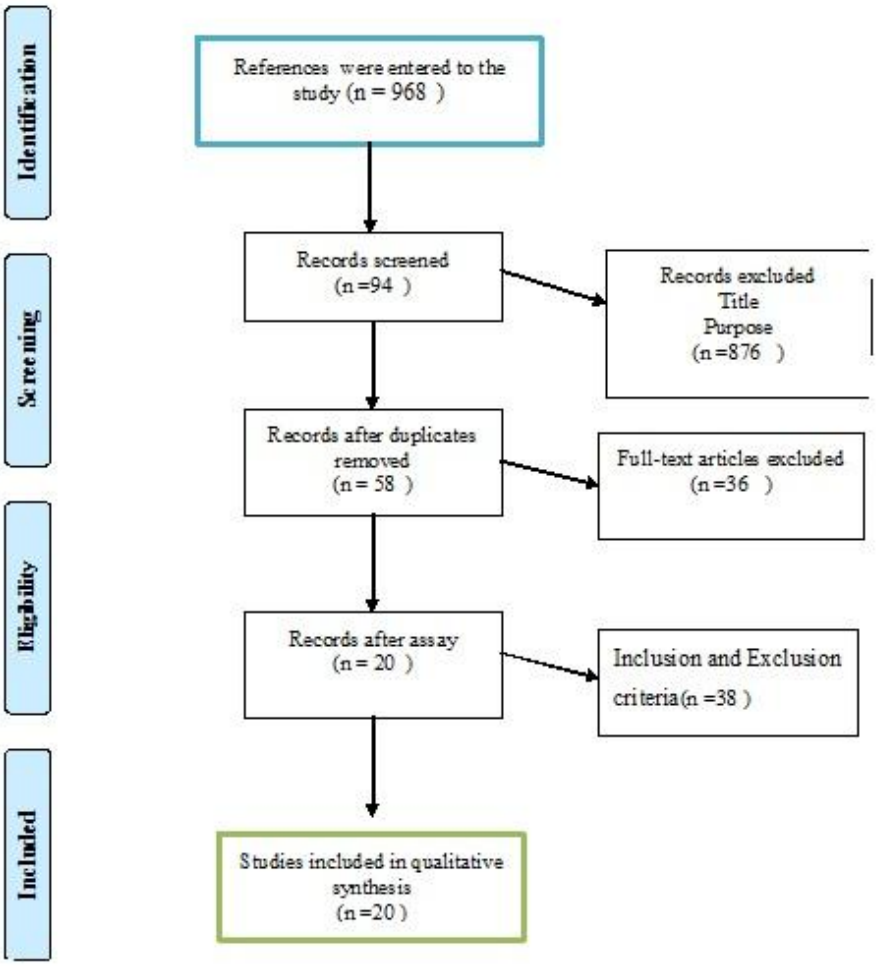

Figure 1. Diagram related to the selection process of the reviewed articles

The objectives and results of these 20 studies are summarized in Table 1. The findings of these studies indicate a relationamong serum levels of vitamin D and neurobehavioral outcomes and approaches (cognitive, motor, language, and behavioral development) in infants and children. 9 studies (45%) in this table examine the relationbetween vitamin D concentration and cognitive and neuronal development in children, of which 6 studies (66.67%) indicated a positive relationship between these two variables[14-19], while 3 studies did not show any association[20-22]. A total of 16,269 mothers and children were examined in these 9 studies; in 13,349 cases (82.05%) high levels of maternal or cord blood vitamin D, could improve intelligence and

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cognitive development and achieve academic success in Children, while in 2920 (17.95%) cases there was no sign of a relationship between vitamin D levels in the mother and cognitive function of children. 5 studies (25%) in this table examined the relationship between vitamin D concentration and motor development in children, of which 3 studies (60%) indicated a positive relationship between these two variables [23-25], while 2 studies (40%) showed no correlation[26, 27]. In a total of 2195 mothers and children who were examined in these 5 studies, in 381 cases (17.38%) the concentration of vitamin D was associated with motor development of children, while in 1814 (82.64) cases no relationship was observed between these variables. 3 studies (15%) in this table examined the relationamongst vitamin D concentration and language and verbal development in children. In these 3 studies, a total of 2265 mothers and children were examined, and in all samples, a positive relationship was seen between these two variables [6, 28, 29]. Tofail et al. showed that higher levels of vitamin D were positively related with improved mood, language, and behavior in children but were not associated with cognitive and motor development [6, 12, 30]. Finally, 3 studies (15%) in this table examined the relation between vitamin D concentration and behavioral development in childhood, of which 2 studies (66.67%) showed a positive relationship between these two variables [31, 32], while 1 study (33.33%) did not show any association [33, 34]. In total, out of 2425 mothers and children who were examined in these 3 studies, in 2325 cases (95.88%), a positive association was observed between vitamin D and primary social and emotional development in children, while in 100 cases (4.12%) no relationship was observed.

Table 1. Results of the studies on the relationship between vitamin D deficiency and neurobehavioral disorders in children

Author	Title	Sample size and method	Results	Conclusion
Keimet. al (2014) [14]	Maternal and cord blood 25(OH)-vitamin D concentrations in relation to child development and behavior	Objective: To investigate the relationship of D (OH) 25 in ≤ 26 weeks of pregnancy in the mother or umbilical cord with growth, IQ, success, and behavior of children in a collaborative project. sample size and method: 3896 mothers and child. Psychologists assessed cognitive growth, IQ and behavior in these cases.	The findings of this research demonstrate that only IQ in children aged seven years old was associated with levels of D (OH) 25 in mother and umbilical cord blood, although the impact estimate was negligible.	These results indicate that the amount of D (OH) 25 in mothers or umbilical cord blood has little correlation with cognitive development, success, and behavior of children in 8 months to 7 years.
Morales et al (2014) [15]	Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development.	Aim: Evaluatingthe relationship between D3 (OH) 25 concentration during pregnancy and neuropsychological development in infants sample size and method: 1820 cases in the first trimester of pregnancy (13.5 ± 2.1 weeks) and their infants. Neonatal IQ and mobility factors were examined at 14 months.	The findings of this researchdemonstrated that the average amount of D3 (OH) 25 in pregnancy was 29.6 ng / ml. There was also a positive linear relationship between D3 (OH) 25 concentrations of mothers during pregnancy and IQ scores in children. Therefore, infants whose mothers' vitamin D concentrations were higher than 30 ng / mL during pregnancy showed higher IQs than those of infants whose mothers had vitamin D levels less than 20 ng/ml.	These results indicate that higher concentrations vitamin D in mothers during pregnancy are related with increased IQ and psychological and motor developments in children.
Zhuet al. (2015) [16]	Cord blood vitamin D and neurocognitive development are nonlinearly related in toddlers	Objective: Evaluating the relationship of cord blood 25 (OH) Dand nerve development. sample size and method: 363 pairs of mother and baby. Mental development and intelligence and psychomotor development scores in toddlers aged 16-18 months were examined.	The findings of this research demonstrated that cases with the lowest levels of vitamin D of umbilical cord had lower MDI and PDI scores compared with the control group. Surprisingly, children with the highest levels of vitamin D of the umbilical cord also showed lower PDI scores compared to the reference group.	These results indicate that there is annegative U-shaped relationamong infant vitamin D levels and neurobehavioral development in children. Further research isrequired on the optimal levels of vitamin D in thechildhood.

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Darlinget al. (2017) [17]	Association between maternal vitamin D status in pregnancy and neurodevelopmental outcomes in childhood: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)	Objective: Evaluating the relation among high serum D (OH) 25 during pregnancy with a decreased risk of neurodevelopmental disorders in children. sample size and method: 7065 pairs of mother and child. The concentration of D (OH) 25 total serum during pregnancy and at least one neurodevelopmental factor in children were assessed.	The findings of this researchdemonstrate that children with maternal vitamin D deficiency (less than 50 nmol / l) were more likely to have lower scores compared to adequate levels of this vitamin. (≥50 nmol / L). No relationship was found amongst vitamin D levels and neural development, including IQ, which wasassessed at older ages.	These findingsdemonstrate that maternal vitamin D deficiency throughout pregnancy caninducenegative effects on some motor and social developmental results in cases under 4 years of age and the prevention of this disorder is important in a normal and desirable development in childhood.
Chi et al. (2018) [18]	The Relationship between Maternal Serum Vitamin D Levels and Infant Neurodevelopment and Anthropometry: A Prospective Observational Study	Objective: Evaluating the relationamong serum levels of vitamin D and nerve growth and anthropometry (the science of measuring different parts of the body) in infants. Samples and Methods: 160 women including 80 pregnant patients with vitamin D deficiency and another 80 pregnant cases with 25 (OH) D levels higher than 50 nmol / L. Follow up was performed for 6 months.	The findings of this researchdemonstrated that the studied groups had significant differencesconsidering the height, weight, or head circumference at birth. However, there is a considerable difference between groups in cognitive and motor development in 6-month-old infants. Also, the results of multivariate analysis demonstrated that maternal vitamin D levels lower 50 nmol /L were related with lower IQ scores at 6 months.	These results indicate that vitamin D levels in the mother are related with neural growth and anthropometry of the child.
Nassar et al. (2012) [19]	Vitamin D status and scholastic achievement in middle age childhood	Objective: Evaluating the associationbetween serum D (OH) 25 status in school children and their academic achievement. sample size and method: 30 children with delayed learning and 15 normal children. In addition to estimating serum D (OH) 25 levels, neurodevelopmental assessments were performed.	The findings of this research demonstrated that the level of D (OH) 25 was considerably lower in children with delayed learning and less academic achievement. On the other hand, image completion scores were considerably lower in cases with insufficient levels or deficiency of D (OH) 25. A positive relation was reportedamong serum D (OH) 25 levels and WISC values. Also, according to the BVRT outcomes, good memory was related with an adequate level of D (OH) 25.	These results indicate that D (OH) 25 deficiency in children with academic achievement impairment causes memory deficits and learning disabilities. Therefore, further studies on a larger scale using learning evaluation tools are suggested to better demonstrate this point and to look for the effect of vitamin D supplementation on academic success in children.
Wanget al. (2018) [20]	Fetal vitamin D concentration and growth, adiposity and neurodevelopment during infancy	Objective: To investigate the relationship between D (OH) 25 of cord blood with growth, obesity, and neural development in infancy. sample size and method: 1244 children. Height, head circumference, and body mass index (BMI) were calculated according to the standard of the WHO.	The findings of this research demonstrated that the mean concentration of D (OH) 25 in cord blood was 22.4 ng/ml. It was also shown that infants born in winter had a lower D (OH) 25 levels. This study showed that there is no association between D (OH) 25 deficiency with Z-score, weight, height and head circumference, or neural development in infancy.	These results suggest that there is no relation among fetal vitamin D concentrations and growth, obesity, or neural development in infancy. It is also obligatory to clarify the effect and mechanical pathway of this vitamin in obesity.

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Veena et al. (2017) [21]	Association between maternal vitamin D status during pregnancy and offspring cognitive function during childhood and adolescence	Objective: Evaluating the relation amongst maternal vitamin D status during gestation and the cognitive ability of children. of sample size and method: 468 children and 472 adolescents Cognitive function in these individuals was assessed using the Kaufman test. Serum D (OH) 25 concentration of mothers was assessed at 30 ± 2 weeks of gestation.	The findings of this researchdemonstrated that 320 women (68%) were deficient in vitamin D during pregnancy (serum D (OH) 25 less than 50 nmol / L). Maternal vitamin D status was not related with the cognitive function of children in both age groups (children and adolescents) both before and after regulation for current child age, sex, maternal age, blood sampling season, gestational age, parental education, maternal intelligence, or home environment.	The findings of this research demonstrated that in this study group, there is no sign of a relationamongst vitamin D levels of the mother and cognitive function of children.
McCarthyet al. (2018) [22]	Antenatal Vitamin D Status Is Not Associated with Standard Neurodevelopmental Assessments at Age 5 Years in a Well-Characterized Prospective Maternal-Infant Cohort	Objective: To investigate the relationamongst maternal and neonatal vitamin D levels and neurodevelopmental outcomes in childhood. Sample size and method: 734 pairs of mother and baby. D (OH) 25 concentration of mothers at 15 weeks of pregnancy and its level in the umbilical cord of newborns were measured at birth. caseswith 5 years of age were also assessed.	The findings of this research demonstrated that the concentration of D (OH) 25 was less than 30 nmol / L in 15% of mothers and 45% of serum umbilical cord of children and the concentrations less than 50 nmol / L was seen in 42% of mothers and 80% of the umbilical cord blood of children. It was also shown that at 5 years of age, the mean IQ scores were 104.6 ± 8.6, verbal tasks were 107.2 ± 10.0 and non-verbal tasks were 99.8 ± 8.8. In addition, growth retardation (scores below 85) was seen in less than 3% of children in all areas. Also, in terms of KBIT-2 and CBCL scores at 5 years of age, there was no difference between children with low levels of maternal vitamin D before delivery (30 or 50 nmol / L). There was no relation between IQ-KBIT and CBCL scores with maternal and umbilical cord D (OH) 25 concentrations.	These findingsshow that there is no sign of anrelation between prenatal D (OH) 25 and neural development outcomes at 5 years of age.
Dhamayantiet al. (2020) [23]	Association of maternal vitamin D deficiency and infants' neurodevelopmental status: A cohort study on vitamin D and its impact during pregnancy and childhood in Indonesia	Objective: Evaluating the relationamongst vitamin D deficiency in the mother and neonatal neurodevelopment. Sample and method: 140 pairs of mother and baby. D (OH) 25 of mothers and child development were assessed at 3, 6, and 12 months of age using the third edition of the Age and Stages Questionnaire (ASQ-3).	The results of this study showed that in 27 mothers (19%) vitamin D deficiency, in 104 infants (76.1%) delayed motor function and in 61 infants (43.7%) delay in problem-solving functions in 3 months of age, was observed. Overall, the mean ASQ score was lower at 3 and 6 months of age in infants whose mothers were deficient in vitamin D. It was also found that the mean ASQ score for motor function at 3 months of age was considerably lower in these children (31.5 vs. 37.9), which increases the risk of delayed motor function at 3 months of age.	These findings indicate that maternal vitamin D deficiency causes neurodevelopmental disorders in infants. In these infants, gross motor function is considerably impaired at 3 months of age.

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Wicklowet al. (2016) [24]	Impact of Vitamin D Supplementation on Gross Motor Development of Healthy Term Infants: A Randomized Dose-Response Trial	Objective: Evaluatingtherelationamongst vitamin D doses and gross motor development at 3 months and 6 months. Sample size and method: 55 healthy infants. These infants received daily vitamin D supplementation at dosages of 400 IU (19 infants), IU 800 (18 infants), and 1200 IU (18 infants).	The results of this study showed that AIMS scores at 3 months of age had no differences but AIMS scores, as well as sitting skills, at 6 months of age in infants who received 400 IU of vitamin D per day were significantly higher in comparison with the daily intake of 800 IU and 1200 IU. However, there is a weak negative association between height and C-3 epimer of D (OH) 25.	These results indicate that, contrary to the initial hypothesis of this study, the achievements and gross motor skills in infants who received IU400 vitamin D daily were significantly higher. These findings also support the theory of a slight delay in motor development of taller infants.
Tavakolizadehet al.[25]	Is There Any Relationship between Vitamin D Deficiency and Gross Motor Development in 12-Month-Old Children?	Objective: Evaluating the possible relationamong vitamin D deficiency and gross motor development in children. Sample size and method of work: 186 healthy one-year-old children referred to children's hospital in Tehran. Of these, 92 were boys (49.5%) and 94 were girls (50.5%). Gross motor development and serum vitamin D concentration of these children were examined.	The results of this study showed that 24 children (12.5%) were able to sit without assistance and support and 40 children (21.5%) stood alone and sat without assistance. In addition, 122 children (65.6%) were able to walk either with or without assistance, sit without support, and stand without assistance. Vitamin D levels were adequate in 148 cases (79.7%) and inadequate in 32 patients (17.2%). Also, 6 people (3.2%) were deficient in this vitamin. Adequate levels of vitamin D were considerablyrelated with the ability to walk.	These outcomes indicate that due to the significant relationamongst vitamin D deficiency and the onset of motor growth in these children, the cases should be carefully examined for vitamin D deficiency in case of delayed motor development.
Filteau S,et al. (2016) [26]	Associations of vitamin D status, bone health and anthropometry, with gross motor development and performance of school-aged Indian children who were born at term with low birth weight	Objective: Evaluating the relationamong vitamin D levels in the motor development of low birth weight (LBW) children. Sample size and method: 912 5-year-old children who participated in the vitamin D test in LBW infants in the first 6 months of age. Using age and stages questionnaire (ASQ) and several criteria of motor function, gross motor development, and its effects on current anthropometry, vitamin D status, bone health, and socioeconomic variables were evaluated.	The results of this study showed that short children (Z height score for age (HAZ) less than negative 2) needed more time to run 20 meters and scored lower in ASQ. Also, the larger arm muscles were related with quicker running time and the ability to perform more standing movements and squats in 15 seconds. On the other hand, low levels of vitamin D wererelated with the ability to perform more standing movements and squats, which indicated that vitamin D status had noeffect on motor development.	These results indicate that there is no relationamong vitamin D status and motor development. HAZ and larger arm muscles are also strongly associated with motor outcomes, possibly due to a combination of physical factors and short stature-related factors.
Trilok-Kumaret al. (2015) [27]	Effects of vitamin D supplementation in infancy on growth, bone parameters, body composition and gross motor development at age 3-6 years: follow-up of a randomized controlled trial	Aim: Evaluating the long-term efficacy of vitamin D supplementation in children. Sample size and working method: 902 children. 446children received vitamin D and 446 children received a placebo. Cognitive development scoreswere assessed to evaluate vitamin D status.	The findings of this research demonstrated that in the group of children receiving vitamin D compared to the group receiving placebo, the Z-scores of body mass index (BMIZ) were lower. As a result, the children in the first group were slightly lower in weight and slightly taller. This group also had less arm and thigh muscle. No differences were seenamong the two groups in terms of body fat percentage, bone QUS (quantitative ultrasound), or blood pressure.	These results showed that consumptionof this vitamin in infants with low birth weight leads to their weight loss at the age of 3 to 6 years, but this vitamin has no effect on the results of motor function.

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Hanieh et al. (2014) [28]	Maternal vitamin D status and infant outcomes in rural Vietnam: a prospective cohort study	Objective: Evaluating the relation between D (OH) 25 in late stages ofgestation and early neonatal growth and developmental results. Sample size and Methods: 960 pregnant cases who had formerlyengaged in a controlled study of prenatal nutritional supplements in rural Vietnam. Maternal D (OH) 25 concentrations were assessed at 32 weeks of pregnancy and infants up to 6 months of age were followed up. Cognitive, motor, linguistic, and socio-emotional criteria were measured and evaluated, and child height was measured at 6 months.	The results of this study showed that among 962 pregnant women studied, 582 (60%) had levels of D (OH) 25 less than 75 nmol / L. It was also shown that children who were born from women with D (OH) 25 deficiencyhad lower lingual development scores than infants born from women with levels of ≥ 75 nmol / L. On the other hand, it was shown that for every 25 nmol increment in D (OH) 25 concentration in late pregnancy, the baby's height z scores at 6 months reduced by 0.08.	These results indicate that low levels of D (OH) 25 are relatedto decreased lingual development at 6 months of age. These findings reinforce the importance of taking vitamin D supplements during gestation.
Gould et al. (2017) [29]	Association of cord blood vitamin D with early childhood growth and neurodevelopment	Objective: Investigating the associationamong D (OH) 25 of cord blood and birth size, childhood growth, and nerve growth. Sample size and Methods: Cord blood samples from 1,040 women who received a docosahexaenoic acid (DHA) supplement during pregnancy in a randomized trial. Height, weight, and head circumference were assessed at birth. A sub-sample of cord blood from 337 infants was selected for nerve growth and development evaluation at 1.5 and 4 years of age. The association between D (OH) 25 and nerve growth outcomes was assessed, considering the treatment with DHA.	The results of this study showed that D (OH) 25 of cord blood was not related with height, weight, or head circumference at birth, 1.5 years, or 4 years of age. It was also shown that D (OH) 25 had no relation with cognitive, motor, socio-emotional scores, or adaptive behaviors at 18 months and cognitive scores at 4 years. On the other hand, an increase in 25 (OH) D of cord blood (>10 nmol / L) was related with an increment in average verbal scores by 0.60 points at 18 months and by 0.68 points at 4 years.	These results suggest that umbilical cord blood vitamin D levels could be positively related with verbal development in early childhood. Randomized controlled studies are required to confirm the relationshipamong vitamin D level and lingual development.
Tofail et al. (2019) [6]	Association of vitamin D nutrition with neuro-developmental outcome of infants of slums in Bangladesh	Objective: Investigating the Associationamong vitamin D and neurobehavioral outcomes in neonates. Sample size and method of work: 265 infants 6 to 8 months. Cognitive, motor, linguistic, and behavioral development of these infants were assessed using the Bayley-III diagnostic-developmental test. Information on infants' mood and communication skills were collected by mothers through the "Mood Scale" and "Developmental Communication List". Serum D (OH) 25 was also measured in 205 neonates.	The findings of this researchdemonstrated that about 28.3% of children in this population had low levels of vitamin D (less than 50 nmol/L). Posterior to controlling all variables, it was shown that cases with vitamin D levels below 50 nmol / L had lower scores in both types of mood (activity and suitability (the ability of infants and children to calm down and recover from anxiety and distress)) than normalcases. These infants also scored low on word comprehension and were less active during the experimental stages. In addition, both groups were similar in cognitive and motor scores.	These results show that despite exposure to sunlight, one in four babies in this impoverished community suffers from vitamin D deficiency. Highlevels of vitamin D in these cases show a positive relation with mood, language, and behavior. These findingsindicatetheefficacyof vitamin D on neurobehavioral outcomes.

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Chawla et al. (2019) [31]	Early prenatal vitamin D concentrations and social-emotional development in infants	Objective: To investigate the relationship between D (OH) 25 concentrations before birth and the social and emotional development of children. Sample size and working method: 218 pairs of mother and baby. Concentrations of D (OH) 25 in the first or second trimester were measured and the emotional-social development of children aged 12 to 24 months was assessed. Results were evaluated based on race and ethnicity.	The results of this study showed that black mothers had significantly lower D (OH) 25 concentrations than white and Native American mothers. Low levels of D (OH) 25 before birth were also associated with higher internalization scores amongst white children and lower scores among black and Native American children. Low levels of prenatal D (OH) 25 also appear to be related with higher scores of behavioral disorders only among white and Native American children.	These results suggest the need for further research on the efficacy of prenatal vitamin D in social and emotional development in children.
López-Vicenteet al. (2019) [32]	Maternal circulating Vitamin D_3 levels during pregnancy and behavior across childhood	Objective: Investigating the relationship between vitamin D3 of the motherand nerve growth and social skills in children. Sample size and working method: 2107 pairs of mother and baby. Maternal vitamin D3 was measured during pregnancy and the results were assessed in children aged 5, 8, 14, and 18 years, through questionnaires.	The results of this study showed that for every 10 ng / mL increase in maternal vitamin D3 levels, children scored higher social scores at age 5, but little correlation was observed among vitamin D3 of the mother and total behavioral disorderds and ADHD and ASD signs in children	These results suggest the need for further research in populations at risk for vitamin D deficiency.
Chowdhury et al. (2017) [33]	Vitamin-D status and neurodevelopment and growth in young north Indian children: a secondary data analysis.	Objective:Investigating the relationamong vitamin D deficiency (less than 10 ng/ml) and neurological and physical development in children. Sample size and working method: 1000 children. In this study, the data from a randomized study, in which infants aged 6 to 30 months received folic acid or vitamin B12 supplements daily for 6 months, was used. Vitamin D in these children was measured and nerve growth was assessed. The follow-up period was six months.	D (OH) 25 was initially measured for 960 children and the results showed that of these, 331 children (34.5%) were deficient in vitamin D (less than 10 ng/ml). Total and subscale ASQ-3 scores (excluding socio-personal scale) did not differ between children with and without vitamin D deficiency. Also, there was no relationamong deficiency of this vitamin and physical growth, at the beginning of the study and during follow-up.	The findingsof this study do not show a relation among vitamin D deficiency and poor physical and neurological development.

Discussion

The objective of this research was to systematically evaluatethe efficacy of vitamin D on neurobehavioral outcomes in children. Out of a total of 968 studies with topics similar to the objective of the study, finally 20 articles were selected for further review. By reviewing these articles, it was found that adequate levels of maternal or cord blood vitamin D are related with better neurodevelopmental outcomes and approaches in childhood, and in contrast, deficiency of this vitamin may cause neurological, behavioral, and motor disorders in children. However, in 6 articles, no relationship was observed between vitamin D levels and cognitive, motor, and behavioral development, which was also observed in other studies [11, 34-38].

The mood could be specified as individual differences in emotional, motor, attention, and self-regulatory reactions [39]. These dimensions constitute behavioral traits and can be biological or innate, existing from birth and persisting over time, and might be influenced by heredity, lifestyle, environment, and nutrition in infancy. Temperament is important in infancy because it is related with an increased risk of future behavioral problems and disorders [40]. Vitamin D is a fat-soluble nutrient that modulates calcium absorption and bone health[41]. It also plays a major role in nerve growth and function and is known as an essential neurosteroid with a variety of functions in the brain. D (OH) 25 crosses the BBB and enters glial cells and nerve cells to be converted to 1,25-dihydroxyvitamin D, the active form of vitamin D. The synthesis and degradation of vitamin D occur in the brain. VDR is an intranuclear steroid receptor that is needed for vitamin D to demonstrate its efficacy in various areas of the brain. Previous

articlesdemonstrated arelation among decreased vitamin D levels and cognitive impairment, dementia, psychosis, and autism[42]. Vitamin D also helps growth plate cells become more susceptible to the growth hormone function, which has a majorefficacyon the development of school-age children [33]. Although there are no guidelines for optimal serum levels of D (OH) 25 as the most important indicator of overall vitamin D status, D (OH) 25 levels less than 50 L / nmol (20 ng / mL),50-75 L / nmol (20-30 ng / mL), and 75-100 L / nmol (30 ng / mL) are considered as deficiencies, inadequate levels and normal levels of the vitamin D, respectively. Also, Serum D (OH) 25 above 150 ng / mL is defined as vitamin D poisoning [43].

Conclusion

In this systematic review, it was shown that inadequate levels of maternal or cord blood vitamin D during pregnancy causes neurobehavioral disorders in infants, however, due to the contradictory results of the studies on the efficacy of vitamin D concentrations on neurobehavioral outcomes in children, it is necessary to conduct more studies in this field, in order to further understand the effect of vitamin D and also to explore the interactions of vitamin D and other factors involved in neuro-behavioral approaches and disorders.

References

[1] Mutua, A.M., Mogire, R.M., Elliott, A.M., Williams, T.N., Webb, E.L., Abubakar, A., &Atkinson, S.H. (2020). Effects of vitamin D deficiency on neurobehavioural outcomes in children: a systematic review. *Wellcome Open Research*, 5, 28. http://doi.org/10.12688/wellcomeopenres.15730.2

[2] Rahbarimanesh, A., Ehsani, M., Karahroudi, M., Rashidi, A., Aghajani, M., Meysami, A., & Keyvani, H. (2015). Cytomegalovirus disease in children with acute lymphoblastic leukemia in the nontransplant setting: case series and review of the literature. *Journal of pediatric hematology/oncology*, *37*(6), 429-432.

[3] Delavar, M.A., &Karimian, P. (2020). Evaluation of the effect of vitamin D in children with asthma: A systematic review.*Pakistan Journal of Medical & Health Sciences,14*(3), 1686-1693.

[4] Dezfouli, S.M.M., &Khosravi, S. (2020). Systematic review of the effective factors in pain management in children. *Pakistan Journal of Medical & Health Sciences*, *14*(2), 1236-1243.

[5] Khosravi, S., & Dezfouli, S.M.M. (2020). Prevention and Treatment Approaches in Children with the Coronavirus. *Systematic Reviews in Pharmacy*, *11*(9), 913-919.

[6] Tofail, F., Islam, M.M., Mahfuz, M., Ashraful Alam, M., Aktar, S., Haque, R., & Ahmed, T. (2019). Association of vitamin D nutrition with neuro-developmental outcome of infants of slums in Bangladesh. *PLoS One*, *14*(9), e0221805. https://doi.org/10.1371/journal.pone.0221805

[7] Mutua, A.M., Nampijja, M., Elliott, A.M., Pettifor, J.M., Williams, T.N., Abubakar, A., & Atkinson, S.H. (2020). Vitamin D Status Is Not Associated with Cognitive or Motor Function in Pre-School Ugandan Children. *Nutrients*, *12*(6), 1662.https://doi.org/10.3390/nu12061662

[8] Zandieh, F., Mirsaed, G.B., Izadi, A., Gharegozlu, M., Aghajani, M., & Sheikh, M. (2014). Papillon Lefevre Syndrome and Footprints of Mycobacterium Tuberculosis. *Iranian Journal of Allergy, Asthma and Immunology*, *13*(4), 286-289.

[9] Dezfouli, S.M.M., & Khosravi, S. (2020). Pain in child patients: A review on managements. *European Journal of Translational Myology*, *30*(2), 8712.

[10] Khosravi, S., & Dezfouli, S.M.M. (2020). Investigating the Rapid Method of Diagnosing Meningitis in Humans. *Journal of Critical Reviews*, *7*(13), 275-280.

[11] Gale, C.R., Robinson, S.M., Harvey, N.C., Javaid, M.K., Jiang, B., Martyn, C.N., & Cooper, C. (2008). Maternal vitamin D status during pregnancy and child outcomes. *European journal of clinical nutrition*, *62*(1), 68-77. https://doi.org/10.1038/sj.ejcn.1602680

[12] Delavar, M.A., & Soheilirad, Z. (2020). Drug and herbal medicine-induced nephrotoxicity in children; review of the mechanisms. *Journal of Renal Injury Prevention*, *9*(3), e21-e21.

[13] Whitehouse, A.J., Holt, B.J., Serralha, M., Holt, P.G., Kusel, M.M., & Hart, P.H. (2012). Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*, *129*(3), 485-493. https://doi.org/10.1542/peds.2011-2644

[14] Keim, S.A., Bodnar, L.M., & Klebanoff, M.A. (2014). Maternal and cord blood 25 (OH)-vitamin D concentrations in relation to child development and behaviour. *Paediatric and perinatal epidemiology*, *28*(5), 434-444. https://doi.org/10.1111/ppe.12135

[15] Eva, M., Mònica, G., Sabrina, L., ClaraL. Rodríguez-Bernal, Adonina, T., Isolina, R., Jesús, I., Nerea, L., Mercedes, E., Agueda, R., & Jordi, S. (2012). Circulating 25-hydroxyvitamin-D3 in pregnancy and infant

neuropsychological development. *Pediatrics*, *130(4)*, e913-e920.https://doi.org/10.1542/peds.2011-3289

[16] Zhu, P., Tong, S.L., Hao, J.H., Tao, R.X., Huang, K., Hu, W.B., & Tao, F. B. (2015). Cord blood vitamin D and neurocognitive development are nonlinearly related in toddlers. *The Journal of nutrition*, *145*(6), 1232-1238.https://doi.org/10.3945/jn.114.208801

[17] Darling, A.L., Rayman, M.P., Steer, C.D., Golding, J., Lanham-New, S.A., & Bath, S.C. (2017). Association between maternal vitamin D status in pregnancy and neurodevelopmental outcomes in childhood: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *British Journal of Nutrition*, *117*(12), 1682-1692. https://doi.org/10.1017/s0007114517001398

[18] Chi, M.Z., Zhu, L., Zhang, Z.L., Jin, F.F., Shao, H.R., Zheng, J.Y., & Hu, G.Q. (2018). The relationship between maternal serum vitamin D levels and infant neurodevelopment and anthropometry: a prospective observational study. *Journal of nutritional science and vitaminology*, *64*(2), 161-167. https://doi.org/10.3177/jnsv.64.161

[19] Nassar, M.F., Amin, D.A., Hamed, A.I., Nassar, J.F., Abou-Zeid, A.E., & Attaby, M.A. (2012). Vitamin D status and scholastic achievement in middle age childhood. *Journal of the Egyptian Society of Parasitology*, *42*(2), 349-358.https://doi.org/10.12816/0006322

[20] Wang, H., Yu, X.D., Huang, L.S., Chen, Q., Ouyang, F.X., Wang, X., & Zhang, J. (2018). Fetal vitamin D concentration and growth, adiposity and neurodevelopment during infancy. *European journal of clinical nutrition*, *72*(10), 1396-1403.https://doi.org/10.1038/s41430-017-0075-9

[21] Veena, S.R., Krishnaveni, G.V., Srinivasan, K., Thajna, K.P., Hegde, B.G., Gale, C.R., & Fall, C.H. (2017). Association between maternal vitamin D status during pregnancy and offspring cognitive function during childhood and adolescence. *Asia Pacific journal of clinical nutrition*, *26*(3), 438-449. https://doi.org/10.6133/apjcn.032016.07

[22] McCarthy, E.K., Murray, D.M., Malvisi, L., Kenny, L.C., O'B Hourihane, J., Irvine, A.D., & Kiely, M.E. (2018). Antenatal vitamin D status is not associated with standard neurodevelopmental assessments at age 5 years in a well-characterized prospective maternal-infant cohort. *The Journal of nutrition*, *148*(10), 1580-1586.https://doi.org/10.1093/jn/nxy150

[23] Dhamayanti, M., Noviandhari, A., Supriadi, S., Judistiani, R.T., & Setiabudiawan, B. (2020). Association of maternal vitamin D deficiency and infants' neurodevelopmental status: A cohort study on vitamin D and its impact during pregnancy and childhood in Indonesia. *Journal of paediatrics and child health*, *56*(1), 16-21.

[24] Wicklow, B., Gallo, S., Majnemer, A., Vanstone, C., Comeau, K., Jones, G., & Rodd, C. (2016). Impact of vitamin D supplementation on gross motor development of healthy term infants: a randomized dose-response trial. *Physical & occupational therapy in pediatrics*, *36*(3), 330-342. https://doi.org/10.3109/01942638.2015.1050150

[25] Tavakolizadeh, R., Ardalani, M., Shariatpanahi, G., Mojtahedi, S.Y., & Sayarifard, A. (2019). Is There Any Relationship between Vitamin D Deficiency and Gross Motor Development in 12-Month-Old Children?. *Iranian journal of child neurology*, *13*(3), 55-60.

[26] Filteau, S., Rehman, A.M., Yousafzai, A., Chugh, R., Kaur, M., Sachdev, H.P.S., & Trilok-Kumar, G. (2016). Associations of vitamin D status, bone health and anthropometry, with gross motor development and performance of school-aged Indian children who were born at term with low birth weight. *BMJ open*, *6*(1), e009268.https://doi.org/10.1136/bmjopen-2015-009268

[27] Trilok-Kumar, G., Kaur, M., Rehman, A.M., Arora, H., Rajput, M.M., Chugh, R., & Filteau, S. (2015). Effects of vitamin D supplementation in infancy on growth, bone parameters, body composition and gross motor development at age 3–6 years: follow-up of a randomized controlled trial. *International journal of epidemiology*, *44*(3), 894-905.https://doi.org/10.1093/ije/dyv116

[28] Hanieh, S., Ha, T.T., Simpson, J.A., Thuy, T.T., Khuong, N.C., Thoang, D.D., & Biggs, B.A. (2014). Maternal vitamin D status and infant outcomes in rural Vietnam: a prospective cohort study. *PloS one*, *9*(6), e99005. https://doi.org/10.1371/journal.pone.0099005

[29] Gould, J.F., Anderson, A.J., Yelland, L.N., Smithers, L.G., Skeaff, C.M., Zhou, S.J., & Makrides, M. (2017). Association of cord blood vitamin D with early childhood growth and neurodevelopment. *Journal of paediatrics and child health*, *53*(1), 75-83.

[30] Shoar, S., Naderan, M., Aghajani, M., Sahimi-Izadian, E., Hosseini-Araghi, N., & Khorgami, Z. (2016). Prevalence and determinants of depression and anxiety symptoms in surgical patients. *Oman medical journal*, *31*(3), 176-181.

[31] Chawla, D., Fuemmeler, B., Benjamin-Neelon, S.E., Hoyo, C., Murphy, S., & Daniels, J.L. (2019). Early prenatal vitamin D concentrations and social-emotional development in infants. *The Journal of Maternal-Fetal & Neonatal Medicine*, *32*(9), 1441-1448.https://doi.org/10.1080/14767058.2017.1408065

[32] López-Vicente, M., Sunyer, J., Lertxundi, N., González, L., Rodríguez-Dehli, C., Espada Sáenz-Torre, M., Vrijheid, M., Tardón, A., Llop, S., &Torrent, M.(2019). Maternal circulating Vitamin D(3) levels during pregnancy and behaviour across childhood. *Scientific Reports*, *9*(1), 14792. https://doi.org/10.1038/s41598-019-51325-3
[33] Chowdhury, R., Taneja, S., Bhandari, N., Kvestad, I., Strand, T.A., &Bhan, M.K. (2017). Vitamin-D status and neurodevelopment and growth in young north Indian children: a secondary data analysis. *Nutrition Journal*, *16*(1), 59. https://doi.org/10.1186/s12937-017-0285-y
[34] Fahimi, D., Delavar, M.A., Karahoudi, M., Honarmand, M., & Eghbalkhah, A. (2014). Comparison of Two Intravenous Fluid Maintenance Therapy with Different Sodium Concentrations in Hospitalized Children: A Randomized Trial Study. *Journal of Pediatric Nephrology*, *2*(3), 110-115.
[35] Laird, E., Thurston, S.W., Van Wijngaarden, E., Shamlaye, C.F., Myers, G.J., Davidson, P.W., & Strain, J.J. (2017). Maternal vitamin D status and the relationship with neonatal anthropometric and childhood neurodevelopmental outcomes: results from the Seychelles Child Development Nutrition Study. *Nutrients*, *9*(11), 1235.https://doi.org/10.3390/nu9111235
[36] Schmidt, R.J., Niu, Q., Eyles, D.W., Hansen, R.L., & Iosif, A.M. (2019). Neonatal vitamin D status in relation to autism spectrum disorder and developmental delay in the CHARGE case–control study. *Autism Research*, *12*(6), 976-988. https://doi.org/10.1002/aur.2118
[37] Rahimi, H., & Karimian, P. (2020). RT-PCR Urine Pool Test, The Probable Method For Congenital Cyto-Megalovirus Infection Diagnosis And Screening in the Near Future; An Observational Study and Literature Review. *Journal of Critical Reviews*, *7*(13), 284-290.
[38] Karimian, P., & Delavar, M.A. (2020). Comparative Study of Clinical Symptoms, Laboratory Results and Imaging Features of Coronavirus and Influenza Virus, Including Similarities and Differences of Their Pathogenesis.*Pakistan Journal of Medical & Health Sciences*, *14*(3), 1405-1411.
[39] Rothbart, M.K., Bates, JE., Damon, W., &Eisenberg, N. (2006). Handbook of child psychology:Social, emotional, and personality development. *Temperament*, 99-166.
[40] Wachs, T.D. (2009). Models linking nutritional deficiencies to maternal and child mental health. *The American journal of clinical nutrition*, *89*(3), 935S-939S.https://doi.org/10.3945/ajcn.2008.26692B
[41] Parodi, V., De Florentiis, D., Martini, M., & Ansaldi, F. (2011). Inactivated influenza vaccines. *Drugs & aging*, *28*(2), 93-106.https://doi.org/10.2165/11586770-000000000-00000
[42] Anjum, I., Jaffery, S.S., Fayyaz, M., Samoo, Z., & Anjum, S. (2018). The role of vitamin D in brain health: a mini literature review. *Cureus*, *10*(7), e2960. https://doi.org/10.7759/cureus.2960
[43] Ali, N.S., & Nanji, K. (2017). A review on the role of vitamin D in asthma. *Cureus*, *9*(5), e1288. https://doi.org/10.7759/cureus.1288