Wasting affects an estimated 52 million children under age 5 years, and stunting, an estimated 165 million children [1]. The need for new nutritional interventions was highlighted in a recent paper on the worldwide progress towards the 2025 World Health Organization (WHO) targets for nutrition, namely, reducing and maintaining the prevalence of childhood wasting to less than 5% and reducing the number of stunted children by 40% [2]. This chapter reviews the data on malnutrition and catch-up growth published between July 1, 2016 and June 30, 2017, by topic:

1. **Biomarkers of malnutrition and stunting**: Three studies describing clinical and metabolic correlations that may assist clinicians in assessing the nutritional and general health status of undernourished children (Lee et al. [3], Rytter et al. [4], McGrath et al. [5]).

2. **Malnutrition and the gut microbiome**: Two studies reviewing the inter-relationships among malnutrition, the microbiome, and growth (Plovier and Cani [6], Velly et al. [7]).

3. **Treatment of malnutrition**: Six trials evaluating the effects of different interventions in the undernourished and malnourished pediatric population, 3 focused on the under-5-year age group (Dewey et al. [8], Iannotti et al. [9], Kureishy et al. [10]) and three on the over-5-year age group (Fatima et al. [11], Baum et al. [12], Ganmaa et al. [13]). Additionally, one review and one meta-analysis evaluating the impact of nutritional interventions on linear growth (Gat-Yablonski et al. [14], Roberts and Stein [15]).
4. Global aspects of treating stunting: One report on the economic implications of improving stunting (McGovern et al. [16]). One report on the investments needed to attain the WHO targets in reducing stunting (Shekar et al. [17]). One review of current thinking on the pathogenesis and risk factors for adverse developmental outcomes among young children at risk for malnutrition, setting the scene for potential interventions (Bhutta et al. [18]). One meta-analysis aimed to determine the impact that community-level sanitation access has on child stunting and health (Larsen et al. [19]).

Key articles reviewed for this chapter

The plasma proteome is associated with anthropometric status of undernourished Nepalese school-aged children
J Nutr 2017;147:304–313

Correlates of thymus size and changes during treatment of children with severe acute malnutrition: a cohort study
Rytter MJ, Namusoke H, Ritz C, Michaelsen KF, Briend A, Friis H, Dorthe Jeppesen D
BMC Pediatr 2017;17:70

Biomarkers to stratify risk groups among children with malnutrition in resource-limited settings and to monitor response to intervention
McGrath CJ, Arndt MB, Walson JL
Horm Res Paediatr 2017;88:111–117

Microbial impact on host metabolism: opportunities for novel treatments of nutritional disorders?
Plovier H, Cani PD
Microbiol Spectr 2017;5:BAD-0002-2016

Mechanisms of cross-talk between the diet, the intestinal microbiome, and the undernourished host
Velly H, Britton RA, Preidis GA
Gut Microbes 2017;8:98–112

Lipid-based nutrient supplementation in the first 1,000 days improves child growth in Bangladesh: a cluster-randomized effectiveness trial
Eggs in early complementary feeding and child growth: a randomized controlled trial
*Pediatrics* 2017;140:e20163459

A mixed method study to assess the effectiveness of food-based interventions to prevent stunting among children under-five years in Districts Thatta and Sujawal, Sindh Province, Pakistan: study protocol
*BMC Public Health* 2017;17:24

Impact of therapeutic food compared to oral nutritional supplements on nutritional outcomes in mildly underweight healthy children in a low-medium-income society
Fatima S, Malkova D, Wright C, Gerasimidis K
*Clin Nutr* 2017;pii:S0261-5164(17)30097-3

The effect of egg supplementation on growth parameters in children participating in a school feeding program in rural Uganda: a pilot study
Baum JI, Miller JD, Gaines BL
*Food Nutr Res* 2017;61:1330097

Vitamin D supplementation and growth in urban Mongol school children: Results from two randomized clinical trials
*PLoS One* 2017;12:e0175237

Which dietary components modulate longitudinal growth?
Gat-Yablonski G, Yackobovitch-Gavan M, Phillip M
*Curr Opin Clin Nutr Metab Care* 2017;20:211–216

The impact of nutritional interventions beyond the first 2 years of life on linear growth: a systematic review and meta-analysis
Roberts JL, Stein AD
*Adv Nutr* 2017;8:323–336

A review of the evidence linking child stunting to economic outcomes
McGovern ME, Krishna A, Aguayo VM, Subramanian SV
*Int J Epidemiol* 2017;46:1171–1191

Reaching the global target to reduce stunting: an investment framework
*Health Policy Plan* 2017;32:657–668
The plasma proteome is associated with anthropometric status of undernourished Nepalese school-aged children

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J Nutr 2017;147:304–313

Background: Our understanding of the biological pathways involved in stunting and wasting of chronically undernourished children remains insufficient. The effects of malnutrition are usually evaluated anthropometrically, but this method does not provide biological insight. Plasma proteomics may serve to highlight relevant biological pathways and single out novel protein markers of childhood growth and body composition.

Aims: To evaluate possible associations of anthropometric markers of height, musculature, and fat mass with plasma proteins in school-aged children using an untargeted proteomics approach.

Methods: A cohort of 500 Nepalese children aged 6–8 years were evaluated in this cross-sectional study. Height, weight, mid-upper arm circumference (MUAC), triceps and sub-scapular skinfolds, upper arm muscle area (AMA), and arm fat area were documented. Tandem mass spectrometry was used to measure relative plasma protein abundance. Associations between anthropometry and protein abundance were evaluated by linear mixed-effects models.

Results: Of the total 982 proteins, 1 was associated with body mass index-for-age z scores (BAZ), 10 with height-for-age z scores (HAZ), 14 with MUAC, and 17 with AMA (q < 0.05). The proteome was most robustly correlated with weight-for-age z score (WAZ; n = 33). There were strong positive associations of insulin-like growth factor (IGF)-I and its binding proteins (IGFALS and IGFBP3) with HAZ, WAZ, and AMA. Other proteins that were associated with HAZ are known to take part in nutrient transport, innate immunity, and bone mineralization. The absence of an association between proteins and measures of adiposity was noteworthy. Myosin light-chain kinase was inversely associated with BAZ, perhaps as a consequence of leakage from muscle.
**Conclusions:** The plasma proteomic profile was in line with recognized biomarkers of childhood growth and provided novel potential biomarkers of lean mass in children with chronic malnutrition. The suggested proteins may contribute to the assessments of growth and nutritional status of undernourished children.

**Comments**

Proteomics, the large-scale study of proteins, has been evolving over the past 2 decades. Although it holds promise for enhancing our understanding of biological processes, the interpretation of its findings is still challenging. Assessment of the plasma proteome specifically in undernourished children, as performed in this study, could help to focus on key proteins in lean body mass metabolism.

Besides confirming known associations between height, IGF1, and its binding proteins, this study identifies several less familiar proteins that may be of interest for future investigations: Carnosinase 1, S100A12, and Tetranectin. Carnosinase 1 is an enzyme that may be associated, based on previous studies, with muscle mass. It was found to be significantly less abundant in the plasma of stunted than non-stunted children. S100A12 has been linked to chronic intestinal inflammation in children; in this study, it was negatively associated with HAZ. Tetranectin is present in bone cartilage. It has been associated with height gain and was found to play a role in bone mineralization. These findings contribute to our investigational toolbox, although they still warrant future validation and research.

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**Correlates of thymus size and changes during treatment of children with severe acute malnutrition: a cohort study**

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*BMC Pediatr* 2017;17:70

**Background:** The high rates of mortality in children with severe acute malnutrition (SAM) may be partially explained by the deleterious effects of malnutrition on the immune system. It has been suggested that thymus atrophy reflects this immunodeficiency.

**Aims:** To investigate associations between clinical and nutritional measures and thymus size in children with SAM and to describe factors affecting the increase in thymus size during nutritional intervention.

**Methods:** The cohort of this observational study, performed in Uganda, comprised of children with SAM, aged 6–59 months, who were hospitalized for nutritional treatment. The thymus area was measured by ultrasound on admission, at discharge, and after 8 weeks of nutritional intervention with ready-to-use therapeutic food (RUTF; F-75 or F-100 formulas). Findings were compared with healthy, adequately nourished children. Anthropometric and biochemical markers of nutritional status were measured and correlated with thymus size and growth.

**Results:** Eighty-five malnourished children of median age 16.5 months were included in the study. The median thymus area was significantly smaller in the malnourished than the healthy children ($p < 0.001$); in 27% of the malnourished children, the thymus was undetectable on ultrasound at admission. There was a significant correlation of thymus area with WAZ and mid-upper-arm-
circumference as well as with levels of serum hemoglobin and plasma phosphate. Thymus area was negatively associated with illness severity (as assessed by caretakers) and elevated inflammatory markers. After 8 weeks of nutritional rehabilitation, the thymus area increased dramatically ($p < 0.001$), in accordance with an increase in mid-upper-arm-circumference. There was a lesser increase in thymus area in children in whom the F-75 formula was partially replaced with rice porridge during their hospital stay.

**Conclusions:** Thymus atrophy is a marker of malnutrition and inflammation in children with SAM, and is reversible under optimal nutritional rehabilitation. The correlation between plasma phosphate levels and thymus size should be further explored to improve our understanding of their possible mutual effects.

**Comments**

This study was prompted by earlier reports of an association between undernutrition and reversible thymus atrophy [20, 21]. The authors sought to identify specific clinical and biochemical correlates of thymus area and predictors of thymus area growth during nutritional rehabilitation. The study confirms the reduction in thymus size in nutritional deprivation and inflammation and adds a novel finding of a positive correlation of thymus size with hemoglobin and phosphate levels. The correlation with phosphate levels is supported by the finding that the children who received the nutritionally inferior rice porridge had both reduced thymus growth and a slower increase in plasma phosphate, and raises a question regarding the role of phosphate in thymus growth and function. In a parallel study on this cohort, the authors found that the children fed with the poorer diet, who had a lower phosphate level on day 2, also had a higher rate of mortality [22]. Further research is needed to determine if thymus atrophy is involved in the pathogenesis of malnutrition and/or inflammation or if it is only a marker of these conditions, and to identify the mechanism whereby nutritional rehabilitation leads to an increase in thymus size.

**Biomarkers to stratify risk groups among children with malnutrition in resource-limited settings and to monitor response to intervention**

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*Horm Res Paediatr* 2017;88:111–117

Although substantial efforts are being directed at lowering rates of childhood undernutrition, interventions so far have not been as effective as expected and gaps remain in our understanding of the mechanisms underlying stunting. Tools are needed to identify the children who are more likely to respond to nutritional rehabilitation in addition to markers of response to treatment.

Environmental enteral dysfunction (EED) is a subclinical intestinal disorder that affects many children in low-income countries. EDD may worsen malnutrition and contribute to the risk of morbidity and mortality in affected children. Alongside EED, changes and insults to the gut flora in the early years of life may lead to impaired growth owing to their adverse effects on nutrient absorption, metabolism, local inflammatory responses, and hormonal regulation.
This review describes the current knowledge on the interplay between EED, the gut microbiome, and impaired linear growth in malnourished children. It highlights novel biomarkers that may help distinguish children at higher risk of malnutrition and to measure the response to nutritional interventions.

**Comments**

This review provides a comprehensive overview of the many biomarkers of growth failure in malnourished children investigated to date. These include urinary, stool, and plasma markers of the different stages of EED (increased intestinal permeability, epithelial damage and repair, gut inflammation, and microbial translocation) as well as markers of microbiome dysfunction, systemic inflammation, and resistance to growth hormone. Because stunting is the result of a series of complex processes, none of these individual markers has the power to predict clinical outcome, and a composite score of several markers might serve as a more efficient tool.

**Microbial impact on host metabolism: opportunities for novel treatments of nutritional disorders?**

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*Microbiol Spectr* 2017;5:BAD-0002-2016

Malnutrition has an impact not only on the human organs but also on the normal development of the human gut microbiota. Studies comparing the relative abundance of different gut bacteria show substantial differences in the microbiome between healthy and undernourished children. Normally, the gut microbiome evolves during the first 3 years of life before reaching the composition observed in adults. Nutritional deficiencies have been shown to alter the relative abundance of different bacterial species within the microbiome, delaying or disrupting this process. The immature microbiota may adversely affect intestinal absorption and take part in the pathogenesis of stunting and wasting seen in malnourished children. This review discusses the involvement of the gut microbiome both in states of undernutrition and in obesity and metabolic syndrome and presents possible therapeutic uses of gut microbes for these nutritional disorders.

**Mechanisms of cross-talk between the diet, the intestinal microbiome, and the under-nourished host**

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*Gut Microbes* 2017;8:98–112

Imbalances in the gut microbiome are emerging as an important contributor to the deleterious effects of malnutrition on child growth. Observational studies show that specific changes occur in the
microbial community in undernourished children, with a decreased variance and richness of taxa and a different relative abundance of various microbial species compared to healthy children. Besides malnutrition, these disruptions also result in decreased resistance to entero-pathogenic bacteria and directly interfere with weight gain and longitudinal growth. This review describes recent studies of alterations in the gut microbiome in malnourished children; outlines the dietary, environmental, and host factors that influence the microbiome; explains the outcomes of dysbiosis on normal physiology, and discusses the various current treatment options, future challenges, and opportunities in this field.

**Comments**

These 2 reviews taken together provide a comprehensive synopsis of the known associations among the gut microbes, undernutrition, and growth. Both discuss the effects of diet on normal microbiome development, including the contribution of human milk oligosaccharides on priming of the microbiome, and present interventional trials targeted at the microbiome which have had limited success so far. Future therapeutic options based on animal models are suggested. The review of Plovier and Cani [6] proposes an interesting connection between 2 seemingly opposite conditions: undernutrition and obesity/metabolic syndrome. Both are characterized by imbalances in the gut microbiome, leading to increased inflammatory potential, a reduced diversity of gut microbiota, and decreased ecological fitness (impaired resistance to colonization). The review by Velly et al. [7] offers a more in-depth description of the mechanisms whereby intestinal dysbiosis develops and the ways in which it may participate in the pathogenesis of stunting in the undernourished host. The shortcomings of current treatment options are discussed along with potential means of overcoming them.

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**Lipid-based nutrient supplementation in the first 1,000 days improves child growth in Bangladesh: a cluster-randomized effectiveness trial**


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**Background:** Stunting during the first 1,000 days of life is very common in developing countries. In Bangladesh, 36% of all children under age 5 years show stunted growth [23]. The need for new nutritional interventions to reduce this prevalence was highlighted in a recent paper on the 2025 WHO targets for nutrition [2].

**Aims:** To assess the effect of different home fortification approaches on linear growth and head size from birth to 24 months.

**Methods:** A researcher-blind, longitudinal, cluster-randomized effectiveness trial was conducted. The population included 4,011 women at ≤20 weeks of gestation within 64 clusters. The interventions (4 arms) were offered to mothers during pregnancy and the first 6 months postpartum and/or to their children, from age 6 to 24 months, as follows:
1. Women and children both received lipid-based nutrient supplements (LNS; 118 kcal, about 10 g fat, 2.6 g protein, multi-vitamins and minerals – different doses in mothers vs. children; LNS-LNS group).
2. Women received iron and folic acid (IFA, 1 tablet of 60 mg Fe and 400 mg folic acid) and children received LNS (IFA-LNS group).
3. Women received IFA and children received micronutrient powder (MNP; containing 15 micronutrients; IFA-MNP group).
4. Women received IFA and children received no supplements (IFA-Control group).

**Results:** A total of 3,379 participants completed the study. At age 24 months, mean length-for-age z score (LAZ) was significantly higher (+0.13) in children exposed to both prenatal and postnatal LNS (LNS-LNS) than in children given MNP (IFA-MNP), with no differences between the LNS-LNS and IFA-LNS groups (–1.72 and –1.73, respectively). Although children exposed only to postnatal LNS had a slightly lower mean LAZ at birth (–0.09) than children exposed to LNS both pre- and postnatally, by 24 months, LAZ was similar in the 2 groups. At 18 months, the prevalence of stunting (LAZ < –2) was lower in the LNS-LNS group than in the IFA-MNP group (OR 0.70; 95% CI 0.53–0.92), but the difference diminished by 24 months (OR 0.81; 95% CI 0.63–1.04). The mean head-circumference-for-age z score at 24 months was significantly higher (+0.14) in the LNS-LNS than the IFA-control group.

**Conclusions:** The results suggest that there are modest improvements in linear growth status and head size in undernourished children given LNS during the first 2 years of life, but not in undernourished children given MNP for the same period.

**Comments**
This large interventional cluster-randomized controlled study by Dewey et al. [8] assessed the effect of different home fortification approaches on growth from birth to 2 years of life in undernourished newborns from Bangladesh. There were modest improvements in linear growth status and head size at 2 years in the children fed LNS (LNS-containing 118 kcal, about 10 g fat, 2.6 g protein, multi-vitamins and minerals) but not in children fed MNP (MNP-containing 15 micronutrients). Giving mothers LNS prenatally yielded no advantage in growth outcomes of their offspring at 2 years. These findings suggest that differences in the nutrient content between LNS and MNP may account for the differences in length-for-age between the LNS-LNS and IFA-MNP groups. However, as pointed out also by the authors, the micronutrient content of the LNS and MNP supplements differed as well, making it impossible to isolate the specific nutrients that were most critical to the improved growth in the LNS-exposed children. LNS provided energy, macronutrients, and several vitamins and minerals (calcium, potassium, phosphorus, magnesium, pantothenic acid, vitamin K) that were not included in MNP. In addition, the LNS supplement contained more zinc (8 compared with 4.1 mg), selenium (20 compared with 17 mg), and vitamin E (6 compared with 5 mg). The most likely candidates contributing to the postnatal linear growth response are energy, macronutrients, and macrominerals (calcium, potassium, phosphorus, magnesium). The dietary fat in the LNS supplements may have played a key role as well, given the importance of polyunsaturated fatty acids for brain development, immune function, and growth [24–26].

The impact of fortified supplements such as LNS containing mixtures of macronutrients and micronutrients should continue to be evaluated in the context of broader strategies to reduce stunting.
Eggs in early complementary feeding and child growth: a randomized controlled trial

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This manuscript is also discussed in Chapter 9, pages 165–175.

**Background:** Most interventions aimed at reducing stunting have used micronutrient-fortified foods or supplements composed of combinations of macronutrients and micronutrients. Evidence for the effectiveness of locally available nutritious foods is limited. Eggs are an affordable and feasible source of nutrients such as high-quality protein, vitamin B12, zinc and iron, important for growth and development.

**Aims:** The aim of the study was to evaluate the growth-related effect of feeding children with one egg per day for 6 months, starting at age 6–9 months.

**Methods:** A randomized controlled trial was conducted in Ecuador over a 6-month period. Children aged 6–9 months were randomly assigned to intervention (n = 83) and nonintervention (control; n = 80) groups. The intervention consisted of 1 medium-sized egg (~50 g) per day for 6 months; the eggs were supplied to the treatment group on a weekly basis. Children in the control group were visited every week and monitored for morbidities. The primary outcomes were changes in anthropometric measures of child growth between baseline and at the end of the intervention. Secondary end points were dietary intake, allergy symptoms, and morbidity symptoms.

**Results:** The baseline prevalence of stunting was 38%, and the mean length-for-age z score (LAZ) was −1.90 ± 1.01. At baseline, the intervention group had a higher prevalence of stunting and underweight than the control group. At the end of 6 months, the intervention group had a higher LAZ than the control group by 0.63 (95% CI 0.38–0.88) and a higher WAZ by 0.61 (95% CI 0.45–0.77). In addition, the intervention resulted in significant reductions of 47% in the prevalence of stunting (prevalence ratio [PR] 0.53; 95% CI 0.37–0.77) and of 74% in the prevalence of underweight (PR 0.26; 95% CI 0.10–0.70). Besides their higher dietary intake of eggs (PR 1.57; 95% CI 1.28–1.92), the intervention group had a better dietary composition than controls, including reduced intake of sugar-sweetened foods (PR 0.71; 95% CI 0.51–0.97). No allergic reactions to the eggs were reported during the study.

**Conclusions:** An affordable and feasible food-based intervention of one egg per day for 6 months beginning at age 6–9 months had a significant positive effect on linear growth and weight gain in a resource-poor pediatric population. These results indicate that eggs have the potential to contribute to global targets to reduce stunting.

**Comments**

Most of the earlier studies on the effect of nutritional intervention on catch-up growth in young children from resource-poor populations used supplements containing mixtures of micronutrients or combinations of both macro- and micronutrients. Eggs are an accessible complete food, rich in growth-promoting nutrients, including high-quality protein, with high concentrations of choline and other micronutrients such as vitamin B12, zinc, and iron. This randomized controlled trial in an Andean pediatric population demonstrated that 6 months of complementary feeding with 1 egg per day starting as early as age 6–9 months, significantly improved the linear growth (in-
crease in LAZ by 0.63 and in WAZ by 0.61) and reduced stunting. Effect sizes for the anthropometric outcomes were similar to those reported for protein supplements in the 2017 meta-analysis by Roberts and Stein (presented later in this chapter; mean effect size, 0.68), and stronger than reported for interventions including multiple micronutrients (mean effect size, 0.26) or a single micronutrient (mean effect size: zinc –0.15, vitamin A –0.05). These results should be validated in larger studies in different pediatric populations.

A mixed methods study to assess the effectiveness of food-based interventions to prevent stunting among children under-five years in Districts Thatta and Sujawal, Sindh Province, Pakistan: study protocol

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BMC Public Health 2017;17:24

Background: The high prevalence of maternal and child malnutrition in low- and middle-income developing countries poses a major challenge. Child malnutrition is attributed to poverty, absence of appropriate child-care practices, poor diet quality, and recurring infections during the first 2 years of life. It has both short- and long-term adverse effects on outcomes, including stunting and wasting, short adult stature, intellectual disability, reduced educational achievements, and lower earnings [27, 28]. It is therefore important to identify effective preventive approaches.

Aims: We present a study proposal with the primary aim of evaluating the effectiveness of food-based interventions to reduce stunting in children aged 6–59 months at risk of malnutrition residing in low- and middle-income countries. The secondary aim is to assess the effect of food-based interventions on micronutrient deficiencies, wasting, anemia, and rates of low birth weight.

Methods: A mixed-methods study design will be used in 3 different settings: (1) a cross-sectional survey of 7,360 study participants; (2) a community-based cluster randomized controlled trial with 5,000 participants; (3) a process evaluation of the acceptability, feasibility, and potential barriers of project implementation through focus group discussions, key informant interviews, and household surveys.

The study participants will include pregnant women and lactating mothers and children less than 5 years old from the Thatta and Sujawal Districts of Sindh Province, Pakistan. The randomized control trial will consist of 3 arms, as follows: (1) children aged 6–23 months given locally produced LNS; (2) children aged 24–59 months given MNP; (3) pregnant and lactating mothers given wheat soya blend. All food-based supplements will be delivered by healthcare workers using a blanket approach. The control group will receive routine public and private health services available within the area. The randomized control trial will consist of 3 arms, as follows: (1) children aged 6–23 months given locally produced LNS; (2) children aged 24–59 months given MNP; (3) pregnant and lactating mothers given wheat soya blend. All food-based supplements will be delivered by healthcare workers using a blanket approach. The control group will receive routine public and private health services available within the area. Study participants will be followed monthly for compliance with the supplements, dietary diversity, pregnancy outcomes, and maternal and child morbidity and mortality. Anthropometric parameters and hemoglobin levels will be measured at baseline, quarterly, and at the end of follow-up.

Comments Various food-based interventions for maternal and child malnutrition have been evaluated to date in developing countries, including LNS, fortified blended foods, and...
MNP. All showed positive effects on child health and growth [29]. However, studies were usually conducted in controlled environments, and the results could not be generalized to programs operating under field conditions.

In the present large community-based study, the authors aim to evaluate the effectiveness of food-based interventions on reducing stunting among children less than 5 years old from low- and middle-income countries who are at risk of malnutrition. The major strengths of this study are the large cohort, the mixed-methods design including a cross-sectional survey, a community-based cluster-randomized controlled trial, and a process evaluation, and the joint interventions in the mothers and children. The results may provide sufficient evidence for the development of policies and programs designed to improve growth outcomes in the pediatric population in poor resource settings.

Impact of therapeutic food compared to oral nutritional supplements on nutritional outcomes in mildly underweight healthy children in a low-medium-income society

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Clin Nutr 2017;pii:S0261-5164(17)30097-3

Background: RUTF is an energy-dense paste that can be stored at room temperature for several months and eaten without the addition of water or milk, thereby reducing the risk of contamination. In children 5 years old or less from low- and middle-income countries, where malnutrition is highly prevalent, RUTF is frequently used for the treatment of severe acute malnutrition. Young children living in more affluent countries are usually given liquid oral nutritional supplements (ONS) to treat disease-associated malnutrition and poor appetite. The effectiveness of these strategies has not been studied in older children, or for long-term effect in moderate malnutrition.

Aims: This study compared the effects of RUTF and ONS on growth parameters in mildly underweight primary school children living in a low-/middle-income country.

Methods: Sixty-eight mildly underweight (weight z score, –2 to –1) Pakistani children aged 5–10 years (93% girls) were recruited and randomized to 4 weeks' intervention with either RUTF or ONS (500 kcal/day), in addition to their regular diet. Height, weight, and subscapular and triceps skinfold thickness were measured at baseline, at the end of the intervention (4 weeks), and again 15 months later. The primary outcome measure was the difference in the change in weight z score between the 2 groups after 4 weeks of supplementation. Secondary outcomes were differences in the changes in height z score, BMI z score, and skinfold z score.

Results: After 4 weeks of intervention, the nutritional status improved in both groups. There were no significant between-group differences in any of the primary and secondary outcome measures. The average weight gain in both groups was 0.6 kg, which was lower than anticipated (2 kg). At 15 months after supplementation, there was a tendency for weight z scores and height z scores to return to baseline.

Conclusions: Intervention with RUTF and ONS produced a similar gain in weight and height in children aged 5–10 years at risk of malnutrition. The effect of both supplements was lower than expected and tended not to persist after supplementation was stopped.
Comments

This is an important attempt to find the best nutritional intervention for catch-up growth in undernourished children. The authors compared the effects of 4 weeks of treatment with RUTF or ONS on growth parameters in mildly underweight primary school children and found that both interventions had a similar small positive effect on weight and height gain. The main strength of this study was the high compliance and low drop-out rate relative to other similar studies. This was achieved by conducting the intervention in a primary school during the school year, having the supplements delivered to the children at school every morning, and asking the children to consume the supplements in addition to their regular diet.

However, this study has several limitations. Most important, owing to the absence of an untreated control (preferably placebo-treated) group, it was impossible to determine if the gains in weight and height were a true effect of treatment or attributable to other factors such as seasonal variation. Furthermore, the duration of the intervention (4 weeks) was probably too short to produce a significant effect on growth or to yield significant between-group differences. The children’s regular dietary intake was not assessed at baseline or during the intervention, so the actual extent of the dietary compensation could not be estimated. This could explain the relatively small effect on weight gain. Other limitations include the small number of participants, their narrow age range, and the predominance of girls (93%), which preclude extrapolation of the findings to older age groups or to boys.

More studies are needed to establish the best composition and the best way of delivery of supplements targeted to induce catch-up growth in undernourished children.

The effect of egg supplementation on growth parameters in children participating in a school feeding program in rural Uganda: a pilot study

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Background: School feeding programs have gained popularity in developing countries. Eggs are an inexpensive source of micronutrients and high-quality protein. Therefore, the objective of this study was to gain preliminary data regarding the impact of egg supplementation on growth in primary school students participating in a school feeding program in rural Uganda.

Methods: Children (ages 6–9; n = 241) were recruited from 3 different schools located in the Kitgum District of Uganda. All participants in the same school received the same dietary intervention: control (no eggs [0 eggs]; n = 56), one egg 5 days per week (1 egg; n = 89), or 2 eggs 5 days per week (2 eggs; n = 96). Height, weight, triceps skinfold thickness, and MUAC were measured monthly over 6 months.

Results: Following 6 months of egg supplementation, participants receiving 2 eggs had a greater increase in height and weight compared to the 0 eggs and 1 egg groups (p < 0.05). In addition, participants receiving 1 egg and 2 eggs had a significantly higher (p < 0.05) increase in MUAC at 6 months compared to 0 eggs.

Conclusion: These results suggest that supplementation with eggs can improve parameters of growth in school-aged children participating in school feeding programs in rural Uganda.
This is an important corroborative study of the value of school age nutrition on growth parameters in African children, supporting the improved growth seen in young infants in Ecuador with egg-based complementary feeding by Iannotti et al. [9], reviewed earlier in this chapter. The findings that eggs can provide an important source of quality protein in older children, also associated with improved linear growth, are notable in that they support the continuation of nutrition programs beyond the preschool period in vulnerable populations. The dose-related effects are also supportive of measures to ensure optimal protein intake in such children and similar findings with improved weight gain and hemoglobin have been reported from older school children in China [30].

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**Vitamin D supplementation and growth in urban Mongol school children: Results from two randomized clinical trials**

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**Background:** Symptomatic vitamin D deficiency is associated with slowed growth in children. It is unknown whether vitamin D repletion in children with asymptomatic serum vitamin D deficiency can restore normal growth.

**Objective:** We tested the impact of vitamin D-supplementation on serum concentrations of 25-hydroxyvitamin D and short-term growth in Mongol children, with very low serum vitamin D levels in winter.

**Design:** We conducted 2 randomized, double-blind, placebo-controlled trials in urban school age children without clinical signs of rickets. The Supplementation Study was a 6-month intervention with an 800 IU vitamin D3 supplement daily, compared with placebo, in 113 children aged 12–15 years. A second study, the Fortification Study, was a 7-week intervention with 710 mL of whole milk fortified with 300 IU vitamin D3 daily, compared with unfortified milk, in 235 children aged 9–11 years.

**Results:** At winter baseline, children had low vitamin D levels, with a mean (±SD) serum 25-hydroxyvitamin D concentration of 7.3 (±3.9) ng/mL in the supplementation study and 7.5 (±3.8) ng/mL in the fortification study. The serum levels increased in both vitamin D groups – by 19.8 (±5.1) ng/mL in the Supplementation Study, and 19.7 (±6.1) ng/mL in the fortification study.

Multivariable analysis showed a 0.9 (±0.3 SE) cm increase in height in the vitamin-D treated children, compared to placebo-treated children, in the 6-month supplementation study (p = 0.003). Although the children in the 7-week fortification study intervention arm grew 0.2 (±0.1) cm more, on average, than placebo children, this difference was not statistically significant (p = 0.2).
There were no significant effects of vitamin D supplements on differences in changes in weight or body mass index in either trial. For the fortification study, girls gained more weight than boys while taking vitamin D3 ($p$ value for interaction = 0.03), but sex was not an effect modifier of the relationship between vitamin D3 and change in either height or BMI in either trial.

**Conclusions:** Correcting vitamin D deficiency in children with very low serum vitamin D levels using 800 IU of vitamin D3 daily for 6 months increased growth, at least in the short-term, whereas, in a shorter trial of 300 IU of D fortified milk daily for 7 weeks it did not.

**Comments**

This study in a population with endemic vitamin D deficiency demonstrates how studies ought to have the appropriate power to evaluate the impact of appropriate doses of vitamin D by high-risk groups and dose-dependent effects, even among older school children. The role of vitamin D in maternal health and child growth and development merits definitive large-scale evaluations, including placebo-controlled trials, with appropriate follow-up information and end points. Designing such studies in populations with endemic deficiencies poses significant ethical challenges and might require the use of quasi-experimental designs or pragmatic incremental adaptive designs. Other studies have failed to find an association between vitamin D status in infancy and growth and morbidity in childhood [31], supported by other studies in Asia [32], although at variance with findings from the ALSPAC cohort [33] which found associations with maternal vitamin D status in pregnancy and neurodevelopmental outcomes in pre-school children. Other studies in India have documented associations between vitamin D status in young children and growth and morbidity [34], underscoring the need for larger, well-designed multi-country evaluation of the role of maternal and infant vitamin D status in affecting childhood morbidity, growth, and neurodevelopment.

**Which dietary components modulate longitudinal growth?**

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This review, recently published by our group, aimed to summarize the most recent knowledge on the role of nutrition in the process of linear growth. Included were peer-reviewed papers mostly published from 2014 onward that explored the effects of macronutrients (specifically, protein and fat), micronutrients (specifically, zinc, iron and iodine), and different nutritional combinations on catch-up growth in undernourished children and food-restricted animal models. Some interesting recent studies regarding the effect of different sources of proteins and specific amino acids were presented.

**Comments**

The well-recognized presence of a link between nutrition and linear growth in children is based on the intuitive wisdom of countless generations. However, only recently has substantial progress been made in clarifying the mechanisms underlying this association and the role of nutrition in catch-up growth.
Various nutritional components serve as essential building blocks for growing tissues. They participate in growth regulation by acting as regulatory agents in the epiphyseal growth plate and by influencing the gut microbiome. Studies have shown that nutritional supplementation with a mixture of macronutrients and micronutrients is more beneficial than supplementation with a single nutrient. However, much work is still required to establish the nutritional composition that produces the best outcomes for catch-up growth without long-term metabolic complications.

The impact of nutritional interventions beyond the first 2 years of life on linear growth: a systematic review and meta-analysis

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Background: There is a large body of evidence emphasizing the importance of nutritional interventions early in life for the prevention and treatment of malnutrition and stunting. However, several recent publications indicate that catch-up growth also occurs after infancy, and suggest that it may be possible to promote catch-up growth even beyond this early window [35, 36].

Aims: The aim of this systematic review was to evaluate the effectiveness of different nutrition-based interventions on linear growth in children ≥2 years of age.

Methods: A systematic search of MEDLINE and EMBASE (1947–2016) was performed using the keywords “nutrition and height and growth”. The primary response variable was a change in height (in centimeters) or height z score.

Results: A total of 69 studies met the inclusion criteria. The meta-analyses showed that protein supplementation had the strongest significant positive effects on linear growth (mean effect size 0.68; 95% CI 0.30–1.05), followed by multiple micronutrients (mean effect size, 0.26; 95% CI 0.13–0.39). In addition, single-micronutrient intervention with zinc (mean effect size, 0.15; 95% CI 0.06–0.24) and vitamin A (mean effect size, 0.05; 95% CI 0.01–0.09) had significant small positive effects on linear growth. Other nutritional interventions, including iron, calcium, and iodine, and food-based interventions had no significant effect on growth. Baseline height-SD score was a significant inverse predictor of the effect size. Baseline age, study duration, and dose were not related to effect size for any nutrient examined.

Conclusions: Adequate nutritional intervention, specifically with protein, multiple micronutrients, zinc, and vitamin A, has the potential to improve linear growth after age 2 years, especially in children with growth failure.

Comments: This systematic review by Roberts and Stein is important because it shows that the window of opportunity to address stunting does not close at 2 years of age, and adequate nutritional intervention, specifically protein, multiple micronutrients, zinc and vitamin A, has the potential to induce catch-up growth, especially in undernourished children with stunting.

This review highlights several limitations of the existing literature. First, approximately half of the included trials were of medium to low quality, as assessed by Jadad scoring (no randomization, no double-blind design, and/or no description of withdrawals and dropouts). Second, the duration of most of the trials was less than 12 months,
which may not be long enough to observe a significant effect on linear growth. Third, in each of the meta-analyses, there was a large heterogeneity among the included studies in terms of supplement composition and dose, duration of the intervention, and demographic and clinical characteristics of the participants. This made it difficult to determine the best intervention (composition and dose), the population most likely to benefit (baseline age, anthropometric and other clinical characteristics), and the expected effect size.

Future high quality and long-term (>12 months) interventional studies that include different pediatric populations from both developing and developed countries are needed to improve our understanding of the effect of different dietary components on linear growth.

A review of the evidence linking child stunting to economic outcomes

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Background: Childhood undernutrition and subsequent stunting may have long-term economic nationwide implications which may, in turn, influence the decisions of policy-makers regarding the allocation of resources towards prevention.

Aims: This study aims to provide accurate information on the long-term cost-effectiveness of intervention programs aimed at reducing childhood undernutrition on a personal and a national level.

Methods: A literature search was conducted for studies focused on childhood stunting and its physical or economic outcomes in adulthood. The strength of the evidence tying the prevalence of stunting to economic growth was evaluated, and the implications of the findings for countries with a high rate of childhood undernutrition were summarized.

Results: Two randomized interventional trials with long-term follow-up showed a significant 25 and 46% increase in wages for adults who had been in the intervention arms. Quasi-experimental studies evaluating the influence of adult height on wages found a median increase of 4% per centimeter for men and 6% for women. Cost-benefit analyses of nutritional interventions demonstrated a median return of 17.9:1 per child. However, an increase in gross domestic product was not unequivocally associated with a reduction in childhood stunting.

Conclusions: Countries afflicted by large-scale childhood stunting should regard policies and programs directed at treating child undernutrition as a cost-beneficial allocation of resources with a high return on the investment. Aiming at general economic growth is probably not effective on its own in reducing the prevalence of stunting unless relevant issues that contribute to childhood malnutrition are specifically addressed.
Reaching the global target to reduce stunting: an investment framework

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Background: Stunting in the first years of life is associated with poorer cognitive development, lower intelligence scores, and a reduction of 5–53% in adult wages. The effect of these personal consequences on economic growth has prompted large-scale investments in nutritional interventions, which have been shown to be cost-effective. In 2015, the World Health Assembly set a series of 10-year global nutrition targets, including a reduction of 40% in the number of children less than 5 years old with stunting.

Aims: To assess the required increase in funding of stunting prevention needed to reach global nutrition targets, and to suggest financing scenarios that may help achieve this goal.

Methods: The analysis focused on interventions with a strong proof of success in reducing stunting. The required annual increase in costs for a sample of 37 countries carrying the highest rates of stunting was estimated, and the effect of the budget scale-up on stunting prevalence was evaluated using the Lives Saved Tool model. Estimates of current spending on key interventions were derived from data on government, donors, and household expenditures. Finally, 2 financing scenarios were modeled: “business as usual,” an extension of current financing, and “global solidarity,” a plan for coordinated additional funding from all sources.

Results: The financial requirement for reaching the 2025 target by intervention scale-up is USD 49.5 billion. The annual average increase in funding required ranges from USD 2.6 billion to USD 7.4 billion. The “business as usual” scenario was not sufficient, and the target was not met.

Conclusions: Achieving the global target of a reduction in stunting is possible, but coordinated global investment and careful planning are required.

Comments: These 2 studies deal with the economic aspects of treating malnutrition. McGovern et al. [16] conducted a comprehensive assessment of the financial benefit of reducing the rate of stunting. There are very few long-term follow-up studies on randomized nutritional interventions in childhood that provide high-quality evidence of the productivity of the affected children as adults. Non-interventional prospective studies and cross-sectional studies should be interpreted more cautiously for obvious methodological reasons. McGovern et al. [16] reevaluated the data derived from previous studies to assess the impact of stunting on economic productivity and improve our understanding of the economic implications of malnutrition. They concluded that a reduction in the prevalence of stunting is likely to yield substantial returns to society. This valuable information is encouraging to policy planners in low-income countries. Another important conclusion of this study is that merely improving the per capita gross domestic product of a country is unlikely to affect the rate of stunting, and only targeted investments in nutrition programs, gender equality issues, and sanitation will result in true improvement. This study sends a practical, well-based message to health policy planners across the world on the importance and significance of treating childhood malnutrition.

The second study, by Shekar et al. [17], sought to provide a practical framework for reaching the WHO global nutrition target of a 40% reduction in stunting by 2025, in terms of both cost and informed selection of effective interventions. For instance, the
Malnutrition and Catch-Up Growth during Childhood and Puberty

The authors recommend investing in 3 interventions that are not widely implemented to date: prophylactic zinc supplementation, balanced energy-protein supplementation, and multiple micronutrient supplementation in pregnancy.

As these 2 studies point out, the treatment of childhood malnutrition and stunting may be costly and demanding, but outcomes will be worse if treated ineffectively, both on a personal basis and on a global scale.

**Neurodevelopment, nutrition, and inflammation: the evolving global child health landscape**

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The last decade has witnessed major reductions in child mortality and a focus on saving lives with key interventions targeting major causes of child deaths, such as neonatal deaths and those due to childhood diarrhea and pneumonia. With the transition to Sustainable Development Goals, the global health community is expanding child health initiatives to address not only the ongoing need for reduced mortality, but also to decrease morbidity and adverse exposures toward improving health and developmental outcomes. The relationship between adverse environmental exposures frequently associated with factors operating in the pre-pregnancy period and during fetal development is well established. Also well appreciated are the developmental impacts (both short- and long-term) associated with postnatal factors, such as immunostimulation and environmental enteropathy, and the additional risks posed by the confluence of factors related to malnutrition, poor living conditions, and the high burden of infections. This article provides the pathogenesis and risk factors for adverse developmental outcomes among young children, setting the scene for potential interventions that can ameliorate these adversities among families and children at risk.

**Comments**

A synthesis of current thinking relating prenatal factors includes epigenetic influences, with important postnatal environmental influences, immunostimulation and nutritional deficits with impaired growth and cognitive development. The review opens the possibility that while critical windows are important, there are opportunities for growth and especially developmental plasticity that goes well beyond the early years of life, opening the possibility of sustained interventions and investments in health, nutrition, and developmental strategies.
An individual-level meta-analysis assessing the impact of community-level sanitation access on child stunting, anemia, and diarrhea: evidence from DHS and MICS surveys

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Background: A lack of access to sanitation is an important risk factor in child health, facilitating fecal-oral transmission of pathogens including soil-transmitted helminthes and various causes of diarrheal disease. We conducted a meta-analysis of cross-sectional surveys to determine the impact that community-level sanitation access has on child health for children with and without household sanitation access.

Methodology: Using 301 2-stage demographic health surveys and multiple indicator cluster surveys conducted between 1990 and 2015, we calculated the sanitation access in the community as the proportion of households in the sampled cluster that had household access to any type of sanitation facility. We then conducted exact matching of children based on various predictors of living in a community with high access to sanitation. Using logistic regression with the matched group as a random intercept we examined the association between the child health outcomes of stunted growth, any anemia, moderate or severe anemia, and diarrhea in the previous 2 weeks and the exposure of living in a community with varying degrees of community-level sanitation access.

Results: For children with household-level sanitation access, living in a community with 100% sanitation access was associated with lowered odds of stunting (adjusted OR [AOR] 0.97, 95% CI 0.94–1.00; n = 14,153 matched groups, 1,175,167 children), any anemia (AOR 0.73; 95% CI 0.67–0.78; n = 5,319 matched groups, 299,033 children), moderate or severe anemia (AOR 0.72, 95% CI 0.68–0.77; n = 5,319 matched groups, 299,033 children), and diarrhea (AOR 0.94; 95% CI = 0.91–0.97); n = 16,379 matched groups, 1,603,731 children) compared to living in a community with <30% sanitation access. For children without household-level sanitation access, living in communities with 0% sanitation access was associated with higher odds of stunting (AOR 1.04, 95% CI 1.02–1.06; n = 14,153 matched groups, 1,175,167 children), any anemia (AOR 1.05, 95% CI 1.00–1.09; n = 5,319 matched groups, 299,033 children), moderate or severe anemia (AOR 1.04, 95% CI 1.00–1.09; n = 5,319 matched groups, 299,033 children) but not diarrhea (AOR 1.00, 95% CI 0.98–1.02; n = 16,379 matched groups, 1,603,731 children) compared to children without household-level sanitation access living in communities with 1–30% sanitation access.

Conclusions: Community-level sanitation access is associated with improved child health outcomes independent of household-level sanitation access. The proportion of children living in communities with 100% sanitation access throughout the world is appallingly low. Ensuring sanitation access to all by 2030 will greatly improve child health.

Comments: This interesting analysis of available information in a range of demographic and health surveys corroborates initial findings from a similar analysis by Spears et al. [37] in India, and the findings from the Cochrane review of the relationship of water and sanitation interventions with childhood growth [38]. The finding that community-level sanitation status may impact linear growth and a range of health outcomes in children strongly supports the need to focus on such interventions alongside nutrition-sensitive interventions in populations.
References


