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Review Article

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# The importance of vitamin B12 for neurological and cognitive function: from pregnancy to childhood

## A importância da vitamina B12 para a função neurológica e cognitiva: da gestação à infância

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**Resumo**
**Introdução:** A vitamina B12 apresenta importância para o sistema nervoso central, estando envolvida em processos como o desenvolvimento cerebral, a mielinização neural e a função cognitiva. **Objetivo:** Examinar as evidências que relacionam a vitamina B12 materna e na infância com o desenvolvimento neurológico e cognitivo. **Materiais e métodos:** Revisão narrativa da literatura dos últimos 40 anos. A questão de pesquisa norteadora para a seleção dos estudos foi: O status de vitamina B12 materna, seja na gestação quanto no período da amamentação, ou ingestão alimentar ou suplementar de B12 para a gestante, nutriz ou prole, pode influenciar o desenvolvimento neurológico e cognitivo desses lactentes e dessas crianças? **Resultados:** O status de vitamina B12 materno durante a gravidez e no período da amamentação apresenta influência no status de B12 dos filhos. Durante a infância a deficiência de B12 se correlaciona com falhas no desenvolvimento cerebral e no crescimento, enquanto os dados sobre sua influência em parâmetros cognitivos infantis apresentam resultados conflitantes. Mulheres veganas ou vegetarianas devem garantir uma ingestão suficiente de vitamina B12 para conseguir fornecer adequadamente também para seu bebê em desenvolvimento uma vez que apresentam maior risco de insuficiência. **Conclusões:** O status de vitamina B12 materno, tanto na gestação quanto durante a amamentação, é um determinante essencial do status de B12 na prole. A heterogeneidade dos estudos impossibilita conclusões definitivas sobre o tema.
**Palavras-chave:** Transtornos do neurodesenvolvimento. Aleitamento materno. Dieta vegetariana.

**Abstract**
**Introduction:** Vitamin B12 is important for the central nervous system, being involved in processes such as brain development, neural myelination and cognitive function. **Objective:** To examine the evidence that links maternal and childhood vitamin B12 with neurological and cognitive development. **Materials and methods:** Narrative literature review of the last 40 years. The guiding research question for the selection of the studies was: The maternal vitamin B12 status, either during pregnancy or during the breastfeeding period, or food or supplemental B12 intake for pregnant women, breastfeeding woman or offspring, can influence the neurological and cognitive development of these infants and children? **Results:** The maternal vitamin B12 status during pregnancy and breastfeeding has an influence on the children's B12 status. During childhood, B12 deficiency correlates with failures in brain development and growth, while data on its influence on children's cognitive parameters show conflicting results. Vegan or vegetarian women must ensure sufficient intake of vitamin B12 to be able to adequately supply their developing baby as well as they are at greater risk of failure **Conclusions:** Maternal vitamin B12 status in both pregnancy and breastfeeding is an essential determinant of B12 status in offspring. The heterogeneity of the studies precludes definitive conclusions on the subject.
**Keywords:** Neurodevelopmental Disorders. Breast Feeding. Vegetarian Diet.

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## Introduction

Micronutrients are essential for the physiological functioning of the body at different stages of life[1,2]. Its deficiencies are still seen in greater prevalence in developing countries[3], and it mainly affects vulnerable populations, such as women in reproductive age, children, adolescents, and the elderly, especially those socioeconomically disadvantaged and food insecure[1,2].

Historically, vitamin B12 deficiency, also known as cobalamin, was studied in the clinical setting when patients had symptoms caused by pernicious anemia, which is an autoimmune clinical condition that causes stomach cells not to produce the intrinsic factor necessary for absorption of this vitamin[4]. However, its importance for the central nervous system, as it is involved in processes such as brain development, neural myelination, and cognitive function[5,6], made us evaluate this deficiency in the child population, as it can cause delays in growth and cognitive development, which, in turn, can be irreversible[7,8].

The aim of this review was to examine the evidence linking the importance of maternal and childhood vitamin B12 to child development, especially neurological and cognitive.

## Materials and methods

The present study consists of a thorough and comprehensive narrative literature review. National and international databases were searched from August to December 2020. Our guiding research question for the selection of the studies was: Can the maternal vitamin B12 status, either during pregnancy or throughout the breastfeeding period, or food or supplemental B12 intake for pregnant women, breastfeeding women, or offspring, influence the neurological and cognitive development of these infants and children? Articles from the last 40 years (1980-2020) were selected and no language restriction was applied.

The search terms were: “vitamin B12”, “vitamin B12 deficiency”, “cobalamin” and “cognition”, “cognitive function”, “cognitive disorders”, “mental processes”, “attention”, “memory”, “intelligence quotient”, “mental development”, “understanding”, and “problem solving” in English, Portuguese, and Spanish. Studies carried out and not published, abstracts of scientific events (published or not), dissertations, and theses were excluded. The searches found 172 articles, and after reading the title and abstracts, 133 articles were excluded. Thus, 39 articles were selected for full reading.

## Definition and metabolism

Cobalamins are members of a cobalt family containing compounds found in nature and called corrinoids. Vitamin B12 is an essential dietary nutrient for humans found in animal foods, such as meat, eggs, milk, and other dairy products[9,10]. Some algae contain vitamin B12; however, the bioavailability varies with algae species and can be very low. In addition, some algae contain considerable amounts of inactive vitamin B12 analogues, which can interfere with the absorption of its active forms[11]. Humans are unable to synthesize vitamin B12 and are totally dependent on dietary, supplements, or fortified foods intake[11,12].

Digestion of vitamin B12 starts in the stomach, facilitated by low pH, where gastric secretions and proteases separate vitamin B12 from peptides. Thus, vitamin B12 is free to bind to the R-factor found in saliva. Pancreatic secretions partially degrade the R-factor, and vitamin B12 is then bound to the intrinsic factor. The intrinsic factor binds to the brush border of the ileum and facilitates the absorption of vitamin B12 that will be released into the plasma[13]. Its absorption is either by the active physiological process or by passive diffusion, but only 1–2% of an oral dose is passively absorbed.[14].

In general, for the dietary vitamin, an absorption of 50% is assumed; however, there is a maximum amount of B12 that can be absorbed per meal[15]. Vitamin B12 has an enterohepatic metabolism, and it is estimated that between 0.5 and 5.0 µg of vitamin B12 is excreted in bile per day. In cases of deficiencies, vitamin B12 is rapidly reabsorbed, and the efficiency of biliary absorption is such that its deficiency may take years to appear after the onset of the deficit in the diet[16].

## Neurological and cognitive function

The development of the central nervous system and the brain begins during the 3rd week of pregnancy and continues through early childhood, and its development rate is influenced by various environmental and genetic factors[17,18]. On the other hand, myelination and synaptogenesis are processes that begin in the third trimester and continue to influence neuronal development in the offspring during the first years of life[19]. Vitamin B12 plays an important role in both with potential effects on cognitive development[20,21], since cognition refers to the mental processes involved in memory, attention, learning, and executive functions[22].

It has been shown for many decades that vitamin B12 deficiency causes demyelination, affecting the peripheral nerves and the central nervous system[23]. The neurological symptoms of B12 deficiency, both in experimental studies and in humans, are associated with alterations in cytokines and epidermal growth factor in the cerebrospinal fluid[24]. Loss of motor function often manifested as gait ataxia may also be associated with vitamin B12 deficiency[25]. Notably, the neurological manifestations of B12 deficiency may precede or occur in the absence of hematological consequences, that is, deficiencies were often not diagnosed until permanent neurological damage had occurred[25].

There are several possible reasons for the seemingly contradictory reports in the literature on whether low levels of vitamin B12 actually contribute to cognitive decline. One of the reasons is that even with serum B12 within the range of reference values, it is possible to be associated with cognitive deficit or with the risk of cognitive decline in the future[26,27]. However, in contrast to the significant improvement in haematological signs after treating patients with pernicious anemia, there is limited evidence that cobalamin treatment improves cognitive status in adult and elderly patients with dementia, for example[28].

## Vegatarian and vegan diets

Most of the initial data on childhood vitamin B12 deficiency comes from case studies of infants exclusively breastfed by mothers on vegan, vegetarian, or ovolactovegetarian diets as vitamin B12 concentrations correlate with consumption and maternal status. Thus, a baby born to a vegetarian or vegan mother is at high risk of being born with low vitamin B12 stores and developing severe clinical signs of deficiency during the first year of life if the mother's intake is inadequate and her stores are low. Importantly, vegetarian women who have had repeated pregnancies put their babies at greater risk because their vitamin B12 stores were likely depleted in previous pregnancies[29].

In vegan diets, the risk of nutrient inadequacy is supposedly greater than in vegetarian diets, as food selection is even more limited and unfortified plant foods, such as seaweed, do not contain any significant amounts of active vitamin B12[30]. There have been many case reports and studies for years that have repeatedly and convincingly demonstrated severe clinical symptoms, such as developmental delay, lethargy, irritability, and infant tremor syndrome due to vitamin B12 deficiency in babies of vegan or vegetarian mothers[31-33]. Current studies indicate that vegan women still have a high prevalence of inadequate dietary intake of vitamin B12 (<83% of recommendations)[34]. A recent case study showed that vitamin B12 deficiency in a 9-month-old girl led to psychomotor regression, hypotonia, and lethargy. The child was exclusively breastfed from birth by a mother who followed a strict vegetarian diet and belonged to a low socioeconomic level. Through a computed tomography of the brain, it was possible to see brain atrophy and delayed myelination[35]. Although infants with vitamin B12 deficiency due to maternal and infant vegetarianism may also be deficient in other nutrients derived from animal foods, such as iron and zinc, it is unlikely that the developmental problems associated with vitamin B12 deficiency could be explained by these other deficiencies[20].

## Prevention of vitamin b12 deficiency

Vitamin B12 deficiency is emerging as a public health problem in many low-income countries with infants, preschool children, and pregnant women being the most vulnerable groups. The relationship of maternal vitamin B12 with that of her offspring highlights the crucial role of pregnancy in preventing B12 deficiency in the next generation. Importantly, there are guidelines for flour fortification with B12 developed by the Food Fortification Initiative[36,37] and approved by the World Health Organization (WHO). Furthermore, as flour is now fortified with folic acid in most countries, cofortification with B12 would eliminate any of the still controversial concerns related to high folate exacerbating B12 deficiency[38,39]. This new idea could have substantial long-term public health benefit.

## Maternal nutrition

It is known that inadequate nutrient availability in the uterus can negatively affect brain development during pregnancy and in the postnatal stages[40]. The child of a mother with a vitamin B12 deficiency can be born with the deficiency or can become deficient during the period of exclusive breastfeeding, usually between 4 and 6 months of age, as the concentrations of vitamin B12 in human milk are strongly related to the state maternal during pregnancy and postpartum[41]. In epidemiological studies, vitamin B12 insufficiency in the uterine phase has been associated with impaired growth and impaired psychomotor function and brain development that may be irreversible[20].

In an Indian study conducted by Bhate et al. (2008)[42], it was found that high levels of vitamin B12 in mothers during the 28$^{th}$ week of gestation (vitamin B12 >224 pmol/L versus <77.0 pmol/L) were associated with better cognitive outcomes in their 9-year-old children on short-term memory tasks, color and backward digit tests, and longer attention span, even after adjusting for confounding factors such as socioeconomic status, gender, and head circumference ($p<0.05$). For the scores on the tests of intelligence and visual agnosia, there were no differences between children in the groups with low and high levels of maternal vitamin B12[42]. Another prospective cohort study investigated the associations between mothers' plasma vitamin B12 concentrations during pregnancy and cognitive outcomes in their 10-year-olds[43]. In this study, children born to women with vitamin B12 concentrations ≥150 pmol/L or <150 pmol/L had no difference in attention or cognitive test scores, except for verbal fluency (ability to retrieve animal names listed in 1 minute), where lower plasma concentrations were associated with greater fluency ($p<0.05$)[43]. In another Indian cohort, higher concentrations of vitamin B12 in maternal plasma (≥ 150 pmol/L) during 28 weeks of gestation were associated with significantly higher mental development quotients ($p=0.035$), and higher social development quotients ($p= 0.029$) in 2-year-old children[44]. In contrast, a cohort study in Canada with these same cutoff points for vitamin B12 that was analyzed between the 16$^{th}$ to 36$^{th}$ week of gestation had no significant association with the neurocognitive outcomes of the 18-month-old offspring[45].

Several observational studies have been conducted to examine associations between vitamin B12 intake in the maternal diet and cognitive outcomes in their children. A large cohort study (n=6259) conducted in England assessed dietary intake at 32 weeks of gestation and the IQ (intelligence quotient) of children at 8 years of age and found that higher vitamin B12 intake was associated with higher IQ in children. However, after adjusting for maternal education, age, parity, alcohol intake, folic acid supplementation, and infections, the results were no longer statistically significant, as well as after additional adjustment for pregnancy duration, breastfeeding duration, and baby weight at birth[46]. In another cohort of 7-year-old children, maternal vitamin B12 intake was also not significantly associated with children's IQs[47]. Furthermore, a study that analyzed the association of maternal vitamin B12 intake in the first semester of pregnancy found worse mental development scores in children of mothers who had adequate daily vitamin B12 intake at 12 months[48].

Recently, some randomized studies on vitamin B12 supplementation for pregnant women have been published. The study by Srinivasan et al. (2017)[49] is a double-blind placebo-controlled trial where a daily dose of 50 µg of vitamin B12 was supplemented from early pregnancy (before the fourteenth week) until 6 months after birth and was related to the cognitive development of babies at 9 months of age. The study found that no significant effect of maternal B12 supplementation was observed on infants' cognitive development[49]. However, another randomized study that also performed vitamin B12 supplementation during pregnancy up to 6 weeks postpartum and assessed children's cognition at 30 months found that maternal B12 supplementation during pregnancy was associated with higher expressive language scores in children ($p<0.05$)[50].

It is important to consider that pregnancy alters the maternal vitamin B12 status in a way that facilitates its transfer to the fetus. Profound physiological and anatomical changes occur in virtually every organ and system during pregnancy with considerable consequences for biochemical markers. These facts can complicate both the assessment of the micronutrient status and also limit the use of established reference ranges in non-pregnant women, as well as the analysis of the results of studies carried out during this period.

## Lactation and childhood


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The risk of a breastfed baby becoming vitamin B12 deficient depends on three factors: first, the mother's vitamin B12 status during pregnancy; second, the baby's vitamin B12 stores at birth; and third, the mother's vitamin B12 status during the breastfeeding period[51]. Typical manifestations of vitamin B12 deficiency in children include failure in brain development and general growth and development, developmental regression, hypotonia, feeding difficulties, tremors, hyperirritability, and even coma, with brain imaging showing atrophy and delays in myelination[35]. And while vitamin B12 supplementation results in rapid improvements in laboratory measurements of individuals' status, there is still ongoing research into the long-term effects of deficiency on infants and children.

A cross-sectional study of children aged 6 to 10 years examined the associations between children's plasma vitamin B12 concentrations and mental processing index, which included measures of reasoning, short-term memory, and speed[52]. In this study, higher concentrations of vitamin B12 in infant plasma (>197.0 pmol/L) were associated with lower recall of numbers and word order, which are indicators of short-term memory[52]. On the other hand, in a prospective cohort study with children aged 12 to 18 months of age, higher concentrations of vitamin B12 in infant plasma were associated with significantly higher mental development scores ($p=0.02$)[53]. In Colombia, a large study (n=3156) was conducted to examine associations between plasma vitamin B12 concentrations and academic achievement in school-age children aged 5 to 12 years[54]. The result found was that the children with vitamin B12 deficiency (<148 pmol/L) had a significantly higher risk of school absenteeism ($p<0.0001$) and failing the school year ($p=0.04$) than non-deficient children (plasma vitamin B12>148 pmol/L)[54]. In another study also with school-age children, the total vitamin B12 intake at breakfast was analyzed and this intake was not significantly associated with short-term memory ($p=0.50$)[55]. However, in that same study, vitamin B12 intake was associated with better school performance (better annual average grades) ($p=0.02$)[55].

Intervention studies were also carried out to examine the effects of vitamin B12 consumption and cognitive function. A survey of school-aged children (average 7.4 years) divided participants into 4 groups: 1) vegetables with corn and beans; 2) milk plus corn and beans; 3) meat (60 g) plus vegetables; and 4) a control group without receiving complementary foods. In the study analysis, a higher intake of vitamin B12 in the children's diet was associated with improved memory, as measured by the digit span test ($p < 0.05$)[56]. In another randomized study carried out with 422 children aged 6 to 30 months, supplementation was made in 4 ways: either vitamin B12, folic acid, or both, or placebo, daily for 6 months. Children who received vitamin B12 and folic acid were found to have higher scores on the motor development and problem-solving scale than children in the placebo group ($p<0.05$)[57]. Recently, a randomized study evaluated the effects of daily vitamin B12 supplementation for 1 year on neurodevelopment, growth, and hemoglobin concentration in infants aged 6 to 11 months at risk of deficiency. Children were randomized to receive 2 μg of vitamin B12, corresponding to approximately 2 to 3 recommended daily intakes (RDAs) or a placebo. In this study, vitamin B12 supplementation in children at risk for vitamin B12 deficiency resulted in an


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improved metabolic response; however, it did not affect neurodevelopment, growth, or hemoglobin concentration[58]. Kvestad et al. (2020)[59], in the same year, also measured the effects of supplementation of vitamin B12 and/or folic acid for 6 months of children aged 6 to 30 months on the cognition of these same children after 6 years, when the children were between 6 and 9 years old. The authors concluded that vitamin B12 and folic acid supplementation have limited relevance for long-term cognition[59]. It is important to note that childhood is a period of rapid growth, during which the demand for vitamin B12 is high and the status of B12 undergoes marked changes due to several environmental factors that may be one reason for the possible differences found in the studies cited in this session.

**Conclusion**

We conclude that the maternal vitamin B12 status during pregnancy and breastfeeding are essential determinants of birth and childhood B12 status. Despite accumulated knowledge about B12 deficiency, many key questions remain unanswered, such as the often-different manifestations between patients regarding neurological complications, where it is possible that genetic factors or nutrient-nutrient interactions may explain these differences in susceptibility.

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