

# Early and Long-term Consequences of Nutritional Stunting: From Childhood to Adulthood

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**Abstract.** Linear growth failure (stunting) in childhood is the most prevalent form of undernutrition globally. The debate continues as to whether children who become stunted before age 24 months can catch up in growth and cognitive functions later in their lives. The potentially irreparable physical and neurocognitive damage that accompanies stunted growth is a major obstacle to human development. This review aims at evaluation and summarizing the published research covering the different aspects of stunting from childhood to adulthood. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Stunting, nutrition, growth, cognition, early and long-term consequences.

## Background

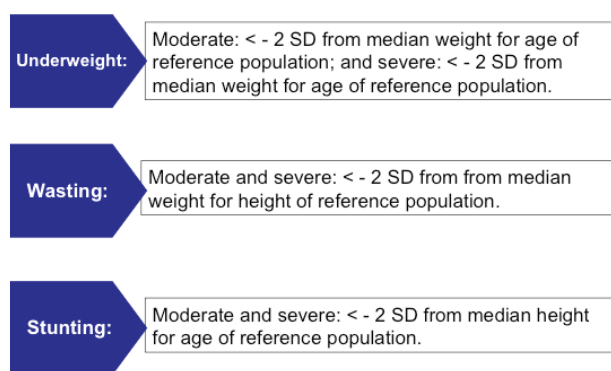
Stunting is a process that can affect the development of a child from the early stages of conception until the third or fourth year of life, when the nutrition of the mother and the child are essential determinants of growth. Stunting is defined as the percentage of children whose height-for-age is below minus two standard deviations for moderate and minus three standard deviations for severe stunting from the median of the 2006 WHO Child Growth Standards (1). Similarly, children are considered severely stunted if their length/height is below  $-3$  SDs from the WHO child growth standards median for the same age and sex. Wasting is defined as the tendency to be too thin for one's height, sometimes called weight-for-height. While wasting is the result of acute significant food shortage and/or disease, stunting represents chronic malnutrition, and the effects are largely irreversible. Underweight, or low weight for age, includes children under 5 with low weight for height (wasting) and low

height for age (stunting) and considered a proxy indicator for undernutrition if data on wasting is not available (2, 3) (Figure 1).

Wasting and stunting are often presented as two separate forms of malnutrition requiring different interventions for prevention and/or treatment. These two forms of malnutrition, however, are closely related and often occur together in the same populations and often in the same children, and there is evidence suggesting that they share many causal factors.

The prevalence of stunting (height or age below 2 SD) and thinness (BMI for age below 2 SD) were globally estimated using data from the Global School-Based Student Health and Health Behavior in School-Aged Children surveys conducted in 57 low- and middle-income countries between 2003 and 2013, involving 129 276 adolescents aged 12–15 years. Globally, the prevalence of stunting was 10.2% and thinness was 5.5% (4).

Nutritional stunting is caused by insufficient maternal nutrition, intrauterine undernutrition, lack



**Figure 1.** UNICEF Categories of undernutrition in children.

of breastfeeding until 6 months of age, later introduction of complementary feeding, inadequate (quantity and quality) complementary feeding, and impaired absorption of nutrients owing to infectious diseases (5,6). Stunting has long-term effects on individuals and societies, including poor cognition and educational performance, low adult wages, lost productivity and, when accompanied by excessive weight gain later in childhood, an increased risk of nutrition-related chronic diseases in adult life (7).

This review aims at evaluation and summarizing the published research covering the different aspects of stunting and its early and the long-term consequences.

### The early and long-term consequences of nutritional stunting

The consequences of child stunting are both immediate and long term and include increased morbidity and mortality, poor child development and learning capacity, increased risk of infections and non-communicable diseases, increased susceptibility to accumulate fat mostly in the central region of the body, lower fat oxidation, lower energy expenditure, insulin resistance and a higher risk of developing diabetes, hypertension, dyslipidaemia, lowered working capacity and unfavourable maternal reproductive outcomes in adulthood. Furthermore, stunted children who experienced rapid weight gain after 2 years have an increased risk of becoming overweight or obese later in life (7, 8).

### Growth and windows of vulnerability

A critical window (sensitive period) represents a period during development when an organism's phenotype is responsive to intrinsic or extrinsic (environmental) factors. The intrauterine and early post-natal months are well known to be particularly critical for future health and brain development

(9,10). Optimal maternal nutrition is an essential component for fetal and infant development, closely linked with maternal supply of essential nutrients, including vitamins and minerals. Furthermore, maternal anaemia, tobacco use, and indoor air pollution can restrict fetal growth and result in low birth weight.

During the first 2 years after birth, nutritional requirements to support rapid growth and development are very high and thus adverse factors have a greater potential for causing growth retardation in early life. Frequent infections during the first 2 years of life also contribute to the high risk of becoming stunted during this period. Catch-up growth is possible in children older than 2 years, although stunting is often well established by this age, in many low- and middle-income countries (LMICs) (11).

Adolescence is another critical window for growth and nutrition. Although there are ~1.8 billion adolescents worldwide and the majority are clustered in low-income and middle-income countries there is a gap in adolescent health data (12). The global estimate for stunting among adolescents' data varies from 52% in Guatemala and 44% in Bangladesh to 8% in Kenya and 6% in Brazil (13). The adolescent growth spurt (AGS) was studied in Indian rural boys, aged 5 years and over, with known childhood nutritional stunting. They entered late into puberty, with significantly depressed intensity, but gained a similar amount of height, as a result of prolonged AGS, that continued till 19.2 years. Thus, a childhood background of undernutrition did not lead to any additional deficit in height during puberty. However, pre-pubertal height deficits were carried into adult height.

### The potential role of mTORC1 pathway in the pathogenesis of child stunting

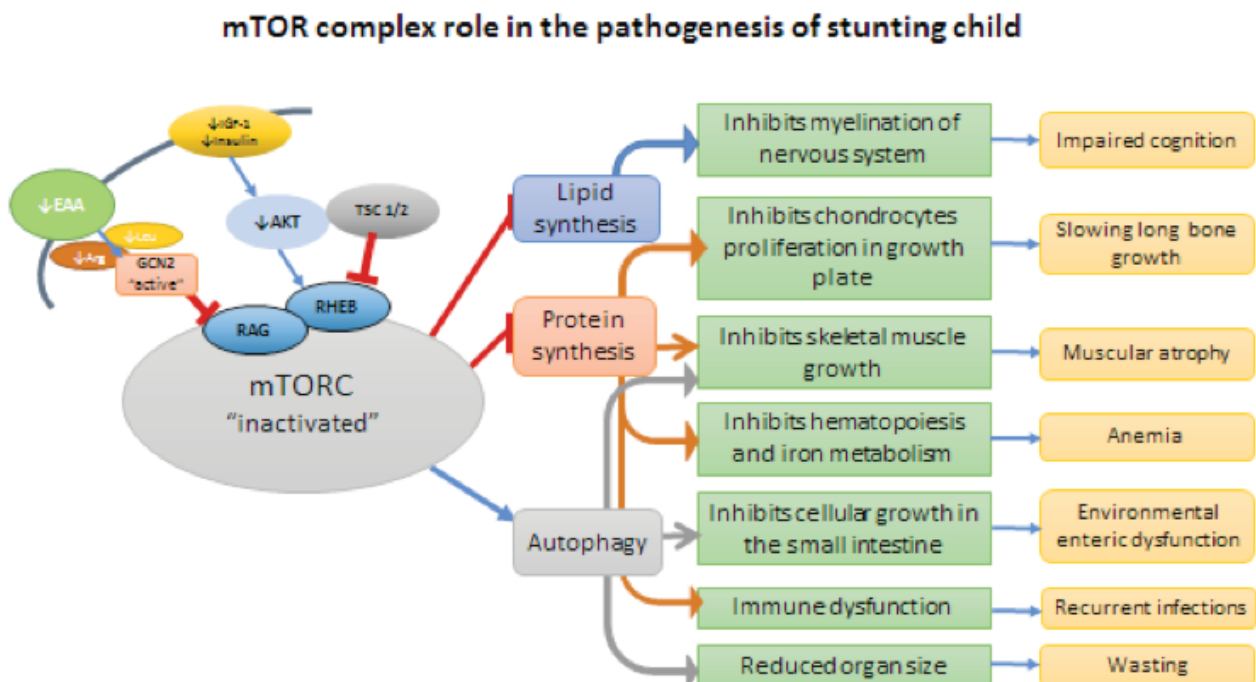
The signals that control weight and food intake are complex and appear to involve multiple pathways

that have as a central control in the hypothalamus, particularly the medial central area, and peripheral cellular control through the Mechanistic Target of Rapamycin Complex 1 (mTORC1). The hypothalamic and mTOR system responses to food deprivation provide a reversible experiment of nature that gives perception into understanding the role of various interactions between nutritional status, psychosocial stress (including poverty, maternal deprivation and abuse), endocrine system, linear growth and skeletal growth (15).

A dietary pattern of poor-quality protein associated with stunting leads to significantly lower circulating essential amino acids than do non-stunted children. These deficient intakes of essential amino acids can adversely affect growth, through their effect on the master growth regulation pathway, the mechanistic target of rapamycin complex 1 (mTORC1) pathway which is exquisitely sensitive to amino acid availability. mTORC1 integrates cues such as nutrients (mainly proteins and amino acids), growth factors, oxygen, and energy to regulate growth in the chondral plate, skeletal muscle growth, myelination of the central and

peripheral nervous system, cellular growth and differentiation in the small intestine, hematopoiesis and iron metabolism and organ size through the Hippo pathway. These organs are relevant to child stunting and its associated morbidities such as anemia, impaired cognition, environmental enteric dysfunction, and immunity against infectious diseases (16).

When amino acids are deficient, mTORC1 represses protein and lipid synthesis and cell and organismal growth. At low amino acid concentrations, mTORC1 is diffusely distributed in the cytosol and becomes inactive (17). Autophagy, an adaptation to nutrient starvation, is a process by which damaged or redundant proteins and other cell components are delivered to the lysosome and then degraded, releasing free amino acids into the cytoplasm. Proteins provide a reservoir of amino acids that are mobilized through autophagy when amino acids are scarce. In addition, in the absence of amino acids other signals, such as growth factors and energy, cannot overcome the lack of amino acids to activate mTORC1 (18). Figure 2 illustrates the complex role of mTOC in the pathogenesis of a stunting child.



**Figure 2.** mTOR complex role in the pathogenesis of stunting.

## CNS growth and cognitive functions in stunted children

The developing brain is particularly vulnerable to nutrient insufficiency between 24 and 42 weeks of gestation because of the rapid course of several neurologic processes, including synapse formation and myelination. (19) In healthy infants, there is well-documented rapid brain growth in the first 2 years, this early period is also critical for long-term neurodevelopment (9,10).

Cognitive functions, receptive and expressive language, and socioemotional skills develop at different ages. Development in brain structure and function supporting acquisition of cognitive, language, and socioemotional skills is most rapid during early childhood, with continued development in later years for many skills. Undernutrition affects areas of the brain involved in cognition, memory, and locomotor skills. The brain has major energy demands in early childhood and most cerebral growth occurs in the first 2 years of life. However, the associations between poor linear growth and impaired neurodevelopment are not well understood (20).

Nutritional stunting is associated with both structural and functional pathology of the brain and a wide range of cognitive deficits. In the CNS, chronic malnutrition can lead to tissue damage, disorderly differentiation, reduction in synapses and synaptic neurotransmitters, delayed myelination and reduced overall development of dendritic arborization of the developing brain. There are deviations in the temporal sequences of brain maturation, which in turn disturb the formation of neuronal circuits. Long term alterations in brain function have been reported which could be related to long lasting cognitive impairments associated with malnutrition (21- 24).

With chronic malnutrition, cognitive delays can occur throughout infancy, childhood, and adolescence, Measurable differences in receptive language by socio-economic groups are apparent in preschool children ages three to five years; differences in cognitive ability have been observed even in the first two years (25).

Stunted children have impaired behavioral development in early life, are less likely to enroll at school, enroll late, and tend to achieve lower grades. They have poorer cognitive ability than non-

stunted children. Furthermore, stunted children are more apathetic, display less exploratory behavior and have altered physiological arousal. Malnourished children performed poor on tests of attention, working memory, learning and memory and visuospatial ability except on the test of motor speed and coordination. Age related improvement was not observed on tests of design fluency, working memory, visual construction, learning and memory in malnourished children.

However, age related improvement was observed on tests of attention, visual perception, and verbal comprehension in malnourished children even though the performance was deficient as compared to the performance level of adequately nourished children (26-29).

Stunted children followed longitudinally in Jamaica were found to have more anxiety and depression and lower self-esteem than non-stunted children at age 17, after adjusting for age, gender, and social background variables (29).

In addition, the brain may be susceptible to poor nutrition during its ongoing remodelling and during recovering from various forms of damage. At approximately age 10, a child's brain represents 5–10% of body mass, consumes twice the glucose and 1.5 times the oxygen per gram of tissue compared with an adult's brain, and accounts for up to 50% of the total basal metabolic rate of the body (9,10,19). Thus, nutritional deprivation during adolescence may have an undesirable impact on brain functions (30).

## Growth failure and hormonal implications

The prevalence of stunting, defined as height-for-age less than the 5th percentile of the NCHS/WHO 1995 reference data, ranges from 26% to 65% (31).

Growth failure in the first 2 years of life is associated with reduced stature in adulthood (32,33). The magnitude of growth deficits is considerable. Coly et al. (32) found that the age-adjusted height deficit between stunted and non-stunted children was 6.6 cm for women and 9 cm for men. Growth restriction in early life is linked not only to short adult height but also to certain metabolic disorders and chronic

diseases in adulthood. The consequences of stunting in adolescence include greater risk of obstetric complications, including obstructed labour in females, and diminished physical capacity among adolescents of both sexes (31,34).

Chronic malnutrition in stunted children is associated with diminished levels of insulin-like growth factor 1 (IGF-1) synthesis. Even a transient 50% reduction in calorie or 33% reduction in protein availability can result in a reversible reduction in IGF-1 concentrations. The reduced levels of IGF-1 lead to a secondary increase in growth hormone (GH) through the negative feedback of low IGF-1 level on pituitary synthesis of GH. The end metabolic result is diversion of substrate away from growth toward metabolic homeostasis. The well-known metabolic effects of growth hormone, which are not IGF-1 dependent, would clearly be adaptive in the face of reduced substrate intake. These include increased lipolysis and mobilization of free fatty acids from adipose tissue stores and inhibition of glucose uptake by muscle tissue (35-37) (Figure 3).

### Effects of protein and amino-acid supplementation on the physical growth of young children in low-income countries

High quality proteins (e.g. milk) in complementary, supplementary and rehabilitation food products have been found to be effective for good growth. Individual amino acids such as lysine and arginine have been found to be factors linked to growth hormone release in young children via the somatotrophic axis and high intakes are inversely associated with fat mass index in pre-pubertal lean girls. Protein intake in early life is positively associated with height and weight at 10 y of age (38). The results of 18 intervention trials in which supplementary protein or amino acids were analyzed in children ages 6-35 months and growth outcomes were reviewed. Eight studies conducted in hospitalized children recovering from acute malnutrition found that the recommended protein intake levels for healthy children supported normal growth rates, but higher intakes were needed for accelerated rates of “catch-up” growth. Micronutrient supplementation

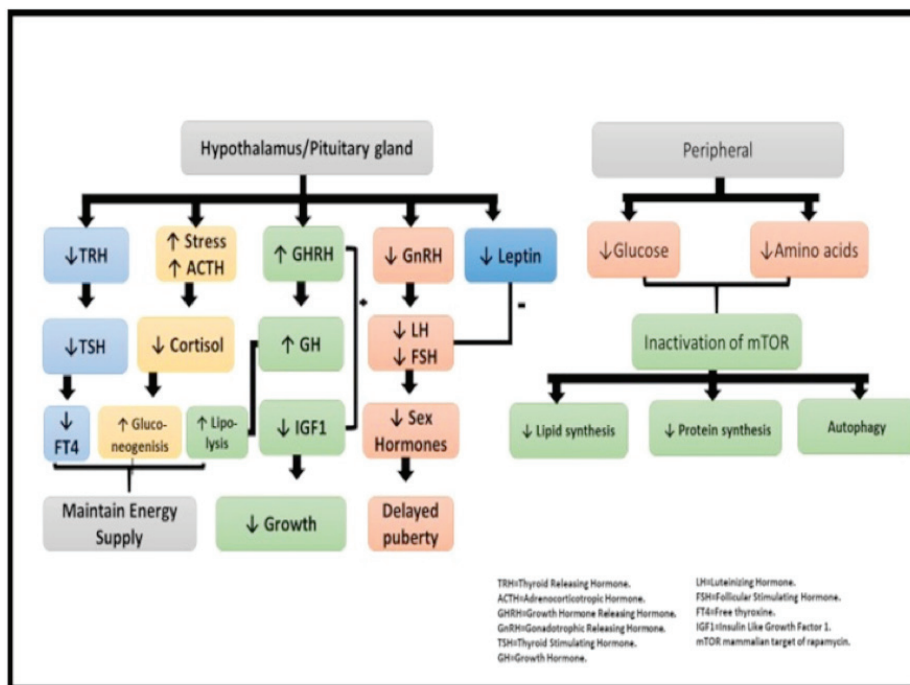


Figure 3. Pathophysiologic mechanisms affecting linear growth during malnutrition.

or lipid-based supplements with micronutrients have little to no effect on stunting (39).

### Glucose homeostasis, insulin secretion and insulin resistance related to nutritional stunting

Data from the Maternal and Child Undernutrition Study Group indicate that lower birth weight (which is strongly correlated with birth length) and undernutrition in childhood are risk factors for high glucose concentrations, high blood pressure and harmful lipid profiles in adulthood after adjusting for adult height and body mass index (BMI) (40).

Glucose homeostasis is of paramount importance in the successful adaptation to chronic malnutrition leading to stunting. Until the brain and other obligate glucose users can adapt to ketones as a fuel source, adequate blood glucose levels must be maintained. Increased gluconeogenesis, stimulated in part by cortisol, plays a role. Diminished glucose uptake by

tissues is also important. In this regard, both decreased insulin secretion and /or increased insulin resistance have been reported during chronic malnutrition. High cortisol and growth hormone levels antagonize insulin and prevent hypoglycemia during malnutrition (41,42) (Figure 4).

Deleterious changes have been reported in the metabolism of glucose in children suffering from undernutrition in infancy. One study that examined the effects of undernutrition in the first year of life on glucose tolerance and plasma insulin found that early undernutrition in the extrauterine period, independent of the birth weight, was associated with hyperinsulinemia and a reduced sensitivity to insulin, which worsened as BMI increased in adult life (43).

Martins et al. (44) examined these hormonal changes in adolescence and observed that the stunted boys and girls showed plasma insulin levels that were significantly lower when associated with a lower homeostasis model assessment-B (HOMA-B), which evaluates pancreatic b-cell function, than those

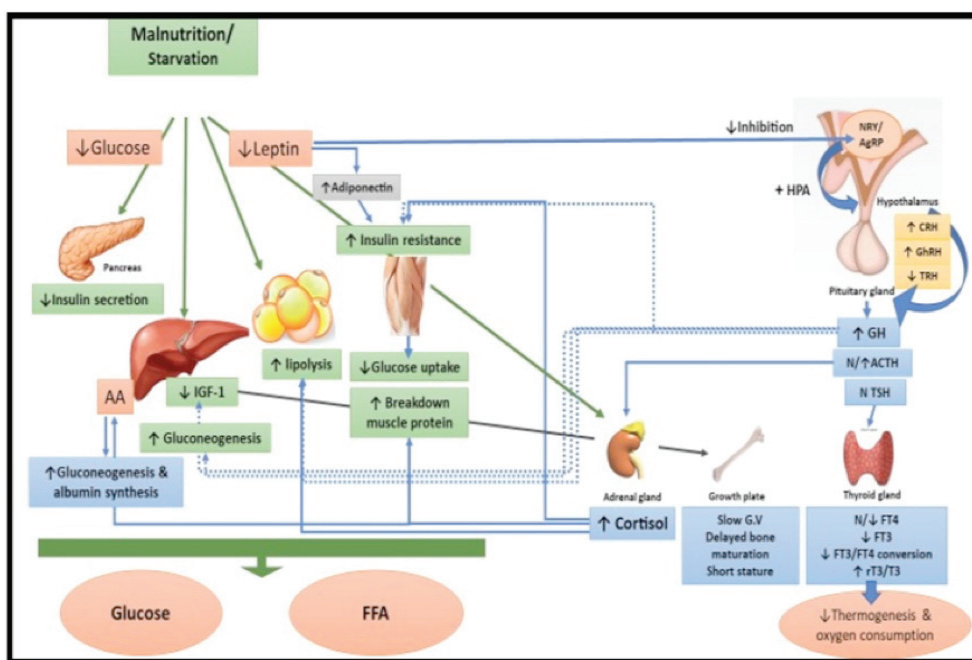


Figure 4. Endocrine adaptation mechanisms during malnutrition.

of a non-stunted group. At the same time, their values for HOMA-S (an evaluation of insulin sensitivity) were significantly greater at this age. The increase in insulin sensitivity might be due to a higher number of peripheral insulin receptors, especially in the adipose and muscle tissues, which may establish a counter-regulatory mechanism to compensate for the low levels of insulin (44).

A study carried out by Fekadu et al. (45) in adult diabetic individuals found a significant association between diabetes and a history of undernutrition and a lack of a clean water supply during childhood, emphasising the importance of adequate post-natal development for the maintenance of health in the long-term.

Apparently, the lower beta cell function is due to a lower beta cell number as a result of malnutrition. Furthermore, this could be a consequence of the increased concentration of glucocorticoids that occurs in undernutrition, as normal levels of glucocorticoids are necessary to ensure the development and maintenance of normal pancreatic architecture, as well as the expansion of the beta cell mass during critical periods of development (46).

Based on the results described above it appears plausible that in adolescence a decrease in the function of the pancreatic cells is compensated by an increase in sensitivity to insulin. However, as the amount of abdominal fat and age increase, this condition begins to place more intense demands on undernourished individuals, causing an increase in pancreatic activity, which accelerates the exhaustion of the organ and the onset of diabetes (47,48).

While it is unclear whether stunting may be a risk factor for obesity per se, rapid weight gain, particularly after the age of 2–3 years among individuals born small at birth, is thought to lead to a particularly high risk of chronic disease in later life (49).

### **Endocrinopathies associated with nutritional stunting**

The endocrinopathies associated with nutritional stunting involve multiple systems and mechanisms designed to preserve energy and protect essential organs. The changes in neuropeptides and in the

hypothalamic axis that mediate these changes also receive input from neuroendocrine signals sensitive to satiety and food intake and in turn may be prepared to provide significant energy conservation (50).

Many studies reported a high cortisol levels in malnourished children. Increased cortisol levels during malnutrition represented an attempt of the organism to adapt to decreased dietary protein and/or energy supply through breakdown of muscle protein to provide the liver with the necessary amino acids for gluconeogenesis and albumin synthesis. This process protects the organism from hypoalbuminemia and hypoglycemia, respectively. The significant correlations between the percent weight deficit and the muscle diameter on the one hand and serum cortisol levels on the other suggest a causal relationship between the increase of serum cortisol and the degree of muscle wasting (51–53). After 4 to 8 weeks of nutritional rehabilitation, the circulating cortisol levels decreased markedly to become indistinguishable from those of the normal children.

Low leptin secretion during chronic malnutrition, appears to be an important signal in the process of metabolic/endocrine adaptation to prolonged nutritional deprivation. Low leptin levels decrease

leptin inhibition on NPY that affects the regulation of pituitary growth and pituitary adrenal axes (42, 54). Stimulation of the hypothalamic-pituitary-adrenal (HPA) axis and possibly the hypothalamic-pituitary-GH axis to maintain the high cortisol and GH levels appear necessary for effective gluconeogenesis and lipolysis to ensure a fuel (glucose and fatty acids) supply for the metabolism of brain and peripheral tissue during nutritional deprivation (42,54).

Most studies of the thyroid hormone adaptation to malnutrition have shown low to normal total T4 levels and free T4 (FT4) levels. In contrast, total and FT3, the physiologically active forms of the hormone, are reduced, with a concomitant increase in rT3, which is metabolically inactive. A reduction in active thyroid hormone levels can decrease thermogenesis and oxygen consumption, leading to energy conservation when energy producing substrate is scarce—an important adaptive response to malnutrition (55–57).

In summary, the decreased synthesis of IGF-1 and the low level of insulin and/or its diminished

effect due to an insulin-resistant status in the presence of high circulating GH and cortisol levels ensure substrate diversion away from growth toward metabolic homeostasis (Figure 4).

## Hypertension

A high prevalence of arterial hypertension has been found in children, adolescents, and adults with nutritional stunting.

Epidemiological studies indicate that there is a correlation between low birth weight (LBW, defined as a birth weight of a live born infant of < 2,500 gram) and hypertension in adulthood. It has been estimated that 8-26% of all childbirth worldwide is LBW, in which higher prevalence is found in developing countries compared to the developed countries (58).

The pathological mechanisms that link LBW and hypertension are multifactorial and include reduction in nephron number (renal mass) associated with retarded fetal growth, genetic factors, sympathetic nervous hyperactivity, endothelial dysfunction, elastin deficiencies, insulin resistance, high plasma glucocorticoid concentrations, and activation of renin-angiotensin system (59).

Franco et al. (60) reported changes in the sympatho-adrenal and renin-angiotensin systems in children small for their gestational age (SGA). They investigated the plasma levels of ACE (angiotensin-converting enzyme), angiotensin and catecholamines in 8 to 13-year-old children to determine correlations between the plasma levels and both birth weight and blood pressure (BP). Circulating noradrenaline levels were significantly elevated in SGA girls compared to girls born with a weight appropriate for their gestational age. In addition, angiotensin II (AngII) and ACE activity were higher in SGA boys. There was a significant association between the circulating levels of both angiotensin II and ACE activity and systolic BP (SBP). These findings support the link between low birth weight and overactivity of both sympatho-adrenal and renin-angiotensin systems into later childhood (60).

It has been suggested that not only intrauterine undernutrition but also its occurrence during

childhood may influence the incidence of hypertension in adulthood and its persistence (61).

One study that investigated arterial pressure in a random sample of adolescents with stunting (10–16 y, n = 56) showed an elevated prevalence of cases (51%, n=27) with a diastolic and systolic BP above the 90th percentile, adjusted for height (95% confidence interval 37%-65%); 6% (n=3) of these individuals had simultaneous diastolic and systolic hypertension (62).

In conclusion, these data reinforce the important association between undernutrition and hypertension from infancy through childhood and adulthood and emphasize the need for monitoring BP in undernourished children. These alterations are amplified with time, depending on the quality of the diet and on environmental factors. Physicians and other health care professionals practicing in developing countries and in large urban centers with low-income populations should be aware of the association between early in life undernutrition and hypertension for a timely detection and treatment of hypertension, and to keep monitoring these individuals throughout their life.

## Stunting and future risk of obesity

There is a fair amount of epidemiological evidence showing that nutritional stunting causes increased risks of obesity. Obesity is increasing dramatically not only in developed countries but also in developing countries, such as Brazil, especially among the poorer. In addition, an increasing number of studies have shown that nutritional stunting causes a series of important long-lasting changes such as lower energy expenditure, higher susceptibility to the effects of high-fat diets, lower fat oxidation, and impaired regulation of food intake. A study from Brazil showed a high prevalence of undernutrition (low weight-for-age and/or low height-for-age) in children (30%) with a shift towards overweight and obesity (high weight-for-height and BMI) among adolescents (21% in girls and 8.8% in boys) and adults (14.6%). In addition, stunting was associated with overweight in children of four nations that are undergoing the nutrition transition (63-67).



## Early nutrition and later physical work capacity

Malnutrition in early childhood continuing into adolescence could be considered to have adverse effect on their work capacity by influencing their body weight. Stunting has important economic consequences for both sexes. A low BMI is related to a greater number of absences from work and also to lower productivity (68,69). A BMI of 17 kg/m<sup>2</sup> appears to be critical for the capacity for work, and below this value, productivity is negatively impacted. In addition, it is possible that work capacity might be reduced before this level is reached. In any case, work requiring the use of the body mass, such as carrying loads, digging, or shoveling earth or coal, pulling, or cycling a rickshaw, stone splitting, would impose a greater stress on people of low BMI (69).

These studies, combined with other measures such as cognitive functioning and reproductive performance, provide strong evidence in support of policies and programs aimed at eliminating the causes of environmental stunting in poor populations (70,71).

## Conclusions

The heightened risks of potentially irreversible loss of growth and cognitive functions and increased morbidities and mortalities associated with stunting demand further work on the etiology, prevention, and early treatment of children with stunting. Further clinical studies are needed that should ensure supplementing adequate high-quality protein intake in addition to providing sufficient energy to guarantee that protein can be utilized for growth rather than potentially being diverted to meet maintenance energy needs. The intervention must be provided for a sufficient time to assess linear growth. Treatment of stunted children should be regarded as a public health priority. Based on available evidence, policy makers and program planners should consider intensifying efforts to prevent stunting and promote catch-up growth over the first few years of life as a way of improving children's physical and intellectual development. Effective nutrition supplementation and follow up can be achieved by identifying children with low weight-for-age Z-score (WAZ)

and height-for-age (HAZ) in pediatric primary health care clinics and including them into a national nutritional program operating at clinics sites, and in the community.

**Conflicts of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

## References

1. UNICEF. Improving Child Nutrition. The achievable imperative for global progress. UNICEF, 2013. [https://www.unicef.org/infobycountry/stats\\_popup2.html](https://www.unicef.org/infobycountry/stats_popup2.html).
2. Semali IA, Tengia-Kessy A, Mmbaga EJ, Leyna G. Prevalence and determinants of stunting in under-five children in central Tanzania : remaining threats to achieving Millennium development goal 4. BMC Public Health. 2015;4-9.
3. Francisco J, Ferrer L, Serra-Majem L. Factors associated with stunting among children. Nutrients. 2017;9:1-16.
4. Caleyachetty R, Thomas GN, Kengne AP, et al. The double burden of malnutrition among adolescents: analysis of data from the Global School-Based Student Health and Health Behavior in School-Aged Children surveys in 57 low- and middle-income countries. Am J Clin Nutr. 2018; 108:414-424.
5. Kramer CV, Allen S. Malnutrition in developing countries. Paediatr Child Health. 2015; 25:422-427.
6. Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. Paediatr Int Child Health. 2014; 34:254-264.
7. Dewey KG, Begum K. Long-term consequences of stunting in early life. Matern Child Nutr. 2011; 7:5-18
8. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition 1- Maternal and child undernutrition: global and regional exposures and health consequences. Lancet. 2008; 371:243- 260.
9. Bergvall N, Iliadou A, Johansson S, Tuvemo T, Cnattingius S. Risks for low intellectual performance related to being born small for gestational age are modified by gestational age. Pediatrics. 2006; 117:460-467.
10. Gale CR, O'Callaghan FJ, Godfrey KM, Law CM, Martyn CN. Critical periods of brain growth and cognitive function in children. Brain,2004; 127:321-329.
11. Roth DE, Krishna A, Leung M, Shi J, Bassani DG, Barros AJD. Early childhood linear growth faltering in low-income and middle-income countries as a whole-population condition: analysis of 179 Demographic and Health Surveys from 64 countries (1993- 2015). Lancet Glob Health. 2017; 5:1249- 1257.
12. Black RE, Victora CG, Walker SP. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013; 382: 427-451.

13. Benedict RK, Schmale A, Namaste S. Adolescent nutrition 2000–2017: DHS data on adolescents age 15–19. DHS Comparative Report No. 47. Rockville, Maryland; 2018.
14. Satyanarayana K, Radhaiah G, Mohan KR, et al. The adolescent growth spurt of height among rural Indian boys in relation to childhood nutritional background: an 18-year longitudinal study. *Ann Hum Biol.* 1989;16 :289–300.
15. Semba RD, Trehan I, Gonzalez-Freire M, et al. Perspective: The Potential Role of Essential Amino Acids and the Mechanistic Target of Rapamycin Complex 1 (mTORC1) Pathway in the Pathogenesis of Child Stunting. *Adv Nutr.* 2016; 7:853–865.
16. Semba RD, Shardell M, Sakr Ashour FA, et al. Child Stunting is Associated with Low Circulating Essential Amino Acids. *EBioMedicine.* 2016; 6:246–252.
17. Sancak Y, Bar-Peled L, Zoncu R, Markhard AL, Nada S, Sabatini DM. Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. *Cell.* 2010; 141:290–303.
18. Demetriades C, Doumpas N, Teleman AA. Regulation of TORC1 in response to amino acid starvation via lysosomal recruitment of TSC2. *Cell.* 2014; 156:786–799.
19. Fall CH, Yajnik CS, Rao S, Davies AA, Brown N, Farrant HJ. Micronutrients and fetal growth. *J. Nutr.* 2003;133:1747–1756.
20. Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. *Paediatr Int Child Health.* 2014; 34:250–265.
21. Levitsky DA, Strupp BJ. Malnutrition and the brain: undernutrition and behavioural development in children. *J Nutr.* 1995;125: 2212–2220.
22. Sandjaja, Poh BK, Rojroonwasinkul N, et al. Relationship between anthropometric indicators and cognitive performance in Southeast Asian school-aged children. *Br J Nutr.* 2013;110 (Suppl 3) 57–64.
23. Fernald LC, Grantham-McGregor SM. Stress response in school-age children who have been growth retarded since early childhood. *Am J Clin Nutr.* 1998; 68:691–698.
24. Rosenberg M. Global child health: burden of disease, achievements, and future challenges. *Curr Probl Pediatr Adolesc Health Care.* 2007; 37:338–362.
25. Walker SP, Wachs TD, Gardner JM, et al; International Child Development Steering Group. Child development: risk factors for adverse outcomes in developing countries. *Lancet.* 2007 ;369:145–157.
26. Kar BR, Rao SL, Chandramouli BA. Cognitive development in children with chronic protein energy malnutrition. *Behav Brain Funct.* 2008 Jul 24;4:31. doi: 10.1186/1744-9081-4-31.
27. Upadhyaya SK, Saran A, Agarwal DK, Singh MP, Agarwal KN. Growth and behaviour development in rural infants in relation to malnutrition and environment. *Indian Pediatr.* 1992;29: 595–606.
28. Upadhyaya SK, Agarwal KN, Agarwal DK. Influence of malnutrition on social maturity, visual motor coordination and memory in rural school children. *Indian J Med Res.* 1989;90:320–327.
29. Alderman H, Behrman JR, Glewwe P, Fernald L, Walker S. Evidence of Impact of Interventions on Growth and Development during Early and Middle Childhood. In: Bundy DAP, Silva Nd, Horton S, Jamison DT, Patton GC, editors. *Child and Adolescent Health and Development.* 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017 Nov. Chapter 7.
30. Galler JR, Koethe JR, Yolken RH. Neurodevelopment: The Impact of Nutrition and Inflammation During Adolescence in Low-Resource Settings. *Pediatrics.* 2017;139 (Suppl 1):S72–S84.
31. Kurtz K. Adolescent nutritional status in developing countries. *Proc Nut Soc.* 1996; 55:321–331
32. Coly AN, Milet J, Diallo A, Ndiaye T, Bénéfice E, Simondon F, Wade S, Simondon KB. Preschool stunting, adolescent migration, catch-up growth, and adult height in young senegalese men and women of rural origin. *J Nutr.* 2006; 136:2412–2420.
33. Stein AD, Thompson AM, Waters A. Childhood growth and chronic disease: evidence from countries undergoing the nutrition transition. *Matern Child Nutr.* 2005;1:177–184.
34. Ozaltin E, Hill K, Subramanian SV. Association of maternal stature with offspring mortality, underweight, and stunting in low- to middle-income countries. *JAMA.* 2010;303:1507–1516.
35. Hawkes CP, Grimberg A. Insulin-Like Growth Factor-I is a Marker for the Nutritional State. *Pediatr Endocrinol Rev.* 2015;13:499–511.
36. Soliman AT, Hassan AEHI, Aref MK, et al. Serum insulin-like growth factors I and II concentrations and growth hormone and insulin responses to arginine infusion in children with protein-energy malnutrition before and after nutritional rehabilitation. *Pediatr Res.* 1986; 20:1122–1130.
37. Bartz S, Mody A, Hornik C, et al. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. *J Clin Endocrinol Metab.* 2014; 99:2128–2137.
38. Uauy R, Kurpad A, Tano-Debrah K, et al. Role of Protein and Amino Acids in Infant and Young Child Nutrition: Protein and Amino Acid Needs and Relationship with Child Growth. *J Nutr Sci Vitaminol (Tokyo).* 2015; 61(Suppl 1):S192–194.
39. Arsenault JE, Brown KH. Effects of protein or amino-acid supplementation on the physical growth of young children in low-income countries. *Nutr Rev.* 2017; 75:699–717.
40. Victora CG, Adair L, Fall C, et al. Maternal and child undernutrition: consequences for adult health and human capital. *Lancet.* 2008; 371: 340–357.
41. Kajubi SK. The endocrine pancreas after kwashiorkor. *Am J Clin Nutr.* 1972; 25:1140–1142.
42. Soliman AT, ElZalabany MM, Salama M, Ansari BM. Serum leptin concentrations during severe protein-energy

- malnutrition: Correlation with growth parameters and endocrine function. *Metabolism*. 2000;49:819–825.
43. González-Barranco J, Ríos-Torres JM, Castillo-Martínez L, et al. Effect of malnutrition during the first year of life on adult plasma insulin and glucose tolerance. *Metabolism*. 2003;52:1005–1011.
  44. Martins VJB, Toledo Florêncio TMM, Grillo L P, et al. Long-Lasting Effects of Undernutrition. *Int J Environ Res Public Health*. 2011;8:1817–1846.
  45. Fekadu S, Yizgaw M, Alemu S, et al. Insulin-requiring diabetes in Ethiopia: associations with poverty, early undernutrition and anthropometric disproportion. *Eur J Clin Nutr*. 2010;64:1192–1198.
  46. Bréant B, Gesina E, Blondeau B. Nutrition, glucocorticoids and pancreas development. *Horm. Res*. 2006, 65:98–104.
  47. Yajnik C S. Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. *J Nutr*. 2004;134:205–210.
  48. Martins PA, Sawaya A L. Evidence for impaired insulin production and higher sensitivity in stunted children living in slums. *Br J Nutr*. 2006;95:996–1001.
  49. Gluckman PD, Hanson MA, Beedle AS. Early life events and their consequences for later disease: a life history and evolutionary perspective. *Am J Hum Biol*. 2007;19:1–19.
  50. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Compr Physiol*. 2016;6:603–621.
  51. Alleyne GAO, Young VH. Adrenocortical function in children with severe protein-calorie malnutrition. *ClinSci*. 1967;33:189–200.
  52. Soliman AT, Aref M K, Hassan AHI. Hormonal changes in protein energy malnutrition. *Indian J Pediatr*. 1988;55:465–469.
  53. Soliman AT, Hassan A, Aref M K, D. Rogol AD. Serum Cortisol Concentrations in Children with Protein-Energy Malnutrition. *Ann Saudi Med*. 1989;9:6. doi: 10.5144/0256-4947.1989.533.
  54. Büyükgöbüz B, Öztürk Y, Yılmaz S, Arslan N. Serum leptin concentrations in children with mild protein-energy malnutrition and catch-up growth. *Pediatr Int*. 2004; 46:534–538.
  55. Carter WJ, Shakir KM, Hodges S, et al. Effect of thyroid hormone on metabolic adaptation to fasting. *Metabolism*. 1975; 24:1177–1183.
  56. Burman KD, Wartofsky L, Dinterman RE, et al. The effect of T3 and reverse T3 administration on muscle protein catabolism during fasting as measured by 3-methylhistidine excretion. *Metabolism*. 1979;28:805–813.
  57. Parra A, Garza C, Garza Y, et al. Changes in growth hormone, insulin and thyroxine values, and in energy metabolism of marasmic infants. *J Pediatr*. 1973; 82:133–142.
  58. Saenger P, Czernichow P, Hughes I. Small for gestational age short Stature and beyond. *Endocr Rev*. 2006;28:219–252.
  59. Rasyid H, Bakri S. Intra-uterine Growth Retardation and Development of Hypertension. *Acta Med Indones*. 2016;48:320–324.
  60. Franco MC, Casarini DE, Carneiro-Ramos MS, Sawaya AL, Barreto-Chaves ML, Sesso R. Circulating renin-angiotensin system and catecholamines in childhood: is there a role for birthweight? *Clin Sci (Lond)*. 2008;114:375–380.
  61. Sawaya AL, Sesso R, Florêncio TM, Fernandes MT, Martins PA. Association between chronic undernutrition and hypertension. *Matern Child Nutr*. 2005;1:155–163.
  62. Fernandes MT, Sesso R, Martins PA, Sawaya AL. Increased blood pressure in adolescents of low socioeconomic status with short stature. *Pediatr Nephrol*. 2003;18:435–439.
  63. Sawaya AL, Dallal G, Solymos G, et al. Obesity and malnutrition in a Shantytown population in the city of São Paulo, Brazil. *Obes Res*. 1995;3 (Suppl 2):107s–115s.
  64. Sawaya AL, Grillo LP, Verreschi I, da Silva AC, Roberts SB. Mild stunting is associated with higher susceptibility to the effects of high fat diets: studies in a shantytown population in São Paulo, Brazil. *J Nutr*. 1998;128 (2 Suppl):415S–420S.
  65. Hoffman DJ, Sawaya AL, Verreschi I, Tucker KL, Roberts SB. Why are nutritionally stunted children at increased risk of obesity? Studies of metabolic rate and fat oxidation in shantytown children from São Paulo, Brazil. *Am J Clin Nutr*. 2000;72:702–707.
  66. Sawaya AL, Roberts S. Stunting and future risk of obesity: principal physiological mechanisms. *Cad Saude Publica*. 2003;19 (Suppl 1):S21–28.
  67. Popkin BM, Richards MK, Montiero CA. Stunting is associated with overweight in children of four nations that are undergoing the nutrition transition. *J Nutr*. 1996;126:3009–3016.
  68. Pryer JA. Body mass index and work-disabling morbidity: results from a Bangladeshi case study. *Eur J Clin Nutr*. 1993;47:653–657.
  69. Durnin JV. Low body mass index, physical work capacity and physical activity levels. *Eur J Clin Nutr*. 1994;48 (Suppl 3): 39–43.
  70. Haas JD, Murdoch S, Rivera J, Martorell R. Early nutrition and later physical work capacity. *Nutr Rev*. 1996;54:41–48.
  71. Martorell R. Improved nutrition in the first 1000 days and adult human capital and health. *Am J Hum Biol*. 2017;29(2):10.1002/ajhb.22952. doi: 10.1002/ajhb.22952

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