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REVIEW

# Experts' opinion on immunity and nutrition to support key cognitive functions

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## Abstract

The interaction of micronutrients and macronutrients has been shown to have a significant impact on children's cognitive development. Furthermore, proper nutrition helps a child's immune system avoid infection and disease, which can impair nutrient absorption and lead to deficiency. Microbiotas in the gut play critical roles in body physiology, including nutrient absorption, infection resistance and immune system development. Furthermore, it is known that the gut microbiota influences immune cell maturation. Finally, these three factors alongside with sufficient cognitive stimulation are thought to influence neurogenesis and cognitive development. A virtual meeting was held with five invited experts to gain a better understanding of the relationship between nutritional factors, the immune system and cognitive development.

**Keywords:** nutrition, gut microbiota, immune system, cognitive development

## Introduction

Cognition is a complicated concept that encompasses a range of thought processes through which an individual registers, encodes, selects, maintains, transforms, stores, and retrieves information.[1] According to Antony and his colleagues, cognition is defined as the capacity to think, learn and remember; as a result, it provides the foundation for an individual's capacity for perception, reasoning, creativity, and problem-solving and possibly intuition as well.[2] The term "cognition" refers to a wide range of mental processes, including memory, attention and processing speed.[3] Cognitive assessment (or intelligence testing) is used to determine an individual's general thinking and reasoning abilities, which are also referred to as intellectual functioning or IQ. Intelligence testing can evaluate various aspects of your child's cognitive ability. The Wechsler Intelligence Scale for Children and the Sandford-Binet are the most commonly used tests for the Intelligent Scale for Children.[4,5]

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It appears that failing to optimize brain development early in life has long-term consequences for education, job prospects and adult mental health.[6] Among the numerous factors affecting early brain development, three stand out as having particularly profound effects: provision of optimal nutrition, reduction of toxic stress and inflammation and the presence of strong social support and secure attachment.[7]

Normal brain development requires appropriate nutrition. Childhood and early childhood are sensitive and rapid periods of brain development that coincide with the emergence of nearly all cognitive, behavioral and social-emotional functions. This is why nutrition is critical during pregnancy and infancy when the brain is forming and laying the groundwork for developing cognitive, motor and socio-emotional skills throughout childhood and adulthood.[8] Nutritional status also plays a significant role in immune competence: undernutrition, which impairs immune function and suppresses immune functions critical for host protection, can be caused by insufficient intake of energy and macronutrients and/or specific micronutrient deficiencies.[7]

Immune cells and molecules are required to shape the nervous system's circuitry and regulate its activity. During the neuronal activity, classical inflammatory cytokines such as interleukin (IL)-1b and tumor necrosis factor (TNF) are released and play a critical role in regulating synaptic transmission strength. The immune system function is critical for normal nervous system function on a systemic level. Immune system dysfunction impairs cognition and neurogenesis.[9] Recent studies also indicate that gut microbiota has a significant role on immune function and also brain development. The gut microbiota is indispensable to human health throughout the lifespan. Early-life exposures [mode of delivery (maternal microbes); infant diet (selective substrates); antibiotics (selective killing); probiotics (selective enrichment); and physical environment (environmental microbes)] result in colonization of gut microbiota, which contributes to the development of the immune system, intestinal homeostasis and host metabolism. A growing number of diseases are associated with gut microbiota disruption, including inflammatory bowel disease, necrotizing enterocolitis, diabetes, obesity, cancer, allergies and asthma.[10-12]

In community setting, detection and screening of inappropriate cognitive development are important, in which parents will play significant role. Therefore, it is important to have simple description and assessment on key parameters on cognitive function that can be easily use by parents or caregivers. There is also a need to provide a framework to show the important interrelation of nutrition, gut microbiota, immune system and cognitive development to optimize child growth and development that can be easily understand and communicated by health care professionals in daily practice to educate the parents.

A multidisciplinary expert meeting is needed to contextualize the important cognitive parameters for community and the interrelation framework of cognitive influencing factors, namely nutrition, gut microbiota and immunity.

## Methods

There were five experts with different disciplinary involved in the discussion in December 2021. Two experts were pediatrician specialist (growth, development and social; allergy and immunology), one expert was clinical nutritionist, one expert was child and adolescent psychiatrist, and one expert was doctor in neuroscience. All experts had more than ten years of work experience in their respective field and were mainly academicians and medical practitioners.

The meeting was performed online via Zoom meeting platform and the discussion was conducted in two sessions. The first session was held on 2 December 2021 with the aim that experts have the same understanding of the relationship between nutrition, immunity and cognitive development through presentations of key references by each of the experts. The second session was conducted in 15 December 2021 as polling session using AhaSlides platform to have a conclusion on the key nutrition to be informed to public and parameters of cognitive development that will be easily understood and implemented by the parents or caregivers. With AhaSlides, each expert can give simultaneous input on the most important key nutrition and key cognitive parameters and most commonly mentioned results were shown real-time.

The expert meeting was recorded, transcribed in verbatim and analyzed by the authors.

## Results

From the discussions that have been carried out, all experts agree there are 3 factors that influence cognitive function and its development in children. These factors include the followings.

### 1. Key nutrients to support immunity and cognitive development

Optimal brain development during the prenatal period and the early years of life is contingent upon providing adequate amounts of critical nutrients during critical time periods. These times correspond to when specific brain regions are undergoing the most rapid development and have the greatest nutrient requirements.[7,13] These periods of maximum growth are also the most detrimental when a specific nutrient is deficient, particularly one that is required for basic neuronal/glial metabolic processes (e.g., protein, iron, glucose). Supplementation of a deficient nutrient after these critical developmental windows has passed typically results in incomplete recovery of the brain insult, increasing the risk of long-term neurodevelopmental deficits.[7]

Nutrition optimal for the best immunological outcomes would be nutrition that supports immune cell functions, allowing them to initiate effective responses against pathogens but also to resolve the response rapidly when necessary and avoid any underlying chronic inflammation.[14] During this period, major neurodevelopmental processes such as synaptogenesis, neurotransmitter system organization, and the onset of myelination occur, most notably in the hippocampus, which serves as the central processing area for declarative learning and memory, the visual system, and the auditory system.[15]

While all nutrients are necessary for brain development, certain nutrients (for example, protein, long-chain polyunsaturated fatty acids (LCPUFAs), iron, copper, zinc, iodine, folate, choline and vitamins A, B6 and B12) have a greater impact early in life and during critical or sensitive periods for neurodevelopment.[6,16] Nutritional deficiency timing has been shown to have a significant effect on both morphological and neurochemistry and neurophysiology brain development and has been validated through successful nutritional intervention studies in humans that result in beneficial neurobehavioral outcomes.[7,8,17-19] Certain micronutrients and dietary components play critical roles in the development and maintenance of an effective immune system over the course of a person's life, as well as in the reduction of chronic inflammation. For instance, the amino acid arginine is required for macrophages to produce nitric oxide, and the micronutrients vitamin A and zinc regulate cell division, making them necessary for a successful proliferative response within the immune system.[14] It is well established that malnutrition impairs immune function, whether caused by food shortages or famines in developing countries or as a result of malnutrition. The degree of impairment that results will vary according to the severity of the deficiency, the presence of nutrient interactions, the presence of infection, and the subject's age.[14]

Provision of nutrients is only one facet of the equation. The recipient's metabolic state, which may include illness and psychological stress, will influence how growth factors are regulated and nutrients are utilized. Thus, stress-related factors are also critical in determining the effectiveness of nutritional therapy in promoting brain growth.[7] Additionally, nutrition in early life (including breastfeeding and diet at one year) was associated with adolescents' cognitive performance, particularly on more fundamental cognitive tasks.[13]

### The key nutrition to support brain development

Nutrition, health and stimulation are all known to improve children's quality of life.[20] Empirical evidence has emphasized the importance of cognitive stimulation at home, particularly in assisting children's cognitive development during their first years of life. A low-cost home activity, such as storytelling, singing or playing with household items, can provide children with experiences that promote their early development stages.[21,22] Nutrition is recognized by all authorities as being of the utmost importance; however, it cannot be reduced to a simple discussion of micronutrients; rather, sufficient macronutrients are essential in order for micronutrients to be absorbed. DHA, folic acid, vitamin D, prebiotics and zinc are just some of the different kinds of nutrients that are mentioned by the specialists as being essential for the development of the brain. These nutrients play an important part in the development of the brain and myelination, as well as in maintaining a child's overall health, which is necessary for optimal brain development. These stand out nutrients are generally recognized as important nutrients that the general public, parents, and caregivers ought to be informed about.[23]

## 2. The role of microbiota on immunity and cognitive development

Important functions of the immune system include the detection and defense of the host against pathogens and other harmful threats, as well as the destruction of tumor cells. Mucosal tissue, which provides protection against the external environment, is the most important and largest immune component in the body. It is believed that early intestinal exposure to specific microorganisms reduces the incidence of inflammatory, obesity, autoimmune and atopic diseases.[18,24,25]

The microbiota plays an essential part in the stimulation, maturation, and operation of the immune system of the host. The immune system is made up of an intricate network of innate and adaptable components that are endowed with an extraordinary capacity to adapt and react to a wide variety of threats.[24]

The fetal gastrointestinal tract is believed to be sterile, with the first exposure of the immune system to commensals occurring during the passage through the birth canal and the interactions establishing the long-term mucosal and systemic immune tone.[10] However, one of the studies used super-resolution scanning electron microscopy to identify bacteria-like structures in fetal meconium of terminated pregnancies and discovered a limited number of *Micrococcaceae* and *Lactobacillus* bacteria in the fetus' intestines, which contribute to prenatal immune priming.[26] The earliest colonizing bacteria, such as *Escherichia* and *Enterococcus*, which are facultative aerobes, eventually establish an anaerobic environment. This permits the transition to obligate anaerobes, such as *Firmicutes* such as *Clostridia*, *Bacteroidetes*, and especially Bifidobacteria.[24]

On the other hand, colostrum and breast milk contain live microbes, metabolites, IgA, immune cells and cytokines, which work together to shape the breast-fed infant microbiota and the host's response to these microbes, as well as to promote the expansion of specific microbiota constituents such as *Bifidobacterium*.[10,26] These initial colonizing species are now recognized as a pioneer microbiome, one that educates the developing immune system and provides favorable conditions for colonization by subsequent microbes by producing an anaerobic environment, favorable substrates for bacterial growth and protection from the systemic immune system.[10,27]

Recent research has demonstrated that the gut microbiota, which contains more than 100 trillion microorganisms and three times the number of human genes, is critical for human health; manipulation of the intestinal microbiota can alter the release of neuroactive metabolites, which affect brain health.[28, 29] Numerous preclinical and observational studies have established that gut dysbiosis causes increased intestinal permeability, which is associated with neuroinflammation and cognitive decline.[30,31]

There is an increasing body of evidence that altering the microbiome can have an effect on the brain and behavior. Numerous studies have shown that mice fed a high-sucrose diet had significant difficulties with cognitive flexibility, working memory and the development of a spatial bias early in long-term memory training. Numerous changes in the microbiome were observed in both the high-sucrose and high-fat groups, but the high-sucrose group demonstrated more significant changes. Increased *Clostridiales* and decreased

*Bacteroidales* were associated with poorer performance in reversal trials assessing cognitive flexibility in the high-fat and high-sucrose diet groups. Both *Bacteroidales* and *Clostridiales* exhibited progressive changes in cognitive flexibility across diets and relationships and have been linked to autism.[32] In a study of autism and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) patients, the most frequently recruited population was *Clostridiales Ruminococcaceae*, which was also increased in expression in both high-energy diet groups in the current study. *Bacteroides fragilis* treatment improves gut permeability and decreases autism spectrum disorders in a mouse model of maternal immune activation.[28,32-34]

A disruption in the balance of the microbiota increases disease susceptibility. Infection, disease and antibiotics all have the potential to transiently alter the stability of the natural composition of the gut microbiota, thereby affecting the host's well-being and influencing the healthy gut bacteria, resulting in the concept of the gut–brain–microbiota.[35] The gut-brain axis is a complex bidirectional communication system between the gut and the brain that is mediated by hormonal, immunological, and neural signals. Additionally, this is a mechanism by which the gut microbiota may have an effect on neurodevelopmental processes and brain functions. Dysregulation of the gut-brain axis communication is associated with metabolic diseases, psychiatric disorders, and comorbid non-psychiatric disorders. These conditions are frequently associated with changes in the composition or function of the gut microbiota, which may also contribute to the disruption of the molecular dialogue between the gut and brain. The central nervous system (CNS), enteric innervation which includes extrinsic fibers of the autonomous nervous system (ANS) and intrinsic neurons of the enteric nervous system (ENS), the HPA-axis and the intestinal microbiota all contribute to the formation of the gut-brain axis. The HPA-axis is a component of the limbic system and is responsible for the majority of the stress response. Additionally, the HPA-axis controls a variety of bodily functions, including bowel function during digestion.[29,36,37]

Stress and its associated HPA-axis activity can have an effect on the composition of the microbiota. Alterations in the gut microbiota caused by diet-induced increases in bacteria belonging to the order *Clostridiales* and decreases in *Bacteroidales* were both associated with decreased cognitive flexibility, implying that they will have long-term effects on cognitive development.[36]

In clinical practice, dietary interventions (in the form of nutritional supplements or special diets) have frequently been used to restore intestinal eubiosis and to prevent and treat cognitive disorders. Nonetheless, the most promising strategy for reversing gut dysbiosis and preserving cognitive function appears to be probiotic, prebiotic and fecal microbiota transplantation.[38]

## 3. Role of immunity on cognitive development

Immunity may have an effect on cognitive development either directly or indirectly. A child with a strong immune system will be less susceptible to illness, allowing them to grow and learn more effectively, as well as perform better cognitively. Numerous studies have been conducted on the relationship between the microbiota and the immune system. However, the mechanisms by which the immune system may influence cognitive function remain unknown and lacking in evidence. The nervous system is universally regarded as the body's command center. Sensory organs and peripheral nerve fibers monitor the external environment, while receptors in the brain monitor chemical changes in the internal environment. As a result, the nervous system can be regarded as the master regulator of homeostasis. However, it does not act alone in this capacity. The immune system, via tissue-resident and patrolling immune cells, is also constantly monitoring the internal environment and attempting to maintain overall body balance.[9] These were seminal experiments that revealed the existence of an intricate network of bidirectional communication between the central nervous and immune systems indirectly. Such communication pathways had previously been hypothesized but not demonstrated.[39] When considering brain/immune interactions, it is necessary to recognize that microglia, a type of immune cell, are also resident myeloid cells in the central nervous system that contribute to homeostasis in physiological conditions. Microglia play a critical role in embryonic development, not only in removing apoptotic debris generated by rapid cell turnover but also in promoting neuronal apoptosis. Another critical function of the microglia is synaptic spine pruning.[9,40]

Microglia are involved in synapse pruning in the hippocampus and barrel cortex during the neonatal period, as demonstrated by electron microscopy and electrical recordings. Additionally, synapses in the lateral geniculate nucleus are engulfed by microglia in a complement-dependent manner. On the other hand, microglia have been shown to induce synaptic formation in the somatosensory cortex during the early neonatal period.[40]

Microglia are classified into three types based on their morphology: resting ramified, activated and amoeboid phagocytic. The amoeboid phagocytic microglia are the predominant type in the perinatal brain. During postnatal maturation, amoeboid microglia differentiate into ramified resting microglia, which persist as a semi-permanent population with a low turnover rate in comparison to peripheral macrophages. They monitor their microenvironment as resting ramified microglia and adapt their morphology and expression of cell surface markers accordingly. They remain dormant until they are activated by injury, infection, or neurodegenerative processes, at which point they transform into amoeboid phagocytic cells.[35,41,42]

Microglia release various cytokines and chemokines upon activation, which contributes to neuropathogenesis in central nervous system inflammation. Microglial activation induced by neurodegenerative stimuli increases the release of nitric oxide and proinflammatory cytokines such as IL-1, IL-6 and TNF-, as well as the expression of major histocompatibility complex (MHC) and co-stimulatory molecules. Additionally, these cells produce free radicals such as superoxide and nitric oxide as a result of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and inducible nitric oxide synthase (iNOS) enzymes. Microglia-derived radicals, as well as their reactive reaction products, hydrogen peroxide and peroxynitrite, have the potential to harm cells and have been implicated in neurological diseases as a cause of oxidative damage and neurodegeneration. Proinflammatory mediators released by microglia appear to be critical contributors to the neurogenesis block, as nonsteroidal anti-inflammatory drug treatment restores hippocampal neurogenesis.[41]

### *Child's stimulation*

During the rapid growth in early childhood, the brain particularly is vulnerable to external factors such as nutritional status, socioeconomic factors, and parent–child relationships.[43] Nutrition plays an important role in cell proliferation and brain growth. Healthy children with adequate nutritional needs have good immune systems and optimal brain development. Psychosocial stimulation, culture and environmental conditions also affect the process of cognitive development.[44,45]

Previous studies shown that a high quality home parenting environment has a continuous positive effect on the cognitive development of children under 5 years old may be because the high-quality home parenting environment can provide children with safe environment, learning support, emotional and verbal responsivity, and sufficient stimulation that are conducive to children's cognitive development.[45-47] Meanwhile, the reasoning ability and depressive symptoms of the mothers, as relevant factors of home parenting environment, also may have an impact on children's early development; however, the negative roles of illness, infection, and poor infant feeding practices will increase the risk of constrained cognitive development in settings with less promotion of development.[45-47]

## Key indicators of cognitive development for infants and above 1 year old

Cognitive encompass visual and somatosensory perception, reasoning, memory and learning. Memory aids in the learning, retention, and reproduction of information. Another critical aspect is attention, an integrated process by which the individual, beginning in childhood, concentrates on information necessary for growth and development. It entails a readiness to respond and an intact capacity to concentrate on a single task while avoiding distraction from other stimuli.

Another critical aspect is attention; it is an integrated process through which the individual, beginning in childhood, focuses on knowledge that is critical for growth and development. It necessitates a state of readiness to respond and the ability to focus on a single item while avoiding other distracting stimuli.

During the first year of life, the child develops the ability to construct mental structures based on expectations and body movements. It strengthens its attention skills even further by identifying and reflecting on novel aspects of its environment and applying them to the testing and organization of knowledge throughout the pre-school years.

Increasing environmental responsiveness, action and motor skills can contribute significantly to the development of the attention system. A lethargic child with delayed motor activity will have fewer opportunities to explore and concentrate on specific items or events. At that age, the operation will be inextricably linked to motor movements. Cognitive development continues as a cycle of concrete operations throughout the school years, with students developing cognitive abilities such as thinking, memory, and language. Several stimuli are appreciated concurrently during this phase, and attention capacities increase with increased understanding and memory, culminating in the development of adult intellect and hypothesized reasoning during adolescence.[1]

A healthy cognitive function is accompanied by a healthy executive function in terms of creativity, adaptability, self-control and discipline. Executive functions are comprised of three abilities: inhibition [inhibitory control, which encompasses self-control (behavioral inhibition) and interference control (selective attention and cognitive inhibition)], working memory (WM), and cognitive flexibility or shifting.[33,48-50] These abilities are critical for mental and physical health, academic and career success, and cognitive, social and psychological development. These abilities also enable us to mentally experiment with concepts, adapt quickly and flexibly to changing circumstances, pause to consider what to do next, resist temptations, maintain focus and overcome novel, unanticipated challenges.[33]

*Inhibition*

Inhibitory control refers to the ability to exert control over one's attention, behavior, thoughts and/or emotions in order to overcome an internal predisposition or external lure and do what is more appropriate or necessary. Inhibitory control enables us to attend selectively, focusing our attention on what we choose and ignoring other stimuli. Self-control is an aspect of inhibitory control that entails exerting control over one's behavior and emotions in order to exert control over one's behavior. Self-control is about restraining one's impulses and not acting rashly. Another aspect of self-control is the discipline required to stay on task in the face of distractions and to complete a task despite temptations to quit, move on to more interesting work, or simply have a good time. This entails compelling yourself to do something or continue doing something even when you would rather be doing something else and is related to deferring gratification or compelling yourself to forego immediate pleasure in exchange for a greater reward later.[33]

*Working memory*

Working memory (WM) is the process of mentally storing and manipulating information. There are two types of WM: content-verbal WM and nonverbal (visual-spatial) WM. Working memory is critical for making sense of anything that unfolds over time, as this always requires recalling previous events and relating them to subsequent events. Thus, it is necessary for comprehending written or spoken language, regardless of the length of the sentence, paragraph, or longer. Without WM, the reasoning would be impossible. WM is critical for our ability to see connections between seemingly unrelated things and to disassemble and recombine elements within an integrated whole, and thus for creativity, as creativity entails disassembling and recombining elements in novel ways. Additionally, WM enables us to consider our remembered past and future hopes when making plans and decisions, rather than just perceptual input.[33]

*Cognitive flexibility*

Cognitive flexibility includes the ability to shift perspectives spatially or interpersonally. To switch perspectives, we must inhibit (or deactivate) our previous one and load (or activate) a new one into WM. Cognitive flexibility, in this sense, requires and builds on inhibitory control and working memory. Another aspect of cognitive flexibility is the ability to alter our perspective on something (thinking outside the box). Cognitive flexibility also entails the ability to adapt to changing demands or priorities, admit errors and capitalize on unexpected opportunities.[33]

According to Jean Piaget's theory of cognitive development, children progress through four distinct stages of mental development. His theory is concerned with not only how children acquire knowledge but also with the nature of intelligence. First, there is the sensorimotor stage, which lasts from birth to two years of age. Infants and toddlers acquire knowledge during this formative stage of cognitive development through sensory experiences. The interaction of the senses and the environment is the primary intellectual activity here. Children lack the ability to label experiences or to symbolize and thus remember, events and ideas. As a result, they see and feel what is happening but lack the ability to categorize their experiences.[33]

Secondly, there is preoperative stage that ranges between the ages of two and seven years.[33] During this stage, an intuitive mode of thought prevails, which is characterized by free association, fantasy and the creation of unique illogical meanings. Additionally, they frequently struggle with the concept of constancy.

Thirdly, there is concrete operational stage for those between the ages of 7 and 11. This stage marks the beginning of the development of concepts of right and wrong. Typically, these begin with specific acts and gradually become generalized. Finally, there is a formal operational stage for those aged 12 and up. The child progresses from the level of concrete operations to the final stage of formal operations at this stage. Since he is well into the socialized speech phase of language development, he is capable of considering and communicating with others' ideas.[33]

*Cognitive parameters*

It was proposed that there are eight key parameters of cognitive development that occur from infancy through childhood and that these parameters can be easily communicated to parents and caregivers. The cognitive development selection criteria were chosen based on the cognitive development selection criteria that were agreed upon by the experts. These cognitive development selection criteria were taken from existing references and have been used in child development within the medical field. Logic Reasoning and Decision Making, Problem Solving, Attention and Focus, Critical Thinking, Psychomotor Skills, Memory, Language and Creativity are all aspects of parameters, and they are divided into two categories. Category one is for those aged less than 2 years, and it includes attention, focus and language. Category two is for those aged more than 2 years. In addition, for children older than two years, they include memory, psychomotor, logical and reasoning skills, as well as decision-making.[23]

**The relationship between microbiome, immunity and cognitive function**

There is a consensus amongst all the experts that even though relationships do exist between nutrition, gut microbiota, immunity and cognitive development, there are few studies and references that explain the interrelationship of those factors as a comprehensive detail.

There are still very limited studies that link nutrition, gut microbiota and immunity to the development of cognitive function in children, despite the fact that it has been demonstrated in a number of journals that a direct relationship exists between these three factors. In this review study, only the use of animals for research purposes has been conducted up until this point.[23]

## Conclusions

There is strong evidence for the role of the gut microbiota in brain function and cognitive function that has come to light recently in research. Although a variety of factors, including health status, can influence the composition of the gut microbiota, diet is widely regarded as one of the most important influences on the human gut microbiota. As a result, all experts agree dietary interventions with the potential to improve cognitive function through neurogenesis must be investigated further.

**Author contribution**: All authors have read and agreed to the published version of the manuscript.

## Conflict of Interest

R.W.B., E.W., and M.S.K. are employees of Danone SN Indonesia. All other authors have no conflict of interest

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