

How to Cite:

Gutiérrez, S., Cruz, S., Abalco, N., Quiroga, E., & Iñiguez, S. (2022). Infant nutritional supplements associated with constipation episodes. *International Journal of Health Sciences*, 6(S1), 12961–12974. <https://doi.org/10.53730/ijhs.v6nS1.8233>

Infant nutritional supplements associated with constipation episodes

Sol Gutiérrez

Pontificia Universidad Católica del Ecuador, Quito, Ecuador.

Email: sol.gutierrez@paradise-one.com

<https://orcid.org/0000-0001-9868-3732>

Stephanie Cruz

Pontificia Universidad Católica del Ecuador, Quito, Ecuador.

Email: stephanie.cruz@paradise-one.com

<https://orcid.org/0000-0003-4100-5898>

Nicole Abalco

Pontificia Universidad Católica del Ecuador, Quito, Ecuador.

Email: nabalco@ectarsa.com

<https://orcid.org/0000-0001-6916-6218>

Elizabeth Quiroga

Universidad Técnica de Ambato, Ambato, Ecuador.

Email: te.quiroga@uta.edu.ec

<https://orcid.org/0000-0001-5251-5143>

Samuel Iñiguez

Pontificia Universidad Católica del Ecuador, Quito, Ecuador.

Email: soiniguez@puce.edu.ec

<https://orcid.org/0000-0002-4722-7611>

Abstract---Dietary supplements are a form of complementary and alternative medicine that includes amino acids, biological extracts, herbs, minerals and vitamins. A theoretical review was carried out on the use of nutritional supplements in the pediatric population and their relationship with constipation, which is the second most important adverse effect associated with the consumption of these preparations, after diarrhea. A search for information was carried out, using specialized databases such as Pubmed, Scielo and Biomed Central, describing the main supplements used in pediatrics, constipation as a side effect, and the most important elements on its diagnosis and treatment.

Keywords---nutritional supplements, iron, calcium, constipation, fiber, laxatives, pediatrics.

Introduction

Dietary supplements are a form of complementary and alternative medicine that include amino acids, biological extracts, herbs, minerals and vitamins, except for homeopathic medicines (1). They are widely used and offer the potential to improve health if properly targeted to those who need them. Inadequate nutrition and micronutrient deficiencies are prevalent conditions that negatively affect global health. Although improvements in dietary quality are essential to address these problems, dietary supplements and/or food fortification could help meet the requirements of those at risk of deficiencies (2).

Continuing, dietary supplements represent an important source of essential nutrients and, if used correctly, can reduce nutrient deficiencies and improve health during certain stages of life. In the United States, almost one-third of children and adolescents consume dietary supplements, and the use of these products is also very common in children and adolescents in several Asian countries such as Korea and Japan. The prevalence of dietary supplement use among younger age groups is comparatively higher than in older age groups (3).

There is increasing evidence that some dietary supplements are beneficial for general health and for the management of some pathologies, examples include omega-3 polyunsaturated fatty acids (4), docosahexaenoic acid (4) and eicosapentaenoic acid in the neurodevelopment of healthy children as a treatment option in attention deficit hyperactivity disorder, or the role of probiotic species in modulating the intestinal microbiota and interacting with the immune system (5). Probiotics may exert pleiotropic effects in the prevention and treatment of different conditions, including gastroenteritis, antibiotic-associated diarrhea, allergic disorders, atopic dermatitis, or respiratory infections (6).

In the case of children, the choice of dietary supplements is often determined by their parents. However, there is a high degree of self-medication, many times these products selected by parents are not necessary, or it is likely that the selected product does not achieve the desired effects. In this regard, there is evidence that despite the use of supplements, more than one third of the children did not meet the calcium and vitamin D recommendations required for their age (7).

On the other hand, consumers of multivitamin preparations are more likely to have potentially excessive intakes, particularly of iron, zinc, vitamin A and niacin. It has been shown that children and adolescents who use dietary supplements have higher intakes of certain nutrients than non-consumers, which means that overdoses and intoxications are possible in some cases. Unfortunately, the increased use of dietary supplements in pediatric populations has not been associated with an understanding of the properties of the supplements and their ingredients, nor with the risks of adverse events or possible drug interactions (8).

Episodic constipation or constipation is one of the most frequent side effects with the use of nutritional supplements, it is reported as the second most frequent adverse effect with most of the preparations available in the market, after diarrhea, especially in preparations containing iron salts (9). Therefore, in the present study, the objective was to analyze constipation as an effect of the consumption of nutritional supplements in the pediatric population.

Methodology

This is a theoretical review with the aim of analyzing constipation as an effect of the consumption of nutritional supplements in the pediatric population. Its sources of information are the scientific papers from indexed journals, collected from specialized databases such as Pubmed, Scielo and Biomed Central. The Selection criteria used include: full scientific papers, published from 2010-2020, in Spanish or English languages, that address the supplement use and constipation as a side effect in the pediatric population.

A search was carried out in the indicated databases, using the key words. A first reading was made of the abstracts of the publications, and the free-access publications were downloaded. A second step was to verify that there were no duplicates and that the above selection criteria were met.

The Mesh terms used for the search were the following: "Dietary supplements" OR "Nutritional supplements" OR "Multivitamins" OR "Mineral supplements" OR "iron supplement" OR "calcium supplement" OR "probiotic" OR "prebiotic" OR "symbiotic" OR "Omega 3 supplements" OR "Fatty acids" AND "children" OR "Infants" OR "pediatrics" AND "constipation" OR "hard stool" [Spanish(lang) AND English(lang)].

Development

There are hundreds of multivitamin preparations that vary in both composition and quality. Some supplements contain vitamins, minerals and some contain probiotics or herbs (10). Multivitamin preparations contain different concentrations of each vitamin, including complex of vitamins B, vitamin E, vitamin A, vitamin C, and folic acid. Some also contain various trace elements and minerals in their composition. The great variability in the composition of multivitamin supplements results in large variations in the nutrient intake of these supplements. Therefore, the use of a single default composition value for all multivitamin products could substantially reduce the variation in nutrient intake and lead to incorrect estimates of intake distributions (11).

Multivitamin/mineral preparations

The administration of multivitamins and supplements containing vitamin A and zinc can improve linear growth in school-aged children and cognitive performance in children who are likely to be micronutrient deficient but in good general health (12). In the same vein, the use of vitamin and mineral supplements is common and the reasons for supplementation with multivitamin and mineral preparations

appear to be multifactorial and such supplements are largely considered unnecessary if one has a varied diet (13).

Still, nearly \$2 billion is spent annually on these supplements, and they are the third most common category of drugs used in the United States. Multivitamin preparations for older children and adolescents are not regulated by the Food and Drug Administration and can cause adverse effects ranging from nausea, vomiting, and abdominal pain to increased cerebrospinal pressure, liver abnormalities, and neuropathy (12). The American Academy of Pediatrics does not recommend the use of vitamin supplements for healthy children older than 1 year who consume a varied diet. Supplemental vitamins are only recommended for certain groups of children, for example, those with chronic diseases, eating disorders, malabsorption, liver disease, and obese children in weight loss programs (12).

Within this group of supplements, products containing iron salts are among the most important, as it is an essential mineral needed to carry oxygen to tissues throughout the body and play important roles in metabolism, respiration and immune function. The body generates reserves of this mineral and carefully maintains a balance between absorbed, stored and lost iron (14). Moving on, ferritin is the cellular storage protein for iron and generally reflects the total body stores. Therefore, serum ferritin (sFer) is the most commonly used measure to predict total body iron stores. Notably, ferritin also has a role as an acute-phase reactant, and ferritin levels measured in individuals with acute or chronic diseases that cause systemic inflammation will not adequately predict iron stores (15).

Micronutrients

Micronutrients are essential for brain development in patients with deficiencies in specific nutrients related to impaired cognitive function. Interventions have been shown to be beneficial for children's mental development, particularly in subjects who were deficient in micronutrients, and it is accepted that supplementation significantly improves neurodevelopment and intelligence (16).

Omega 3 and fatty acids

Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are derived from alpha-linolenic acid (ALA). Fish is considered the main source of omega-3 fatty acids, although they are also found in eggs, milk and some vegetables (17).

Vegetable oils such as sunflower, safflower and corn oils are the main source of fatty acids that can be metabolized to omega-6s such as gamma-linolenic acid (GLA) and arachidonic acid. Arachidonic acid can then be converted to prostaglandins and leukotrienes, which are responsible for proinflammatory effects. In contrast, omega-3 fatty acids reduce the synthesis of proinflammatory mediators by acting as competitive inhibitors of omega-6 fatty acids (18).

In this context, in addition to their anti-inflammatory and hypolipidemic effects, omega-3 fatty acids have been shown to affect serotonin and dopamine neurotransmission by altering the composition of phospholipids and, therefore, the fluidity of the cell membranes of the central nervous system. These alterations modify the structure and function of membrane proteins. Therefore, decreased omega-3 fatty acids in the modern diet and skewed fatty acid balance can theoretically influence both somatic and psychiatric function through several mechanisms and is considered detrimental to health (19).

Omega-3 dietary supplements are widely available and popular among consumers. This is problematic given that Omega-3 dietary supplements are subject to many of the same concerns as other dietary supplements, including the lack of strict regulation. In pediatrics, their use is less common than in adults, and is mostly focused on the treatment of neuropsychiatric disorders, such as attention deficit hyperactivity disorder, concentration disorders, management of atopic symptoms, and to improve nutritional status (20).

Probiotics, prebiotics and symbiotic

Probiotics and prebiotics are considered functional and novel ingredients that can be applied to influence the host microbiota, which in turn plays an important role in the nutrition, development, health and well-being of the host (21). Probiotics are considered to be preparations of live microorganisms, which, when administered in a specific amount, benefit the consumer. On the other hand, prebiotics are elaborated ferments that have the property of modifying the characteristics of the gastrointestinal flora, so that their effect is favorable to the digestive functioning of the consumer, and finally, symbiotics have the characteristics of both probiotics and prebiotics (21).

Probiotics have numerous advantageous functions in the human organism. Their main benefit is the effect on the development of the microbiota, thus ensuring an adequate balance between pathogens and bacteria that are necessary for the normal functioning of the organism (22). Therefore, probiotics can effectively inhibit the development of pathogenic bacteria such as *Clostridium perfringens*, *Campylobacter jejuni*, *Salmonella Enteritidis*, *Escherichia coli*, several species of *Shigella*, *Staphylococcus* and *Yersinia*, thus preventing food poisoning. They also increase the efficiency of the immune system, improve the absorption of vitamins and mineral compounds and stimulate the generation of organic acids and amino acids. Probiotic microorganisms can also produce enzymes, such as esterase, lipase and coenzymes A, Q and nicotinamide coenzymes. Some products of probiotic metabolism may also exhibit antibiotic (acidophilin, bacitracin, lactacin), anticarcinogenic and immunosuppressive properties (23).

On the other hand, prebiotics will stimulate the growth of different indigenous gut bacteria. These preparations have enormous potential to modify the gut microbiota, but these modifications occur at the level of individual strains and species and cannot be easily predicted a priori. In addition, the intestinal environment, especially pH, plays a key role in determining the outcome of interspecies competition. For both efficacy and safety reasons, the development of prebiotics intended to benefit human health must take into account the highly

individual species profiles that may result (24). Prebiotics are present in natural products, but can also be added to foods. The purpose of these additions is to improve their nutritional and health value. Some examples are: inulin, fructooligosaccharides, lactulose, galactose derivatives and β -glucans. These substances can serve as a medium for probiotics by stimulating their growth (23). Prebiotics are not digested by host enzymes and reach the colon in a practically unaltered form, where they are fermented by saccharolytic bacteria. The consumption of prebiotics greatly affects the composition of the intestinal microbiota and its metabolic activity, producing the modulation of lipid metabolism, an increased capacity for calcium absorption, effects on the immune system and modification of intestinal function (25).

Safety of nutritional supplements

Beyond product quality, the safety of dietary supplements depends largely on the dose ingested. High doses of some nutrients are more likely to pose more problems than others, although there is disagreement about the levels at which complications arise. For example, some dialysis patients receiving very large doses of calcium and the active form of vitamin D chronically may exceed the tolerable upper level (UL) and incur adverse health effects, including soft tissue calcification. Very high doses of vitamin D may also cause adverse effects in persons with normal renal function (26).

There is little evidence that the usual doses and forms of these nutrients give rise to health problems. The potential for excessive nutrient intakes from food supplements is greater in countries with programs to strengthen their food supply than in others and should also be evaluated (27). Dose-response data to establish safe levels of intake of non-nutrient bioactives in supplements are often lacking. Some dietary supplements containing intentionally added non-target herbs or others such as black cohosh, kava extract, green tea, and others have been associated with liver injury of various types even after accounting for concomitant use with acetaminophen, alcohol, and fasting consumption (28).

The causes of liver toxicity of supplements appear to be due to insufficient regulatory authority, inaccurate product labeling, adulterants, and inconsistent ingredient sourcing. Controversy exists as to whether the evidence of causality is sufficient for regulators to take action against supplements that appear to pose a hepatotoxic risk (29). Some possible actions include requirements for warning labels with instructions for use, as is done for drugs, and/or removal of products from commerce. Contaminated adulterated or fraudulent products sold as dietary supplements are illegal and subject to recall (30).

Risks from the indiscriminate use of nutritional supplements

Excessive consumption of nutritional supplements has been widely addressed in the medical literature. Because the most commonly used vitamins and mineral supplements provide amounts of vitamins and minerals that generally do not exceed (or minimally exceed) 100% of the daily value, excessive intakes are more likely to occur among vitamin and mineral supplement users who also use single-vitamin supplements (31).

Some adverse effects of nutrients in multivitamin preparations can be interpreted as common responses in the general population. Examples include yellowing of the skin with sustained β -carotene intake; increases in serum triglyceride levels with vitamin A supplementation, and mild bleeding with vitamin E supplementation. However, there is no consistent evidence to suggest that vitamin E supplementation produces more severe bleeding episodes, such as hemorrhagic stroke (32).

In the pediatric population, the adverse effects due to the use of nutritional supplements do not differ significantly from those of the adult population. Intoxications due to overdoses of vitamins, especially vitamin A, dermatological lesions, alterations in gastrointestinal function, such as diarrhea, colic, and constipation have been described, which has been especially related to iron and calcium supplements, and is described as the second most important adverse effect with the use of nutritional supplements in childhood (33).

Episodic constipation, as a consequence of the use of nutritional supplements

Constipation and bloating are among the most common side effects associated with the use of nutritional supplements rich in iron salts. Recent research has shown that increased methane production by archaeal bacteria in the intestinal microbiome is related to the slowing of intestinal transit and constipation through inhibition of smooth muscle contractility (34,35). Constipation in children is often a long-standing pediatric functional gastrointestinal disorder with a worldwide prevalence ranging from 0.7% to 29.6%. The pathophysiology of childhood constipation is multifactorial and not fully understood; however, stool impaction, which begins after a hard, painful, or frightening defecation experience, is the most common cause found in children (36).

Clinical manifestations

The use of nutritional supplements may worsen chronic constipation in the pediatric population, or may cause new episodes characterized by infrequent bowel activity, gas and foul-smelling stools, excessive flatulence, irregular stool texture, occasional huge or frequent small pellets, impaction or straining to stop stool passage, soiling or overflow, pain, bloating or discomfort, lack of appetite, lack of energy, unhappy, angry or irritable mood, and general malaise (37).

Painful defecation is an important factor in constipation, but is not always recognized; "holding" behaviors to prevent the passage of painful stool are often mistaken for straining to defecate. Families may delay seeking help for fear of a negative response from health care professionals. It has been suggested that some health professionals underestimate the impact of constipation on the child or young person and their family. This may contribute to the poor clinical outcomes often seen in children and young people with constipation (38).

Some children and youth with physical disabilities, such as cerebral palsy, are more prone to constipation as a result of nutritional supplement use and reduced

mobility. Similarly, those with Down Syndrome and autism are also more likely to develop constipation as a result of nutritional supplement use. It is important that the evaluation and ongoing management of these children and youth be conducted in the same manner as recommended for the rest of this population (39, 40).

Without early diagnosis and treatment, an acute episode of constipation can lead to anal fissure and become chronic. By the time the child or young person is seen, he or she may be in a vicious cycle. Children, adolescents, and their families often receive conflicting advice and practice is inconsistent, making treatment potentially less effective and frustrating for all concerned (41).

Diagnosis

Constipation related to nutritional supplements is often considered a minor problem that will resolve spontaneously or respond to excess fiber and fluids in the diet. Parents feel that it is a transient problem and is overlooked, especially in cases where the supplements were not prescribed by a healthcare professional and they were not warned about the likelihood of this problem arising with their use. Therefore, many times, the importance of constipation episodes and their impact on the wellbeing of infants is not known or is underestimated. A thorough and complete history is the most essential part of the initial diagnostic and treatment process for idiopathic constipation. The first step in this process is to exclude other medical conditions and to facilitate a rapid diagnosis of this disorder (42).

Careful questioning in conjunction with physical examination should identify "red flags" that would suggest that constipation is due to an organic cause that requires further investigation. A positive diagnosis of constipation associated with the use of nutritional supplements will allow correct and timely interventions and avoid repetitive and often unnecessary investigations; but other organic or functional causes of constipation must be ruled out first, so a key aspect during the history taking is to inquire about the use of nutritional supplements, whether or not indicated by another health professional (43).

The main causes of organic constipation that should be ruled out during the anamnesis and physical examination are Hirschsprung's disease, celiac disease, hypothyroidism, anorectal malformations, neurological conditions and abdominal tumors (42). Other aspects to take into account are changes in stool frequency, stool consistency or appearance, the presence of pain or difficulty in defecation, changes in the frequency of fecal incontinence episodes, use of laxatives, and to inquire about parents' opinions on the patient's quality of life.

Physical examination

The physical examination of a pediatric-aged patient with constipation does not differ from the general physical examination, with emphasis on examination of the abdomen for distention, pain or palpable mass. Digital rectal examination (DRE) is recommended by a number of guidelines as part of the routine examination of children with constipation, but is mostly used in chronic cases.

However, there are doubts about its value in the evaluation of children with this problem, as it is an investigation that is often not well tolerated by children or their parents. Rarely, it may be necessary to perform a digital rectal examination to exclude an anatomical cause of constipation, e.g., anal stenosis (42). In cases of secondary constipation, the use of nutritional supplements is not a common procedure, unless there are suspicions of local anatomical alterations, to which the effect of the use of these supplements is superimposed.

Treatment

The current standard treatment consists of education, sphincter control, disimpaction, maintenance therapy, discontinuation of nutritional supplements that may be influencing the presence of constipation, especially those rich in iron and calcium salts. If these supplements cannot be discontinued, the use of mild osmotic laxatives should be considered, in addition to the non-pharmacological measures already mentioned (43). As this is a transient constipation, due to the use of supplements, it should improve with the intake of liquids and fiber, in the form of fruits or vegetables. At this point, parental education is essential and, if necessary, consideration should be given to discontinuing the use of nutritional supplements (44).

Parent education

Parent education regarding their understanding of etiology, symptoms, and principles of management remains critical to success. Management begins with explaining the physiologic basis of constipation and fecal incontinence to the child and family. Under no circumstances should the child be blamed for soiling and this should be explained to the parents (43, 44). The family should be encouraged to adhere to the treatment plan, which may include the use of laxatives or establishing a regular toileting schedule. Underlying psychosocial problems should be considered at the first meeting. These can range from bullying to pressure to use a single-family restroom quickly. These strategies should be accompanied by clear and simple messages to avoid overwhelming the family (43).

Diet

The main dietary recommendation is to increase fiber and fluid intake. Thus, a minimum intake of 15 grams of fiber and liquids is recommended: 1.3 liters (children from 1 to 3 years old), 1.7 (children from 4 to 8 years old), 2.4 (children from 9 to 13 years old). The main recommendation in addition to diet is to engage in moderate or vigorous aerobic physical activity for a minimum of 60 minutes daily (43, 44).

Pharmacological treatment

The pharmacological treatment consists of two phases: in the first phase, disimpaction will be achieved and in the second phase, the objective is to maintain adequate evacuation of feces (44). Table 1 shows a summary of the pharmacological treatment of constipation.

Table 1. Pharmacological treatment of constipation in pediatrics

| | |
|---|--|
| Phase I: Disimpaction (2-3 days) | <ul style="list-style-type: none"> - Polyethylene glycol (PEG-3350): 1-1.5 g/kg/day (VO). - Enemas can be used, with the same effectiveness as Polyethylene glycol. |
| Phase II: Maintenance (as long as the use of supplements lasts, in case it is impossible to remove them). | <p>Osmotic laxatives</p> <ul style="list-style-type: none"> - Polyethylene glycol 3350 (0.2-0.8 g/ kg/day). - Lactulose (1-2 g/kg up to twice a day) <p>Stimulant laxatives:</p> <ul style="list-style-type: none"> - Bisacodyl (5-10 mg/kg) - Senna derivatives (2.5-5 mg/kg) - Sodium picosulfate (2.5-10 mg/kg) - Mineral oil |

Source: Avelar et al. (45)

Limitations of the study

A theoretical review was carried out on the proposed topic. To improve the quality of evidence, a systematic review and subsequent meta-analysis is recommended.

Conclusions

The use of nutritional supplements in the pediatric age is widespread. The use of nutritional supplements is associated with a variety of side effects, mostly related to the digestive system, such as transient constipation, which is one of the most frequent side reactions, requiring a comprehensive therapeutic approach, including discontinuation of the supplement, family education, dietary modifications, disimpaction, or the use of laxatives, in very disabling cases. If not identified and adequately treated, it can become a chronic disorder.

References

1. Smolinske SC. Dietary Supplements in Children. *Pediatr Clin North Am* [Internet]. 2017 Dec 1 [cited 2020 Nov 23];64(6):1243–55. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0031395517301487>
2. Gigato Mesa E. Intervención alimentaria y nutrimental en la anemia ferripriva en los niños desnutridos. *Rev Cuba Aliment Nutr* [Internet]. 2014 [cited 2020 Nov 21];24(1):106–20. Available from: <https://www.medigraphic.com/pdfs/revcubalnut/can-2014/can141i.pdf>
3. Bailey RL, Gahche JJ, Thomas PR, Dwyer JT. Why US children use dietary

- supplements. *Pediatr Res* [Internet]. 2013 Dec [cited 2020 Nov 23];74(6):737–41. Available from: <https://pubmed.ncbi.nlm.nih.gov/24002333/>
4. Chang JPC, Su KP, Mondelli V, Pariante CM. Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. *Neuropsychopharmacology* [Internet]. 2018 Feb 1 [cited 2020 Nov 23];43(3):534–45. Available from: <https://pubmed.ncbi.nlm.nih.gov/28741625/>
 5. Gonzalez-Ochoa G, Flores-Mendoza LK, Icedo-Garcia R, Gomez-Flores R, Tamez-Guerra P. Modulation of rotavirus severe gastroenteritis by the combination of probiotics and prebiotics. *Arch Microbiol* [Internet]. 2017 Sep 1 [cited 2020 Nov 23];199(7):953–61. Available from: <https://link.springer.com/article/10.1007/s00203-017-1400-3>
 6. Azad MAK, Sarker M, Li T, Yin J. Probiotic Species in the Modulation of Gut Microbiota: An Overview. Vol. 2018, *BioMed Research International*. Hindawi Limited; 2018.
 7. Bailey RL, Fulgoni VL, Keast DR, Lentino C V., Dwyer JT. Do dietary supplements improve micronutrient sufficiency in children and adolescents? *J Pediatr* [Internet]. 2012 [cited 2020 Nov 23];161(5). Available from: <https://pubmed.ncbi.nlm.nih.gov/22717218/>
 8. Liu H, Zhang S, Zou H, Pan Y, Yang Q, Ouyang Y, et al. Dietary supplement use among chinese primary school students: A cross-sectional study in Hunan province. *Int J Environ Res Public Health* [Internet]. 2019 Feb 1 [cited 2020 Nov 23];16(3). Available from: </pmc/articles/PMC6388182/?report=abstract>
 9. Nishijima C, Kobayashi E, Sato Y, Chiba T. A Nationwide Survey of the Attitudes toward the Use of Dietary Supplements among Japanese High-School Students. *Nutrients* [Internet]. 2019 Jun 28 [cited 2020 Nov 21];11(7):1469–78. Available from: <https://www.mdpi.com/2072-6643/11/7/1469>
 10. Tayyem RF. Vitamin and Mineral Supplements: The Story So Far. *Can J Clin Nutr* [Internet]. 2018 Jan 1 [cited 2020 Nov 23];5(2):1–6. Available from: <http://globalscienceheritage.org/downloads/vitamin-and-mineral-supplements-the-story-so-far/>
 11. Blumberg JB, Cena H, Barr SI, Biesalski HK, Dagach RU, Delaney B, et al. The Use of Multivitamin/Multimineral Supplements: A Modified Delphi Consensus Panel Report. *Clin Ther* [Internet]. 2018 Apr 1 [cited 2020 Nov 23];40(4):640–57. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0149291818300894>
 12. Robert J, Stein A. The Impact of Nutritional Interventions beyond the First 2 Years of Life on Linear Growth: A Systematic Review and Meta-Analysis. *Adv Nutr* [Internet]. 2017;8(2):323–336. Available from: <https://academic.oup.com/advances/article/8/2/323/4558094>
 13. Elliott C. Assessing Vitamins, Minerals and Supplements Marketed to Children in Canada. *Int J Environ Res Public Health* [Internet]. 2019 Nov 6 [cited 2020 Nov 23];16(22):4326–30. Available from: <https://www.mdpi.com/1660-4601/16/22/4326>
 14. Paganini D, Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: A review. *Am J Clin Nutr* [Internet]. 2017 Dec 1 [cited 2020 Nov

- 23];106(6):1688–93. Available from: <https://pubmed.ncbi.nlm.nih.gov/29070552/>
15. Truman-Rosentsvit M, Berenbaum D, Spektor L, Cohen LA, Belizowsky-Moshe S, Lifshitz L, et al. Ferritin is secreted via 2 distinct nonclassical vesicular pathways. *Blood* [Internet]. 2018 Jan 18 [cited 2020 Nov 23];131(3):342–52. Available from: </pmc/articles/PMC5774206/?report=abstract>
 16. Lam LF, Lawlis TR. Feeding the brain – The effects of micronutrient interventions on cognitive performance among school-aged children: A systematic review of randomized controlled trials. *Clin Nutr* [Internet]. 2017 Aug 1 [cited 2020 Nov 23];36(4):1007–14. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0261561416301467>
 17. Manson JE, Cook NR, Lee I-M, Christen W, Bassuk SS, Mora S, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med* [Internet]. 2019 Jan 3 [cited 2020 Nov 23];380(1):23–32. Available from: <https://pubmed.ncbi.nlm.nih.gov/30415637/>
 18. Hilleman DE, Wiggins BS, Bottorff MB. Critical Differences Between Dietary Supplement and Prescription Omega-3 Fatty Acids: A Narrative Review. *Adv Ther* [Internet]. 2020 Feb 1 [cited 2020 Nov 23];37(2):656–70. Available from: </pmc/articles/PMC6999166/?report=abstract>
 19. Agostoni C, Nobile M, Ciappolino V, Delvecchio G, Tesei A, Turolo S, et al. The Role of Omega-3 Fatty Acids in Developmental Psychopathology: A Systematic Review on Early Psychosis, Autism, and ADHD. *Int J Mol Sci* [Internet]. 2017 Dec 4 [cited 2020 Nov 23];18(12):2608–14. Available from: </pmc/articles/PMC5751211/?report=abstract>
 20. Bozzatello, Rocca, Mantelli, Bellino. Polyunsaturated Fatty Acids: What is Their Role in Treatment of Psychiatric Disorders? *Int J Mol Sci* [Internet]. 2019 Oct 23 [cited 2020 Nov 23];20(21):5257–60. Available from: </pmc/articles/PMC6862261/?report=abstract>
 21. Lauzon HL, Dimitroglou A, Merrifield DL, Ringø E, Davies SJ. Probiotics and Prebiotics: Concepts, Definitions and History. In: *Aquaculture Nutrition* [Internet]. John Wiley & Sons, Ltd; 2014 [cited 2020 Nov 23]. p. 169–84. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/9781118897263.ch7>
 22. Markowiak P, Ślizewska K. Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients* [Internet]. 2017 Sep 15 [cited 2020 Nov 23];9(9):56–68. Available from: </pmc/articles/PMC5622781/?report=abstract>
 23. Jäger R, Mohr AE, Carpenter KC, Kerksick CM, Purpura M, Moussa A, et al. International Society of Sports Nutrition Position Stand: Probiotics. *J Int Soc Sports Nutr* [Internet]. 2019 Dec 21 [cited 2020 Nov 23];16(1):62. Available from: </pmc/articles/PMC6925426/?report=abstract>
 24. Hurtado-Romero A, Del Toro-Barbosa M, Garcia-Amezquita LE, García-Cayuela T. Innovative technologies for the production of food ingredients with prebiotic potential: Modifications, applications, and validation methods. Vol. 104, *Trends in Food Science and Technology*. Elsevier Ltd; 2020. p. 117–31.
 25. Castañeda C. Actualización en prebióticos. *Rev Cubana Pediatr* [Internet]. 2018 Mar 1 [cited 2020 Nov 23];90(4):64–8. Available from: <http://www.revpediatria.sld.cu/index.php/ped/article/view/648>
 26. Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL. Trends in use of high-dose Vitamin D supplements exceeding 1000 or 4000

- international units daily, 1999-2014 [Internet]. Vol. 317, JAMA - Journal of the American Medical Association. American Medical Association; 2017 [cited 2020 Nov 23]. p. 2448-50. Available from: <https://pubmed.ncbi.nlm.nih.gov/28632857/>
27. Boyles AL, Yetley EA, Thayer KA, Coates PM. Safe use of high intakes of folic acid: Research challenges and paths forward. *Nutr Rev* [Internet]. 2016 [cited 2020 Nov 23];74(7):469-74. Available from: <https://pubmed.ncbi.nlm.nih.gov/27272334/>
 28. Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series [Internet]. Vol. 107, Food and Chemical Toxicology. Elsevier Ltd; 2017 [cited 2020 Nov 23]. p. 472-501. Available from: <https://pubmed.ncbi.nlm.nih.gov/27402097/>
 29. Avigan MI, Mozersky RP, Seeff LB. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States [Internet]. Vol. 17, International Journal of Molecular Sciences. MDPI AG; 2016 [cited 2020 Nov 23]. Available from: <https://pubmed.ncbi.nlm.nih.gov/26950122/>
 30. Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series [Internet]. Vol. 107, Food and Chemical Toxicology. Elsevier Ltd; 2017 [cited 2020 Nov 23]. p. 449-71. Available from: <https://pubmed.ncbi.nlm.nih.gov/27818322/>
 31. Or F, Kim Y, Simms J, Austin SB. Taking Stock of Dietary Supplements' Harmful Effects on Children, Adolescents, and Young Adults. *J Adolesc Heal* [Internet]. 2019 Oct 1 [cited 2020 Nov 23];65(4):455-61. Available from: <http://www.jahonline.org/article/S1054139X19301636/fulltext>
 32. Or F, Kim Y, Simms J, Austin SB. Taking Stock of Dietary Supplements' Harmful Effects on Children, Adolescents, and Young Adults. *J Adolesc Heal*. 2019 Oct 1;65(4):455-61.
 33. Kobayashi E, Sato Y, Nishijima C, Chiba T. Concomitant use of dietary supplements and medicines among preschool and school-aged children in Japan. *Nutrients* [Internet]. 2019 Dec 1 [cited 2020 Nov 21];11(12). Available from: <https://pubmed.ncbi.nlm.nih.gov/31817183/>
 34. Smith S, Haworth J, Treadway S, Hobson A. Iron supplementation microbiome related methanogenesis and constipation- novel model to explain an age-old problem. *Gut* [Internet]. 2019;68(2):269-70. Available from: https://gut.bmj.com/content/gutjnl/68/Suppl_2/A198.3.full.pdf
 35. Parthasarathy G, Chen J, Chen X, Chia N, O'Connor HM, Wolf PG, et al. Relationship between Microbiota of the Colonic Mucosa vs Feces and Symptoms, Colonic Transit, and Methane Production in Female Patients with Chronic Constipation. *Gastroenterology*. 2016 Feb 1;150(2):367-379.e1.
 36. Muguie S, Di Lorenzo C, Benninga M. Constipation in childhood. *Nat Rev Gastroenterol Hepatol* [Internet]. 2011;8(2):502-11. Available from: <https://www.nature.com/articles/nrgastro.2011.130>
 37. National Collaborating Centre for Women's and Children's Health (UK). Constipation in Children and Young People: Diagnosis and Management of Idiopathic Childhood Constipation in Primary and Secondary Care. 2010; Available from: <https://pubmed.ncbi.nlm.nih.gov/22220325/>
 38. Rajindrajith S, Devanarayana NM, Perera BJC, Benninga MA. Childhood constipation as an emerging public health problem [Internet]. Vol. 22, World

- Journal of Gastroenterology. Baishideng Publishing Group Co., Limited; 2016 [cited 2020 Nov 23]. p. 6864–75. Available from: [/pmc/articles/PMC4974585/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/29961644/)
39. Lewanda AF, Gallegos MF, Summar M. Patterns of Dietary Supplement Use in Children with Down Syndrome. *J Pediatr* [Internet]. 2018 Oct 1 [cited 2020 Nov 23];201:100-105.e30. Available from: <https://pubmed.ncbi.nlm.nih.gov/29961644/>
 40. Gogou M, Kolios G. The effect of dietary supplements on clinical aspects of autism spectrum disorder: A systematic review of the literature [Internet]. Vol. 39, *Brain and Development*. Elsevier B.V.; 2017 [cited 2020 Nov 23]. p. 656–64. Available from: <https://pubmed.ncbi.nlm.nih.gov/28438367/>
 41. Philips EM, Peeters B, Teeuw AH, Leenders AGE, Boluyt N, Brilleslijper-Kater SN, et al. Stressful life events in children with functional defecation disorders [Internet]. Vol. 61, *Journal of Pediatric Gastroenterology and Nutrition*. Lippincott Williams and Wilkins; 2015 [cited 2020 Nov 23]. p. 384–92. Available from: <https://pubmed.ncbi.nlm.nih.gov/26192701/>
 42. Joinson C, Grzeda MT, von Gontard A, Heron J. Psychosocial risks for constipation and soiling in primary school children. *Eur Child Adolesc Psychiatry* [Internet]. 2019 Feb 10 [cited 2020 Nov 23];28(2):203–10. Available from: <http://link.springer.com/10.1007/s00787-018-1162-8>
 43. Afzal N, Mark T, Thompson M. Constipation in children. *Ital J Pediatr* [Internet]. 2011;37(28):23–31. Available from: <https://pubmed.ncbi.nlm.nih.gov/21668945/>
 44. Shin JE, Jung H-K, Lee TH, Jo Y, Lee H, Song KH, et al. Guidelines for the Diagnosis and Treatment of Chronic Functional Constipation in Korea, 2015 Revised Edition. *J Neurogastroenterol Motil* [Internet]. 2016 Jun 28 [cited 2020 Nov 23];22(3):383–411. Available from: [/pmc/articles/PMC4930295/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/26192701/)
 45. Avelar D, Toro EM, Ramírez JA. Constipación funcional en pediatría: criterios de Roma IV, Diagnóstico y tratamiento. *Acta Pediatr Mex* [Internet]. 2018 [cited 2020 Nov 23]; 39(1): 81-84. Available from: http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S0186-23912018000100081&lng=es&nrm=iso