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Preface

Nutrition is essential for survival, and fortunately even an inadequate nutrition may keep us alive. However, nutrition for growth requires a delicate balance between avoiding insufficient growth and avoiding the provision of too much energy and nutrients that will result in an increased risk of non-communicable diseases, mainly obesity, and may adversely affect children with chronic diseases.

Stunting is one of the world's largest challenges. In 2016, a WHO report indicated that 22.9% of the children under the age of 5, summing up to 154.8 million children globally, suffer from stunting. This led stunting to be at the top of the list for the WHO targets for 2,025, aiming at 40% reduction in stunting by that year.

Our understanding of the pathophysiology of inappropriate growth and the pathways involved in optimal growth and catch-up growth is evolving, and new data are emerging on the role of our genes, the interaction between nutrition and epigenetic changes involved in growth, the interplay between nutrition and growth factors and hormones in health and in disease states.

As in previous years, leading specialists in nutrition and growth selected a limited number of leading studies in various aspects of nutrition and growth that were published from July 1, 2017 to June 30, 2018.

A summary of these studies and a commentary provided by the section editors can be found in this 2019 Year Book on Nutrition and Growth.

We hope that similar to previous years, the summary of the published manuscripts will assist health care providers, physicians, nurses, dietitians, scientists, and anyone interested in nutrition to explore studies that they have missed, stimulate a search for other important studies, and lastly the editorial comments will provide an additional and helpful view of interpretation.

Nutrition and Growth Yearbook covers pregnancy, prematurity, infancy, childhood and adolescence and involves multiple disciplines. Acknowledging that we could not cover all important publications and may have missed some, we hope that all health care providers treating and studying nutrition and growth will find this fifth edition of the yearbook on nutrition and growth

useful and helpful in providing our children and parents the best practice possible.

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The Physiology and Mechanism of Growth

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Introduction

The physiology of growth in children is still not fully elucidated. In recent years, with the availability of new technologies, our understanding of the interactions between the genetic, epigenetic, internal (microbiome) and external environments and children's growth has increased. In this chapter, we will discuss the manuscripts published in peer-review journals in the past year, which contributed to the expansion of our understanding of the physiology of growth and especially the interaction between nutrition and growth. We tried to select the most important manuscripts and added comments of experienced researchers/physicians, which we hope will stimulate the readers to continue and study the amazing phenomena of children's growth.

Key articles reviewed for this chapter

Association of picky eating with growth, nutritional status, development, physical activity, and health in preschool children

Chao HC

Front Pediatr 2018;12:22

Effect of increased enteral protein intake on growth in human milk-fed preterm infants: a randomized clinical trial

Maas C, Mathes M, Bleeker C, Vek J, Bernhard W, Wiechers C, Peter A, Poets CF, Franz AR

JAMA Pediatr 2017; 171: 16–22

Vegetables and lean proteins-based and processed meats and refined grains-based dietary patterns in early childhood are associated with pubertal timing in a sex-specific manner: a prospective study of children from Mexico City

Jansen EC, Zhou L, Perng W, Song PX, Rojo MMT, Mercado A, Peterson KE, Cantoral A

Nutr Res 2018; 56: 41–50

Effects of oral zinc supplementation on zinc status and catch-up growth during the first 2 years of life in children with non-organic failure to thrive born preterm and at term

Cho JM, Kim JY, Yang HR

Pediatr Neonatol 2018;pii:S1875-9572(17)30066-9

Higher longitudinal milk intakes are associated with increased height in a birth cohort followed for 17 years

Marshall TA, Curtis AM, Cavanaugh JE, John J Warren JJ, Levy SM

J Nutr 2018; 148: 1144–1149

Catch-up growth, rapid weight growth, and continuous growth from birth to 6 years of age in very-preterm-born children

Toftlund LH, Halken S, Agertoft L, Zachariassen G

Neonatology 2018; 114: 285–293

Leptin stimulates aromatase in the growth plate: limiting catch-up growth efficiency

Masarwi M, Shamir R, Phillip M, Gat-Yablonski G

J Endocrinol 2018; 237: 229–242

Differential aging of growth plate cartilage underlies differences in bone length and thus helps determine skeletal proportions

Lui JC, Jee YH, Garrison P, Iben JR, Yue S, Ad M, Nguyen Q, Kikani B, Wakabayashi Y, Baron J

PLoS Biol 2018; 16:e2005263

New genetic tools in the diagnosis of growth defects

Dauber A

Growth Horm IGF Res 2018; 38: 24–28

Regulation of body growth by microRNAs

Lui JC

Mol Cell Endocrinol 2017; 456: 2–8

Dominant-negative STAT5B mutations cause growth hormone insensitivity with short stature and mild immune dysregulation

Klammt J, Neumann D, Gevers EF, Andrew SF, Schwartz ID, Rockstroh D, Colombo R, Sanchez MA, Vokurkova D, Kowalczyk J, Metherell LA, Rosenfeld RG, Pfäffle R, Dattani MT, Dauber A, Hwa V

Nat Commun 2018; 9: 2105

Association of picky eating with growth, nutritional status, development, physical activity, and health in preschool children

Chao HC[1, 2]

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Background: Children having strong food preferences, consuming inadequate variety of foods, restricting the intake of some food groups, eating a limited amount of food, or being unwilling to try new foods are called picky eaters. Prevalence of picky eating is high (up to 50%) in both normally developing children as well as in those with medical or developmental disorders. One of the aims of this study was to determine the effect of this type of eating behavior on growth in pre-school children.

Methods: A cross-sectional descriptive study was performed in 300 primary caregivers of children aged 2–4 years, representative of a population in Taiwan. A structured questionnaire was used in face-to-face interviews by a skillful interviewer regarding food preferences, eating behavior, development, physical activity, and possible health issues. Body weight and height were measured.

Results: Approximately one half of children (54%) were regarded as picky eaters. No differences in sex, age, primary caregiver, education levels of caregiver, or family size between picky and non-picky eaters were determined, and families with low economic income possibly influencing food intake were not included in the study. Picky eaters were shorter (mean height percentile, height for age, height SDS, proportion of children <15th percentile) compared to non-picky-eaters. In addition, they had lower weight, weight for height, and BMI for age. Picky-eating also had an effect on children's development and lower performance values of physical activities.

Conclusions: In this pre-school cohort of children, it was determined that picky eating has a significant detrimental impact on linear growth as well as on anthropometric measures reflecting nutritional status.

Comments Picky-eating is prevalent in small children of up to 4 years, and it later declines. It can, however, persist in some individuals and is associated with later eating disorders [1]. Children with picky-eating are at risk for nutritional deficits, their median daily energy intake is lower than the age-appropriate [2]. The effect of picky eating on linear

growth has not been thoroughly investigated. In the present study, it was determined that picky eating is associated with lower height in prepubertal children. Picky eating was specifically related to decreased consumption of vegetables, meat, fruit, fish, and specific kinds of vegetables and interestingly with excessive milk-drinking. The present study, therefore, underlines both the importance of adequate caloric intake and diet composition in growth of children up to 4 years. Although no significant effects on growth were previously reported in a longitudinal study, it would be interesting to obtain even more long-term data on the influence of picky eating, for example on final height [1].

Effect of increased enteral protein intake on growth in human milk-fed preterm infants: a randomized clinical trial

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Background: Protein intake has an important effect on early postnatal growth in very preterm infants. This study was aimed at evaluating the effects of different levels of enteral protein supplementation on the growth of predominantly preterm breastfeed infants.

Methods: A total of 60 preterm infants (gestation <32 weeks and weight <1,500 g at birth) were recruited in a randomized clinical and partially blinded single-center trial. In addition to breastfeeding, infants received either a lower protein (1 g of bovine protein/100 mL of breast milk) or a higher protein supplement (1.8 g of bovine protein/100 mL of breast milk or individualized high-protein supplementation based on protein and fat content of administered breast milk) for a median of 6 weeks.

Results: Weight gain was similar in the lower and higher protein supplementation groups: mean (95% CI), 16.3 g/kg/day (15.4–17.1 g/kg/day) in the lower protein group versus 16.0 g/kg/day (15.1–16.9 g/kg/day) in the higher protein group; $p = 0.70$), despite an increase in the actual protein intake by 0.6 g/kg/day (0.4–0.7 g/kg/day; $p < 0.001$). In addition, head circumference and lower leg longitudinal growth were also similar.

Conclusions: Further increase in protein intake of human milk-fed preterm infants did not result in enhancement of growth in the studied population. Authors suggest that this might point to a ceiling effect for enteral protein intake with respect to its influence on growth.

Comments Fortifying breast milk with fixed dose of protein has been shown to have beneficial effects on the growth of preterm infants [3]. This could, however, be suboptimal in some infants resulting in early postnatal growth restriction compared with preterm formula fed infants [4–6]. Possible reasons are that the protein content in breast milk of certain women could be insufficient or that it could become insufficient over time. The question of protein dosing has, therefore, been addressed in this article: would it

be more feasible to further increase the protein intake in breast feed milk by fortification and should protein fortification be more individualized and depend on the protein content in breast milk? The answer to both questions is no. By increasing the average protein intake to 4.3 g/kg/day over an interventional period of 6 weeks, did not improve weight gain, head circumference, and lower leg longitudinal growth, which is similar to another study by Miller et al in more mature infants [7]. In addition, individualizing protein content strategy did not result in additional growth. The results suggest that increasing enteral protein intake beyond 3.5–4.0 g/kg/day might not further improve growth, at least not in this population.

Vegetables and lean proteins-based and processed meats and refined grains-based dietary patterns in early childhood are associated with pubertal timing in a sex-specific manner: a prospective study of children from Mexico City

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Childhood diet has been implicated in the timing of sexual maturation with evidence of advanced puberty in those on red meat or energy dense diets. The current investigators hypothesized that dietary patterns characterized by fruits and vegetables during early childhood (age 3 years) would be associated with delayed pubertal timing, whereas energy-dense and meat-based dietary patterns would relate to earlier puberty. The study population included 496 participants from an urban city. The exposures of interest were dietary patterns derived from principal component analysis of dietary data collected via a semi-quantitative food frequency questionnaire when the children were 3 years of age, and the outcomes were physician-assessed pubertal stages of pubic hair, breast (girls), genitalia, and testicular volume (boys) between 9 and 18 years, and initiation of menarche (girls). The investigators found that a diet that consisted of a higher amount of *vegetables and lean proteins* was related to delayed breast development among girls. In contrast, a higher amount of *processed meats and refined grains* was related to advanced testicular development among boys. Other patterns of diet were not statistically significantly associated with any of the sexual maturation markers. This study raises interesting questions about the programming of diet on puberty.

Effects of oral zinc supplementation on zinc status and catch-up growth during the first 2 years of life in children with non-organic failure to thrive born preterm and at term

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Abstract: In their study, the authors investigated the effect of oral zinc supplementation on serum insulin-like growth factor-1 (IGF-1) levels and catch up growth in infants with non-organic failure to thrive (NOFTT) who were born preterm as compared to those born at term. A total of 105 NOFTT infants aged 2 years or less participated in the study and were divided into 2 groups according to their gestational age at birth. Oral zinc sulfate was administered for 6 months to 49/66 children born term and 21/39 children born preterm. The authors measured serum zinc, IGF-1, weight, and height at baseline and at 6 months.
The authors found that there were no differences in the parameters measured (beside serum, zinc levels) between those who got the zinc supplement and those who did not get it. The authors concluded that the overall nutritional support rather than supplementation of a single nutrient may be more effective for catch-up growth in NOFTT infants born preterm.

Comments	Whether zinc supplementation stimulates catch-up growth of children suffering from NOFTT is an open and controversial issue. Unfortunately, most of the studies published in the literature suffer from methodological limitations. In the present study, the authors showed that in both groups (preterm and term children) suffering from NOFTT, zinc supplementation did not change the weight, height or IGF-1 levels compared to the children who did not get zinc supplementation. However, it is unclear whether the children were randomized to the treated and non-treated groups. The lack of placebo group and data on what the children got to eat is missing. And a good prospective randomized, placebo-controlled study, powered appropriately, is still needed.

Higher longitudinal milk intakes are associated with increased height in a birth cohort followed for 17 years

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Abstract: In the present study, authors investigated the longitudinal association between childhood and adolescent beverage intakes, nutrient adequacy, or energy intake, and height in a birth cohort. The authors accumulated data of 717 participants (353 males, 364 females) through ages 2–17 years. Information on beverages intake was gathered by beverage-frequency questionnaires at 3- to 6-month intervals. Nutrient data were obtained from 3-day food diaries, completed at 3- to 6-month

intervals, through age 8.5 years from Block kids' food frequency questionnaires at 2-years intervals after the age of 8.5 years. The nutrient adequacy ratio was calculated by investigators using age- and sex-specific estimated average requirements. Height was measured when participants were approximately 5, 9, 11, 13, 15, and 17 years old. Linear mixed model were used to study the longitudinal association between dietary components and height. The authors report that milk intake adjusted for mean adequacy ratio, energy intake, and baseline socioeconomic status was associated with height; for each additional 8 ounces (236 mL) of milk consumed per day through childhood and adolescence, height increased, on average by 0.39 cm.

| Comments | Many studies in the past investigated the association between cow milk consumption and height gain [8–10]. Currently, many non-cow milk beverages are produced, marketed, and sold in many countries as a substitute product for children. |
| | The present study is special since it follows children from birth, throughout childhood and adolescence. Despite the fact that we know today more than ever what a healthy diet for young children should look like, we still did not figure out the exact mechanism of the interaction between nutrition and growth, and especially between cow's milk and linear growth. Recently, in a basic research study with animal model it has been shown that even different proteins (casein and whey) might have different effects on longitudinal bone growth and bone structure with complex possible theoretical mechanism that also involves the microbiome [11]. More basic research exploring the mechanism and better well-designed prospective studies are needed to produce the ideal growth-supporting diet for the pediatric age group [3]. |

Catch-up growth, rapid weight growth, and continuous growth from birth to 6 years of age in very-preterm-born children

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Neonatology 2018;114:285–293

There is great interest in the timing and extent of catch-up growth in very preterm infants and its relationship with early feeding, as there is some evidence to suggest that the pattern of catch-up growth may have a bearing on long-term metabolic outcome. The three broad categories of feeds that infants can receive include unfortified breast milk, fortified breast milk, and preterm formula. The purpose of this study was to assess the influence of post-discharge nutrition on the childhood growth of a large cohort ($n = 281$) of such infants at 6 years of age. The investigators found that in a large proportion of infants, substantial catch-up growth had already occurred before discharge. When fed unfortified breast milk, catch-up in height seemed to continue until 6 years of age. Rapid weight gain was significantly associated with the type of feeding regimen following discharge and was most pronounced in preterm-formula-fed infants when compared to breastfed infants. Breastfed boys seemed to have a larger growth potential and seemed to show the greatest amount of increase in height and weight. SGA compared to AGA children demonstrated increased linear growth in height for a longer period of time, especially when fed unfortified breast milk. Thus, the investigators concluded that to achieve catch-up growth before discharge, there is no need for very low birth weight infants to have fortified breast milk or enriched formula milk. In addition, they suggested that mothers of preterm infants should be encouraged to breastfeed for as long as possible.

Leptin stimulates aromatase in the growth plate: limiting catch-up growth efficiency

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Background: Catch-up growth is a phase of accelerated growth that follows the correction of disorders that lead to decreased growth. One of these is nutritional deprivation. Leptin is an adipokine whose levels are associated with nutritional intake. Estrogens have an important role in the maturation of the growth plate. Both have roles in the process of endochondral ossification that is responsible for the elongation of long bones and therefore linear growth. In this study, authors investigated the mechanisms by which leptin and sex hormones affect catch-up growth and possible final height after nutritional deprivation.

Methods: Young male Sprague Dawley rats were fed ad libitum or subjected to a period of 40% food restriction, and thereafter to unrestricted re-feeding for up to 90 days. Growth velocity and height of growth plate was measured. Series of in vitro studies were performed in chondrogenic on ATDC5 cells to study the effect of leptin on aromatase gene expression, and protein and estrogen levels.

Results: Food restriction significantly decreased the growth velocity, which increased at re-feeding, and the final height was similar to non-restricted rats. Growth plate was significantly greater after food deprivation but was not different between the groups after re-feeding. Re-feeding was associated with an increase in leptin level, augmented aromatase mRNA expression and protein content, and augmented leptin and estrogen receptors gene expression.

In vitro studies showed that leptin significantly increased aromatase gene expression and protein level as well as the expression of estrogen and leptin receptors in a dose- and time-dependent manner. The effect of leptin was mediated through the MAPK/Erk, STAT3 and PI3K signaling pathways.

Conclusions: In this study, a crosstalk between leptin and aromatase in chondrocytes at the growth plate is described for the first time. Results of the study suggest that re-feeding during puberty may lead to increased estrogen level and activity in the growth plate, and consequently, irreversible premature epiphyseal closure. These results may have important implications for the development of novel treatment strategies for short stature in children.

Comments	One of the basic mechanisms as to how nutrition influences growth is linked to the effects of leptin on growth plate in longitudinal bones. Nutrition is also linked to timing and progression in pubertal development, both of which have important effects on growth pattern and final height [12, 13]. Therefore, to investigate crosstalk between leptin, main adipokine of the adipose tissue and estrogen, sex hormone that promotes both growth and senescence of the growth plate in the growth plate, is of high importance. In this study, authors link leptin's actions on aromatase expression and function in growth plate chondrocytes, thereby influencing local estrogen levels. The results of the study could have important consequences on the strategies of weight regain in growing children and treatment strategies for children with short stature where catch-up is the goal. These data also provide new insights into studies that investigated the use of aromatase inhibitors for the promotion of final height by decreasing the rate of growth plate senescence.

Differential aging of growth plate cartilage underlies differences in bone length and thus helps determine skeletal proportions

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Abstract: In their work, the authors tried to shed light on the mechanism responsible for the differences in bone length of the growing animal. They wondered what makes the difference between long bones like the tibia and shorter bones like the phalanges in the fingers and toes. In a very well-designed set of structural, histological, and molecular experiments, they showed that a variety of mechanisms are involved in the process. Bone elongation occurs within the growth plate, and the authors studied the changes within the growth plate in their search for trying to understand why different bones reach different lengths. The authors claimed that the progressive slow growth with age is due to developmental program termed "growth late senescence" which includes decline in cell proliferation and hypertrophy, depletion of cells in all growth plate zones, and extensive underlying changes in the expression of growth-regulating genes. They claimed and showed that these changes occur earlier in the growth plate of the smaller bone (metacarpal and phalanges) than in the larger bones (tibia and femurs). They also showed that the molecular mechanism involves changes of critical paracrine regulatory pathways, including insulin-like growth factor, bone morphogenetic protein, and wingless and Int-1 signaling. They concluded that the disparities in the length of bones in the body is achieved in part by modulating the progression of growth plate senescence.

Comments Bone elongation occurs in the growth plate and determines the magnitude of growth pace, and eventually the height of an individual. The mechanism that controls the chondrocytes proliferation and hypertrophy within the growth plate and their interaction with the endocrine and paracrine systems was never fully elucidated. The common theory is that the linear growth is influenced mainly by the genetic coding but it is also influenced by epigenetic and environmental factors. The sophisticated work presented in this article indeed sheds more light on the processes that occur within the growth plate during its growth and senescence. Exploring the mechanisms that control the event within the growth plate might lead to new approaches to children with growth issues and improve the tool of intervention in such cases.

New genetic tools in the diagnosis of growth defects

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Background: Many signaling pathways and genes are involved in the regulation of linear growth in children. Using new genetic tools, we are able to analyze much more genetic material in less time. **Methods:** The author reviews two new genetic tools in the determination of genetic causes of idiopathic short stature; chromosomal microarrays for genome-wide copy variants and whole exome sequencing for sequence variant determination.
Results: The principles of the two methods are explained clearly and are placed in the diagnostic flowchart of idiopathic short stature. Feasibility of different approaches are illustrated in case studies, for example, copy number variants approach in large-scale clinical databases and whole genome sequencing in the determination of novel genes involved in ISS as are *PAPPA2* and *ACAN*.
Conclusions: By using copy number variants and whole genome sequencing approach, it is now possible to comprehensively assess the presence of copy number variants as well as sequence variants in essentially all of the protein coding genes in the genome. As there are thousands of genes which can potentially contribute to growth disorders, genomic technologies will be a tremendous benefit for the evaluation of patients with severe short stature, in addition to its role in novel gene discovery.

Comments	Clinical examination and hormonal laboratory tests are the cornerstone of short stature diagnosis. When no cause can be determined, short stature is called idiopathic. This presents a burden for both the patient and his/her family and also the pediatric endocrinologist as long-term growth outcome is difficult to predict. In addition, treatment with growth hormone cannot be prescribed in certain regions [14].
	With the progress of genetic technologies described in this review, new possibilities in several fields of research and therapeutic strategy planning are opened. By determining novel genes and pathways involved in linear growth, possibilities for the development of new therapeutic possibilities are possible [15]. Making the diagnosis is, however, also very important for the child and his/her family and the pediatric endocrinologist. By using novel genetic tools, diagnosis is made in larger proportion of patients. Interestingly, spectrum of clinical features associated with certain growth disorders is broadened. By determining the etiology decision regarding the use of growth hormone and possible other therapeutic modalities can be made in a more informed manner. Currently, costs of these tools are still relatively high, limiting their everyday use for many centers. With further developments in the field, it is expected that this hurdle will also be overcome.

Regulation of body growth by microRNAs

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Regulation of growth is known to occur at a local growth plate level as well as at a systemic endocrine level. This review summarizes recent studies that investigated the role of microRNAs (miRNAs) in controlling both the linear and longitudinal growth of bones. miRNAs are small non-coding RNAs between 18 and 24 nucleotides long and play an important role in the regulation of gene expression. Most genes are regulated by one or more miRNAs, and each miRNA can regulate a larger number of target miRNAs. Because of this ability to regulate gene expression, miRNAs have been shown to play important roles in many physiological and developmental processes, as well as human diseases. It seems that miRNAs may be involved in regulating growth at several levels. At the level of the growth plate and associated chondrocytes, there is accumulating evidence that miR-140, the let-7 family of miRNAs, miR-199a, miR-145 and miR-675 may all play an important role in regulating growth. Evidence is also emerging that miRNAs may play important roles in regulating insulin-like growth factor-1 (IGF-I) signaling. For instance, in breast cancer cells, 2 miRNAs that suppress IGF1R expression, miR-148a and miR-152, were found to be downregulated. Lastly, there is also some evidence that miRNAs may play a role in regulating organ growth. The discovery of this new family of growth regulators opens up a new exciting avenue for understanding as well as modulating growth.

Dominant-negative STAT5B mutations cause growth hormone insensitivity with short stature and mild immune dysregulation

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Growth hormone insensitivity syndrome (GHIS) that presents as impaired postnatal growth and low or undetectable serum insulin-like growth factor-1 concentrations despite normal growth hor-

mone (GH) concentration is usually due to autosomal-recessive mutations of the GH receptor and in its classic form has been described as Laron syndrome. STAT5B deficiency is a very rare cause of GHIS, and to date has been described as an autosomal recessive disorder in which the severe short stature was also associated with T-cell lymphopenia and progressive pulmonary disease. In the current study, the investigators describe heterozygous STAT5B germline mutations that exert dominant-negative effects through impaired DNA binding which results in a condition characterized by significant postnatal growth impairment, mild GH insensitivity, eczema, and elevated IgE. None of the cases had the severe form of immune deficiency typically associated with STAT5b deficiency.

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Obesity, Metabolic Syndrome and Nutrition

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Introduction

The current epidemic of childhood obesity is one of the largest public health challenges facing healthcare providers and policy makers worldwide. Obesity is a significant risk factor for several health conditions and is a major cause of mortality and morbidity across the globe. Genetic factors, inappropriate eating habits in the early years of life, and insufficient physical activity have been shown to be associated with overweight and obesity in children and adolescents.

Given the long-term adverse sequelae of childhood obesity, identification of early life factors related to fetal growth and childhood obesity is warranted. A growing body of evidence suggests that the increased risk for childhood obesity is associated with early-life factors, such as the pregnancy period and maternal health. Insights on the potential impact of maternal diet and vitamin D status during pregnancy on childhood adiposity have been provided by several studies reviewed below.

It is well established that breastfeeding promotes healthy growth trajectories during infancy. However, the extent to which breastfeeding is protective against later-life obesity is debated, as described in the manuscripts below.

Many factors influence infant feeding practices and the development of obesity. Inconsistent associations between breastfeeding and infant obesity risk could be related to variations in human milk composition. In addition to macro- and micronutrients, human milk contains many bioactive components with the potential to influence infant growth, including cytokines, microbiota, oligosaccharides, and hormones. Some evidence suggests that breast milk hormones and adipocytokines are associated with body composition in the first 6 months of life. However, assessment of exclusive breastfeeding extension with baby-led approach to delay introduction of

complementary foods was not associated with lowered childhood or adolescent obesity risk.

Emerging evidence suggests that nutrition during early life, including meal habits and the type of consumed food may have consequences extending into adulthood. The fast food (FF) industry and people's FF consumption have grown rapidly. FF is high in unhealthy fats, salt, and sugar, which contributes to obesity and elevated blood pressure and has been positively associated with the obesity epidemic due to its increasing availability, energy density, and large portions. Data from observational studies and clinical trials have also shown an association between sugar-sweetened beverages consumption and obesity and the cardiometabolic profile.

Evidence from randomized controlled trials does not clearly support the intended benefits of nonnutritive sweeteners for weight management, and observational data suggest that routine intake of nonnutritive sweeteners may even be associated with increased body mass index (BMI) and cardiometabolic risk.

Research over the last decade has demonstrated that the microbes that colonize the human gut may play key contributory roles in the pathogenesis of obesity and diabetes mellitus. Gut microbes are known to have symbiotic relationship with the host, and play a role in maintaining health and metabolic homeostasis, including the production of a diverse array of metabolites.

Gut microbes are strongly influenced by the mode of birth and early diet and nutrition, as well as environmental and other factors including antibiotic exposure. Gut microbes contribute to human health through roles in polysaccharide breakdown, nutrient absorption, inflammatory responses, gut permeability, and bile acid modification.

Dysbiosis is associated with the promotion or aggravation of chronic metabolic diseases, including obesity and type 2 diabetes. Therefore, dietary alteration of the gut microbiome is an important target in the treatment of obesity. Dietary agents for modulation of the gut microbiome are essential tools in the treatment of obesity and lead to significant reductions in BMI, body weight, and fat mass when compared to placebo. In a placebo-controlled trial described below, prebiotic selectively altered the intestinal microbiota and significantly reduce body fat and serum level of interleukin-6 in children with overweight or obesity. However, further studies are needed to determine the ideal formulation for supplementation and to identify specific populations of overweight patients who would benefit most from gut microbiome modulation, in addition to assessing the durability of this effect.

This chapter reviews a selection of notable articles published between July 2017 and June 2018, focusing on the relation between nutrition, obesity, and metabolic syndrome in childhood and young adulthood. This selection of articles published in the course of a single year indicates the range and intensity of the continuing efforts being made by researchers worldwide to confront the problem of childhood obesity.

Key articles reviewed for the chapter

Maternal Diet During Pregnancy and Risk of Childhood Obesity

Beverage intake during pregnancy and childhood adiposity

Gillman MW, Rifas-Shiman SL, Fernandez-Barres S, Kleinman K, Taveras EM, Oken E

Pediatrics 2017; 140:e20170031

Maternal dietary intakes of refined grains during pregnancy and growth through the first 7 y of life among children born to women with gestational diabetes

Zhu Y, Olsen SF, Mendola P, Halldorsson TI, Yeung EH, Granström C, Bjerregaard AA, Wu J, Rawal S, Chavarro JE, Hu FB, Zhang C

Am J Clin Nutr 2017; 106: 96–104

The relationship between maternal 25-hydroxyvitamin D status in pregnancy and childhood adiposity and allergy: an observational study

Boyle VT, Thorstensen EB, Thompson JMD, McCowan LME, Mitchell EA, Godfrey KM, Poston L, Wall CR, Murphy R, Cutfield W, Kenealy T, Kenny LC, Baker PN; The children of the SCOPE study

Int J Obes (Lond) 2017; 41: 1755–1760

Breastfeeding and Nutrition During Early Life and Risk of Childhood Obesity

Associations of infant feeding with trajectories of body composition and growth

Bell KA, Wagner CL, Feldman HA, Shypailo RJ, Belfort MB

Am J Clin Nutr 2017; 106: 491–498.

Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood

Rzehak P, Oddy WH, Mearin ML, Grote V, Mori TA, Szajewska H, Shamir R, Koletzko S, Weber M, Beilin LJ, Huang RC, Koletzko B; for the WP10 working group of the Early Nutrition Project

Am J Clin Nutr 2017; 106: 568–580

Associations between human breast milk hormones and adipocytokines and infant growth and body composition in the first 6 months of life

Fields DA, George B, Williams M, Whitaker K, Allison DB, Teague A, Demerath EW

Pediatr Obes 2017; 12(suppl 1):78–85

Effect of a baby-led approach to complementary feeding on infant growth and overweight: a randomized clinical trial

Taylor RW, Williams SM, Fangupo LJ, Wheeler BJ, Taylor BJ, Daniels L, Fleming EA, McArthur J, Morison B, Erickson LW, Davies RS, Bacchus S, Cameron SL, Heath AM

JAMA Pediatr 2017; 171: 838–846

Effects of promoting long-term, exclusive breastfeeding on adolescent adiposity, blood pressure, and growth trajectories: a secondary analysis of a randomized clinical trial

Martin RM, Kramer MS, Patel R, Rifas-Shiman SL, Thompson J, Yang S, Vilchuck K, Bogdanovich N, Hameza M, Tilling K, Oken E

JAMA Pediatr 2017; 171:e170698

The effect of early feeding practices on growth indices and obesity at preschool children from four European countries and UK school children and adolescents

Moschonis G, de Lauzon-Guillain B, Jones L Oliveira A, Lambrinou CP, Damianidi L, Lioret S, Moreira P, Lopes C, Emmett P, Charles MA, Manios Y

Eur J Pediatr 2017; 176: 1181–1192

Nutrition During Childhood and Risk of Childhood Obesity and Metabolic Syndrome

Breakfast habits, dairy product consumption, physical activity, and their associations with body mass index in children aged 6–18

Koca T, Akcam M, Serdaroglu F, Dereci S

Eur J Pediatr 2017; 176: 1251–1257

Fast food consumption and its associations with obesity and hypertension among children: results from the baseline data of the childhood obesity study in China mega-cities

Zhao Y, Wang L, Xue H, Wang H, Wang Y

BMC Public Health 2017; 17: 933

Sweetened beverage intake in association to energy and sugar consumption and cardiometabolic markers in children

Seferidi P, Millett C, Laverty AA

Pediatr Obes 2018; 13: 195–203.

Sugar intake by type (added vs. naturally occurring) and physical form (liquid vs. solid) and its varying association with children's body weight, NHANES 2009–2014

Welsh JA, Wang Y, Figueroa J, Brumme C

Pediatr Obes 2018; 13: 213–221

Fructose replacement of glucose or sucrose in food or beverages lowers postprandial glucose and insulin without raising triglycerides: a systematic review and meta-analysis

Evans RA, Frese M, Romero J, Cunningham JH Mills KE

Am J Clin Nutr 2017; 106: 506–518

Discouraging soft drink consumption reduces blood glucose and cholesterol of Brazilian elementary students: Secondary analysis of a randomized controlled trial

de Moraes MM, Mediano MFF, de Souza RAG, Moura AS, da Veiga GV, Sichieri R

Prev Med 2017; 100: 223–228

Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies

Azad MB, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, Mann A, Jeyaraman MM, Reid AE, Fiander M, MacKay DS, McGavock J, Wicklow B, Zarychanski R

CMAJ 2017; 189:E929–E939

The Intestinal Microbiota and their Relation to Metabolic Programming

Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity

Nicolucci AC, Hume MP, Martínez I, Mayengbam S, Walter J, Reimer RA

Gastroenterology 2017; 153: 711–722

Maternal Diet During Pregnancy and Risk of Childhood Obesity

Beverage intake during pregnancy and childhood adiposity

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Background: Sugar-sweetened beverage (SSB) intake is a prime target of obesity prevention and treatment strategies in non-pregnant adults and children. The purpose of this study was to investigate associations of SSB and non-sugary beverage consumption during pregnancy with obesity-related outcomes in mid-childhood among mother-child pairs participating in the pre-birth cohort study.
Methods: In this prospective pre-birth cohort study (Project Viva), 1,078 mother-child pairs were evaluated. By using a food frequency questionnaire, exposures of SSB and non-sugary beverage intake were assessed in the first and second trimesters of pregnancy.
Main outcome measures were offspring adiposity parameters evaluated by: body mass index (BMI) z-score, fat mass index (FMI, kg/m^2) based on dual-energy radiograph absorptiometry, sum of subscapular (SS) and triceps (TR) skinfold thicknesses and central adiposity (SS:TR ratio and waist circumference).
Results: The mean maternal age at enrollment was 32.1 ± 5.4 years, pre-pregnancy BMI was 24.6 ± 5.2, and total gestational weight gain was 15.6 ± 5.3 kg; 10% smoked during pregnancy, and 68% were college graduates. The mean SSB intake was 0.6 ± 0.9 servings per day in the second trimester, with fewer than 10% who drank more than 2 servings per day.
In mid-childhood, the mean BMI z-score was 0.38 ± 1.00, and the FMI was 4.4 ± 1.9 kg/m^2.
In models adjusted for multiple maternal and child covariates, each additional serving per day of SSB during the second trimester of pregnancy was associated with higher BMI z-scores, FMI, SS + TR, and waist circumference, without differences between boys and girls. Stratified models suggested that the associations were due primarily to maternal SSB intake and to sugary soda rather than fruit drinks or juice.

Conclusions: Mothers who consumed more SSB in mid-pregnancy had children with greater levels of adiposity in mid-childhood.

Comments	High intake of sugar-sweetened beverage (SSB) has been linked to increased risk of obesity. However, the association of SSB intake during pregnancy with child body composition have been unclear. A previous study [1] based on the Generation R Study in the Netherlands reported that mothers' total SSB intake in the first trimester of pregnancy was positively associated with children's BMI ≤6 years of age, and intakes of total SSB and fruit juice were associated with a higher FMI of the 6-year-old children. Interestingly, the current study demonstrated that first-trimester SSB intake was not associated with any of the mid-childhood levels of adiposity outcomes.
	The observations of both studies may point that intake of SSB during pregnancy may influence the intrauterine programming of the child towards obesity. Potential effects of SSB intake during pregnancy on child body composition may be hypothesized by several mechanisms including changes in the insulin response. Another possible mechanism could be that the epigenetics of the fetus changes when a mother has frequent intake of SSB during pregnancy. These changes could lead to altered gene expression, which may result in children becoming more susceptible to having higher fat mass. SSB intake during pregnancy might also affect the insulin sensitivity of the child with the subsequent stimulation of the development of fat mass in the child.
	The strengths of the current study include the large sample size, the prospective data collection since early pregnancy; robust dietary assessment at 2 points in pregnancy; and the adjustment for multiple covariates. The limitations include: the self-report of diet and intake of SSB, and the relatively high percentage of loss to follow-up, that may bias the results.
	Finally, maternal diet during pregnancy may supply sufficient developmental cues to offer effective prevention of obesity in the offspring. These findings provide motivation to evaluate the long-term effects of interventions to reduce SSB intake once women become pregnant with the aim of childhood obesity prevention.

Maternal dietary intakes of refined grains during pregnancy and growth through the first 7 years of life among children born to women with gestational diabetes

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Background: Accumulating evidence suggests that the sources and types of grains may have a different impact on glycemic response and cardiometabolic outcomes. Refined grains with a high glycemic index and reduced fiber and nutrient contents have been linked to increased adiposity and a

higher risk of metabolic syndrome among adults. Women with gestational diabetes mellitus (GDM) may predispose their offspring to an increased risk of cardiometabolic disorders later in life.

The aim of the study was to investigate prospectively the association between refined-grain intake during pregnancy and offspring growth and risk of obesity through the first 7 years of life among women with GDM.

Methods: The analysis was based on data from the Danish National Birth Cohort, a population who traditionally consume relatively large amounts of grains, and included mother-singleton child dyads ($n = 918$). Maternal dietary intakes were estimated by using a validated 360-item food-frequency questionnaire distributed at gestational week 25, which included questions about dietary intake during the previous month.

Offspring body mass index z scores (BMIZs) were calculated at birth, 5 and 12 months, and 7 years. Overweight or obesity was defined by WHO cutoffs. Linear and Poisson regressions were used, with adjustment for maternal demographic, lifestyle, and dietary factors.

Results: Among the women with pregnancies complicated by GDM, the mean age at the index childbirth was 31.3 ± 4.6 years, and the mean intake of refined grains during pregnancy was 86.2 ± 49.4 g/day. Across increasing quartiles of maternal refined-grain intake during pregnancy, women tended to have a higher intake of total energy and a higher percentage of energy from total fat and a lower percentage of energy from protein.

Offspring characteristics at baseline, including sex, gestational age at delivery, birth weight, and other measures of birth size, did not vary significantly across quartiles of maternal refined-grain intake during pregnancy.

Refined-grain intake during pregnancy was positively associated with offspring BMIZ and risk of overweight or obesity at age 7 years. The association was more pronounced among children who were breastfed <6 months. The substitution of 1 serving refined grains/day with an equal serving of whole grains during pregnancy was related to a 10% reduced risk of offspring overweight or obesity at 7 years of age.

Conclusions: A significant and positive association was found between maternal refined-grain intake during pregnancy and offspring BMIZ and the risk of overweight or obesity at age 7 years among the high-risk children born to women with GDM.

Comments	Children exposed to gestational diabetes mellitus (GDM) in utero are at high risk of developing many health problems such as obesity later in life. Therefore, there is an urgent need to find new strategies to prevent obesity development among high-risk populations such as those children.
	The inherent low-fiber content of refined-grain foods may alter profiles of satiety hormones and expression of genes involved in glucose and lipid metabolism and increase adiposity in offspring. The present study showed that dietary substitution of refined grains with whole grains during pregnancy was associated with a lower risk of offspring overweight or obesity at 7 years of age.
	The strengths of the study include: the large sample size, the prospective design with repeated measures of childhood anthropometric variables, which represents the opportunity to investigate the intergenerational association of refined-grain intake during pregnancy with offspring obesity, and adjustment for important confounders.
	The study limitations include: childhood weight and height at age 7 years were based on reports by the parent or parents on the basis of measurements from health professionals, the pre-pregnancy weight and height and maternal dietary intakes were self-reported, all that can contribute to biased results. Also, data regarding maternal diet in the third trimester after GDM diagnosis was missing.
	However, this study underlines the need for future prospective dietary intervention studies with longer follow-up through later childhood and adolescence to confirm its findings.

The relationship between maternal 25-hydroxyvitamin D status in pregnancy and childhood adiposity and allergy: an observational study

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Background: Vitamin D insufficiency (defined as <75 nmol/L) is widespread among pregnant women.

Obesity in childhood is on the rise, coinciding with a re-emergence of vitamin D deficiency. Vitamin D promotes adipocyte maturation and inhibits adipocyte proliferation. An in-utero insult such as vitamin D deficiency may therefore set a life course towards fat accumulation.

The aim of this study was to investigate the relationship between vitamin D status in pregnancy at the beginning of the second trimester of pregnancy and the development of obesity in their children between 5 and 6 years of age.

Methods: The offspring of 1,208 mothers were followed up at age 5–6 years. Data collected included height, weight, percentage body fat (PBF; measured by bioimpedance). The maternal 25-hydroxyvitamin D concentrations were analyzed in serum samples collected at 15 weeks' gestation from participants of the prospective Screening for Pregnancy Endpoints cohort study ($n = 1,710$). Linear regression analysis was performed to investigate the relationship between 25-hydroxyvitamin D and child's PBF and BMI z-score. Multivariable linear regression was performed to control for maternal BMI at 15 weeks' gestation, ethnicity, maternal smoking during pregnancy, socioeconomic status, sex of the child and age at sampling, and season of sample collection.

Results: Maternal serum samples were available for 25-hydroxyvitamin D analysis from 1,715 women, child BMI z-scores from 1,207 children, and PBF from 1,176 children.

The mean PBF was higher in children with maternal 25-hydroxyvitamin D concentration <50 nmol/L compared with >50 nmol/L (23.9 ± 6.8 vs. $22.7 \pm 6.3\%$, $p = 0.02$), and was similar between children with maternal 25-hydroxyvitamin D concentration <75 and >75 nmol/L ($p = 0.09$). In multivariate linear regression analysis, each 10 nmol/L increase in maternal 25-hydroxyvitamin D at 15 weeks' gestation was associated with a decrease in child PBF of 0.2%, ($p = 0.02$). Similarly, this association was seen with body fat, but there were no associations with lean mass, weight, height or BMI z-score. After adjustment for ethnicity, this effect was no longer significant. The mean BMI z-score was similar in children with maternal 25-hydroxyvitamin D concentrations above and below 50 nmol/L and likewise for concentrations above and below 75 nmol/L. Linear regression analysis showed no significant association between BMI z-score and maternal total 25-hydroxyvitamin D analyzed as a continuous variable.

Conclusions: Adjusting for maternal BMI and child age and sex, it was found that lower maternal 25-hydroxyvitamin D concentration at 15 weeks' gestation was associated with higher PBF in children aged 6 years.

Comments	Adipose tissue is an active participant in the regulation of food intake and metabolic regulation. Vitamin D promotes adipocyte maturation and inhibits adipocyte proliferation [2].
	An in-utero insult such as maternal vitamin D deficiency may therefore be linked to programmed differences in offspring fat mass and set a life course towards adiposity. Little is known of the effects of low vitamin D status in pregnancy on offspring body composition. Maternal vitamin D status during pregnancy has been associated with infant birth and postnatal growth outcomes, but reported findings have been inconsistent, especially in relation to postnatal growth and adiposity outcomes [3, 4].
	The findings of the current study that lower maternal 25-hydroxyvitamin D concentration at 15 weeks' gestation was associated with higher PBF in children aged 6 years, may point that these children are at higher risk for obesity and metabolic risk in adulthood.
	Vitamin D is best known for its role in increasing intestinal calcium absorption, and the effects of vitamin D on PBF may be mediated through calcium. Studies in rat models of adult obesity have shown that high calcium diets reduce PBF [5]. The active form of vitamin D, 1,25 dihydroxyvitamin D, has been shown to prevent adipogenesis in vitro by suppressing adipogenic factors, such as peroxisome proliferator activated receptor-γ and lowering lipid accumulation [6, 7].
	The major limitations of this study is the lack of data to adjust for some possible additional confounding variables, as maternal exercise and diet, sunlight exposure during pregnancy, and factors known to affect childhood adiposity as the child's own exercise levels and dietary patterns. Participants in SCOPE were self-selected from a specific origin and cannot be representative of all pregnant women.
	Nevertheless, the findings of this study support the evaluation of randomized trials of vitamin D supplementation during pregnancy on formal measurements of adiposity in their children.

Associations of infant feeding with trajectories of body composition and growth

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This manuscript is also discussed in Chapter 6 page 123.

Background: Obesity is defined as an excess of body fat; however, the most available methods to assess body composition, such as the body mass index (BMI), do not discriminate between fat and lean tissues. Limited information is available about differences in infant body composition between breastfed and formula-fed infants, which may reflect future obesity risk. The extent to which breastfeeding is protective against later-life obesity is still controversial.

The aim of the study was to assess associations of infant feeding (formula-fed versus breastfed infants) with trajectories of growth and body composition from birth to 7 months in healthy infants.

Methods: A total of 276 participants from a previous randomized clinical trial of maternal vitamin D supplementation during lactation were studied. Mothers used monthly feeding diaries to report the extent of breastfeeding. Infants' anthropometrics and dual-energy X-ray absorptiometry to assess body composition were assessed at 1, 4, and 7 months. Changes in infant size (z scores for weight, length, and BMI [in kg/m^2]) and body composition (fat and lean mass, body fat percentage) were compared between predominantly breastfed and formula-fed infants, adjusting in linear regression for sex, gestational age, race/ethnicity, maternal BMI, study site, and socioeconomic status.

Results: In this study, 214 infants (78%) were predominantly breastfed (median duration: 7 months) and 62 were exclusively formula fed. Formula-fed infants had lower birth-weight z scores than breastfed infants (–0.22 ± 0.86 and 0.16 ± 0.88, respectively; $p < 0.01$) but gained more in weight and BMI through 7 months of age (weight z score difference: 0.37; 95% CI 0.04, 0.71; BMI z score difference: 0.35; 95% CI 0 – 0.69), with no difference in linear growth (z score difference: 0.05; 95% CI –0.24 to 0.34). Formula-fed infants gained more lean mass (difference: 303 g; 95% CI 137–469 g) than breastfed infants, but not fat mass (difference: –42 g; 95% CI –299 to 215 g).

Conclusions: Formula-fed infants gained weight more rapidly and out of proportion to linear growth than did predominantly breastfed infants. These differences were attributable to greater accretion of lean mass, rather than fat mass. Any later obesity risk associated with infant feeding does not appear to be explained by differential adiposity gains in infancy.

Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood

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Background: Infant nutrition has long-lasting effects on later health and risk of disease. Growth patterns of breastfed and formula-fed infants may differ, with formula-fed infants growing more rapidly than breastfed infants into childhood and adulthood. Formula feeding increases the fat mass in infancy, and compared with the body composition of breastfed infants, formula-fed infants have more fat mass at 12 months of age.

The objectives of the study were to identify growth patterns and investigate early nutritional programming potential on growth patterns at 6 years and on body composition at 20 years.

Methods: The West Australian Pregnancy Cohort (RAINE) study and 3 European cohort studies (European Childhood Obesity Trial, Norwegian Human Milk Study, and Prevention of Celiac Disease) that collaborate in the European Union-funded Early Nutrition project combined, harmonized, and pooled data on full breastfeeding, anthropometry, and body composition. Inclusion criteria were anthropometric measurements of weight and length at birth with ≥1 anthropometric follow-up in the first 6 years of life for any of the potential 12 semi-annual follow-up measurements and age at each measurement for both weight and height. At 20 years, measurements of body composition were only available for the RAINE cohort. Fat mass in kilograms and fat mass index (FMI; kg fat mass/height m^2) were determined by whole-body dual-energy X-ray absorptiometry, scanning latent growth mixture modeling was applied to identify growth patterns among the 6,708 individual growth trajectories. The association of full breastfeeding for <3 months compared with ≥3 months with the identified trajectory classes was assessed by logistic regression. Differences in body composition at 20 years among the identified trajectory classes were tested by analysis of variance.

Results: Three body mass index (BMI; in kg/m^2) trajectory patterns were identified and labeled as follows – class 1: persistent, accelerating, rapid growth (5%); class 2: early, non-persistent, rapid growth (40%); and class 3: normative growth (55%). A shorter duration of full breastfeeding for <3 months was associated with being in rapid-growth class 1 (OR 2.66; 95% CI 1.48–4.79) and class 2 (OR 1.96; 95% CI 1.51–2.55) rather than the normative-growth class 3 after adjustment for covariates. Both rapid-growth classes showed significant associations with body composition at 20 years ($p < 0.0001$). Children having a higher probability of being in either rapid-trajectory class had higher absolute BMI, skinfolds, absolute fat mass, and FMI values at 20 years compared with children with a normative-trajectory class.

Conclusions: Full breastfeeding for <3 months compared with ≥3 months may be associated with rapid growth in early childhood and body composition in young adulthood. Rapid-growth patterns in early childhood could be a mediating link between infant feeding and long-term obesity risk.

Comments	During the complete lifespan, body composition may be assessed using laboratory methods, allowing differentiation between fat and fat-free mass compartments. However, in this regard, there is little information in some specific age groups, especially infancy and the effect of early changes in body composition on later body composition compartments.
	Breastfeeding has been related to the establishment of infant appetite regulation, feeding patterns development, and body composition changes during infancy and later in childhood. In the previous reviewed study by Bell et al. (page 21), it was observed that differences were attributable to greater accretion of lean mass in formula-fed infants as compared with breastfed infants. These differences were not attributable to fat mass. The study by Rzehak assessed the body composition at the age of 20 years, but by just focusing on fat mass. In a previous study [8] using robust body composition methods (4-compartment model) at a mean age of 11.4 years, they observed that greater relative weight gain during early infancy (0–3 months and from 3 to 6 months) was positively associated with later fat mass and central fat distribution and with fat-free mass. As results for body composition in this regard are very scarce, there is an urgent need for studies using as much robust methods of body composition as possible, from infancy into adulthood. This will allow us to disentangle the early determinant factors of body composition changes related with obesity and other metabolic disorders, such as type 2 diabetes, dyslipidemia or hypertension.

Associations between human breast milk hormones and adipocytokines and infant growth and body composition in the first 6 months of life

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Background: Human breast milk is a complex, biological fluid with its composition depending on some factors, including genetic factors timing within a given feeding, length of lactation, and maternal body composition; however, limited information on human breast milk composition currently exists and this is especially the case for nonnutritive bioactive components and whether they affect growth and development of the offspring in the first months of life.

The purpose of this study is to extend the knowledge on human breast milk by investigating the role of maternal body mass index, sex, and stage of lactation (month 1 vs. 6) on human breast milk insulin, glucose, leptin, IL-6, and TNF-α and their associations with infant body composition.

Methods: A total of 37 exclusively breastfeeding infants ($n = 37$; 16 females, 21 males) and their mothers (19–47 kg · m^{-2}) were studied at 1 and 6 months of lactation. Human breast milk insulin, glucose, leptin, IL-6, and TNF-α were measured at 1 and 6 months of lactation. Infants had body composition measured using dual-energy X-ray absorptiometry.

Results: A significant interaction between maternal BMI and infant sex on insulin levels ($p = 0.0322$) was observed such that insulin was 229% higher in obese mothers nursing female infants than in normal weight mothers nursing female infants and 179% higher than obese mothers nursing male infants. For leptin, a significant association with BMI category was observed ($p < 0.0001$) such that overweight and obese mothers had 96.5 and 315.1% higher leptin levels than normal weight mothers, respectively. Leptin was also found to have a significant ($p = 0.0004$) 33.7% decrease from months 1 to 6, controlling for BMI category and sex. A significant inverse relationship between month 1 leptin levels and infant length ($p = 0.0257$), percentage fat ($p = 0.0223$), total fat mass ($p = 0.0226$), and trunk fat mass ($p = 0.0111$) at month 6 was also found. No associations or interactions were observed for glucose, TNF-α or IL-6.

Conclusions: These data show that maternal BMI, infant sex, and stage of lactation affect the human breast milk compositional make-up of insulin and leptin and that leptin levels were inversely associated with body fat composition in the offspring.

Comments	In human breast milk, there are some active compounds, including leptin, insulin, ghrelin, adiponectin, resistin, obestatin, insulin-like growth factor-1, copeptin, apelin, and nesfatin, among others. At least some of these molecules may influence the energy balance by stimulating orexigenic or anorexigenic pathways. Some of these compounds may also regulate the growth and development of infants; however, studies in this respect, especially long-term, are not available.
	Some recent observational studies have shown that human breast milk concentrations of protein, fat, and carbohydrate are associated with infant growth and body composition. The same is true for human milk oligosaccharides. For human breast milk micronutrient concentrations and microbiota composition, the relationship with infant growth is still not clear.
	In this study, an inverse association between human breast milk leptin concentrations and infant growth and body composition was observed. Similar results have been observed with other human breast milk hormones concentrations such as adiponectin (inverse association) or ghrelin (positive association with body weight) [9], but results are inconsistent between the different studies and there is also a lack of studies aiming to elucidate the effect of these hormones on infants' growth and metabolism. High-quality studies investigating the relationship between human milk composition and infant growth are necessary to strengthen the health-promoting effect of breast milk on the offspring.

Effect of a baby-led approach to complementary feeding on infant growth and overweight: a randomized clinical trial

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Background: Baby-led approaches to complementary feeding, which promote self-feeding of all non-liquid foods are proposed to improve energy self-regulation and lower obesity risk. However, infants may not eat large enough portions, especially if their feeding skills are insufficient. There is no information coming from observational studies, but they have important limitations, such as growth patterns may be different according to socio-demographic variables. This is the first randomized clinical trial that aimed to determine whether a baby-led approach to complementary feeding results in a lower body mass index (BMI) than traditional spoon-feeding.

Methods: The 2-year Baby-Led Introduction to Solids (BLISS) randomized clinical trial recruited 206 women (168 [81.6%] of European ancestry; 85 [41.3%] primiparous) in late pregnancy from December 19, 2012, through March 17, 2014, as part of a community intervention in Dunedin, New Zealand. A total of 206 of 879 women approached (response rate, 23.4%) were randomized to the control ($n = 101$) or BLISS ($n = 105$) group after stratification for parity (first child and subsequent child) and maternal educational level (non-tertiary and tertiary). All outcomes were collected by staff blinded to group randomization, and no participants withdrew because of an adverse event. Intention to treat analysis was performed.

All families had access to government-funded routine midwifery and well-child care. The BLISS group received 8 additional contacts from pregnancy to 9-months of age. Mothers in the BLISS group received lactation consultant support (≥5 contacts) to extend exclusive breastfeeding and delay introduction of complementary foods until 6 months of age and 3 personalized face-to-face contacts (at 5.5, 7.0, and 9.0 months).

The primary outcome was BMI z score (at 12 and 24 months). Secondary outcomes included energy self-regulation and eating behaviors assessed with questionnaires at 6, 12, and 24 months and energy intake assessed with 3-day weighed diet records at 7, 12, and 24 months.

Results: Among the 206 participants (mean [SD] age, 31.3 [5.6] years), 166 were available for analysis at 24 months (retention, 80.5%). Using the imputed data, the mean (SD) BMI z score was not significantly different at 12 months (control group, 0.20 [0.89]; BLISS group, 0.44 [1.13]; adjusted difference, 0.21; 95% CI −0.07 to 0.48) or at 24 months (control group, 0.24 [1.01]; BLISS group, 0.39 [1.04]; adjusted difference, 0.16; 95% CI −0.13 to 0.45). At 24 months, 5 of 78 infants (6.4%) were overweight (BMI ≥95th percentile) in the control group compared with 9 of 87 (10.3%) in the BLISS group (relative risk, 1.8; 95% CI 0.6–5.7). Lower satiety responsiveness was observed in BLISS infants at 24 months (adjusted difference, −0.24; 95% CI −0.41 to −0.07). Parents also reported less food fussiness (adjusted difference, −0.33; 95% CI −0.51 to −0.14) and greater enjoyment of food (adjusted difference, 0.25; 95% CI 0.07–0.43) at 12 months in BLISS infants. Estimated differences in energy intake were 55 kJ (95% CI −284 to 395 kJ) at 12 months and 143 kJ (95% CI −241 to 526 kJ) at 24 months.

Conclusions: A baby-led approach to complementary feeding did not result in more appropriate BMI than traditional spoon-feeding, although children were reported to have less food fussiness. Further randomized clinical trials should also determine whether these findings apply to individuals using unmodified baby-led weaning.

Comments Weaning is the period in which infants are gradually introduced to solid foods. It is a critical period because it coincides with the time of rapid infant's growth, during the first year of life, but also because food preferences and eating behaviors develop. The process of weaning may have short- and long-term influence on individual's health. In most countries, infants used to have complementary feeding using spoons. Baby-led weaning is an infant feeding strategy to introduce solid foods, giving control of the feeding process to the infant. Baby-led weaning is becoming popular among parents, but scientific research is limited to a few publications. Those proposing the approach, argue that baby-lead weaning may promote healthy eating behaviors and optimal weight gain trajectories, but this feeding strategy still causes concern to health professionals and parents, given the scarcity of scientific information. In the present study, no effect on BMI was observed, but less food fussiness was observed. One important concern of the baby-led weaning strategy is the increased risk of iron deficiency. In another report of the BLISS study [10], the authors assessed the intervention effect on iron intake, plasma ferritin, hemoglobin, soluble transferrin receptor, C-reactive protein, and α_1-acid glycoprotein concentrations. The conclusion of this analysis was that the intervention did not increase the risk of iron deficiency when the parents are given advice to offer "high-iron" foods with each meal. Further randomized clinical trials are guaranteed to assess potential the positive/negative effects of baby-led weaning. Currently, available evidence does not support relevant effects in objective health-related outcomes.

Effects of promoting long-term, exclusive breastfeeding on adolescent adiposity, blood pressure, and growth trajectories: a secondary analysis of a randomized clinical trial

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Background: Evidence that breastfeeding and its duration reduces child obesity risk and lowers blood pressure is based on potentially confounded observational studies. Between these confounding factors, social patterning of both breastfeeding and growth and publication bias are the most relevant.
The aim was to investigate the effects of a breastfeeding promotion intervention on adiposity and blood pressure at age 16 years and on longitudinal growth trajectories from birth.
Methods: The study was based on the Cluster-randomized Promotion of Breastfeeding Intervention Trial. Belarusian maternity hospitals and affiliated polyclinics (the clusters) were allocated to the intervention ($n = 16$) or control arms ($n = 15$) in 1996 and 1997. The trial participants were 17,046 breastfeeding mother-infant pairs; of these, 13,557 children (79.5%) were followed up at 16

years of age between September 2012 and July 2015. The intervention included breastfeeding promotion, modeled on the Baby-Friendly Hospital Initiative.

The main outcomes included: body mass index (BMI); fat and fat-free mass indices and percentage of body fat from foot-to-foot bioelectrical impedance; waist circumference; overweight and obesity; height and blood pressure. The analyses of growth trajectories included 17,042 children (99%) with at least 1 measurement of weight, length (at up to age 2 years), or height (after age 2 years). The relationships of weight, stature, or BMI z-score with age were parameterized using linear splines with 5 knot points at 3 months, 12 months, 2.8 years, 8.5 years, and 14.5 years to describe periods of approximately linear growth based on the data. The primary analysis was modified intention-to-treat (without imputation for losses to follow-up) accounting for within-clinic clustering.

Results: Children (n = 13,557) at a median age of 16.2 years (48.5% were girls) were examined. The intervention substantially increased breastfeeding duration and exclusivity compared with the control arm (exclusively breastfed: 45 vs. 6% at 3 months, respectively). The mean differences at 16 years between intervention and control groups were 0.21 (95% CI 0.06–0.36) for BMI; 0.21 kg/m^2 (95% CI –0.03 to 0.44) for fat mass index; 0.00 kg/m^2 (95% CI –0.21 to 0.22) for fat-free mass index; 0.71% (95% CI –0.32 to 1.74) for percentage body fat; –0.73 cm (–2.48 to 1.02) for waist circumference; 0.05 cm (95% CI –0.85 to 0.94) for height; –0.54 mm Hg (95% CI –2.40 to 1.31) for systolic BP; and 0.71 mm Hg (95% CI –0.68 to 2.10) for diastolic BP. The OR for overweight/obesity (BMI ≥85th vs. <85th percentile) was 1.14 (95% CI 1.02–1.28) and the OR for obesity (BMI ≥95th vs. <95th percentile) was 1.09 (95% CI 0.92–1.29). The intervention resulted in a more rapid rate of gain in post-infancy height (1–2.8 years), weight (2.8–14.5 years), and BMI (2.8–8.5 years) compared with the control arm. The intervention had little effect on BMI z-score changes after 8.5 years.

Conclusions: A randomized intervention that increased the duration and exclusivity of breastfeeding was not associated with lowered adolescent obesity risk or blood pressure. On the contrary, the prevalence of overweight/obesity was higher in the intervention arm. All mothers initiated breastfeeding, so findings may not apply to comparisons of the effects of breastfeeding versus formula feeding.

Comments	The current study is the only randomized trial aiming to assess the long-term effect of breastfeeding promotion in the context of the WHO, Baby-Friendly Hospital Initiative. For this reason, we should pay special attention to the obtained results. In this paper, the authors report the results obtained at the age of 16 years; this means beyond the adiposity rebound and when most of the participants nearly attained adult height. Moreover, adiposity and blood pressure levels at 16 years should be good predictors of adult adiposity and blood pressure.
	Concerning obesity, it should be considered that breastfed infants are introduced to a variety of flavors that may be identified in human milk and thus the transition from maternal milk to complementary foods may be easier for these children. In addition, breastfed infants seem also to have healthier dietary patterns later in life than those receiving formula feeding. However, several confounding factors may influence these associations; especially maternal characteristics as ethnicity, education level or occupation and variations on how mothers feed their children have been identified according to these characteristics.
	Blood pressure in adult life has been associated with small birth size and rapid postnatal growth. Longer breastfeeding may also be associated with lower adult blood pressure. In a systematic review on the association between breastfeeding and blood pressure, no associations were found, supporting the current results [11].
	Despite the strong evidence provided by the current study on the lack of association between breastfeeding and obesity and blood pressure later in life, breastfeeding should be promoted, as recommended by international organizations.

The effect of early feeding practices on growth indices and obesity at preschool children from four European countries and UK school children and adolescents

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This manuscript is also discussed in Chapter 6 page 135.

Background: Childhood obesity partly originates from early life. The current work aimed to examine the association of feeding practices during infancy with growth and adiposity indices in preschool children from 4 European countries and in UK schoolchildren and adolescents.
Methods: Existing data from 4 European birth cohorts (ALSPAC-UK, EDEN-France, EuroPrevall-Greece, and Generation XXI-Portugal) were used. Anthropometrics and body composition indices were collected. Bioelectrical impedance analysis measurements were conducted in all cohorts, with equipment and procedures that were site-specific. Parallel multivariate regression analyses were performed to examine the research hypothesis.
Results: Overall, the analyses showed that breastfeeding and timing of complementary feeding were not consistently associated with height z-score, overweight/obesity, and body fat mass in children or adolescents. However, breastfeeding duration for less than 6 months was associated with lower height z-scores in 5-year-old French children ($p < 0.001$) but with higher height z-scores in 4-year-old UK children ($p = 0.006$). Furthermore, introduction of complementary foods earlier than 4 months of age was positively associated with fat mass levels in 5-year-old French children ($p = 0.026$).
Conclusions: Early feeding practices, that is, any breastfeeding duration and age on introduction of complementary foods, do not appear to be consistently associated with height z-score, overweight/obesity, and body fat mass in preschool children from 4 European countries and in UK schoolchildren and adolescents.

Comments	The current study, analyzing 4 European birth cohorts (ALSPAC-UK, EDEN-France, EuroPrevall-Greece, and Generation XXI-Portugal), confirm the inconsistency between different studies in terms of the impact of very early nutrition (breastfeeding/formula feeding and complementary feeding) on growth and body composition later in life. Very likely, the significant associations observed in some studies are presented because of the impact of different confounding factors.
	In this report, findings related to breastfeeding were discussed in relation to previous articles. For complementary feeding, a systematic review showed that the introduction of solid foods before the age of 4 months increased the obesity risk, despite the majority of studies included in this review reporting no effect [12].
	Ideally, randomized controlled trials should be performed. However, this is not possible in practice, for ethical reasons, at least for breastfeeding. Therefore, we should

give emphasis to only one existing cluster randomized trial (PROBIT study) and cumulate additional evidence from well-designed observational studies using strong methods to assess body composition.

Nutrition during Chilhood and Risk of Childhood Obesity and Metabolic Syndrome

Breakfast habits, dairy product consumption, physical activity, and their associations with body mass index in children aged 6–18

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Background: Several studies have identified a possible role of breakfast consumption in maintaining normal weight status in children and adolescents. A number of cross-sectional studies have reported an inverse correlation between body mass index (BMI) or adiposity and dairy product consumption in children. The aim of the study was to determine breakfast habits, dairy product consumption, and physical activity in schoolchildren and adolescents and to investigate the association between them and the BMI.

Methods: This cross-sectional survey included children aged 6–18 years from 10 schools in the region of southwest Turkey. Breakfast consumption frequency, intake of dairy products, physical activity habits, and mothers' employment status were assessed via a self-report questionnaire. Height and weight were measured, and a BMI z-score was calculated for each child. The association between these habits and BMI z-scores was evaluated by using multiple linear regression analysis.

Results: The study included 7,116 children, (48.4% female), with a mean age of 11.7 ± 2.7 years (range 5.8–18.9 years). Analysis of dietary habits showed that 62.6% of children had breakfast daily. Boys had breakfast daily, significantly more often than girls ($p < 0.001$). The percentage of children eating breakfast daily decreased with age, from 79.1% of children aged 6–11 to 52.1% among children aged 12–18 years ($p < 0.001$). Most children (84%) consumed dairy products.

Milk intake was negatively and significantly associated with BMI z-score ($p < 0.001$), whereas cheese consumption was positively associated with BMI z-score ($p < 0.001$). Children engaging in physical activity had higher BMI z-score values than others ($p < 0.001$).

Conclusions: Skipping breakfast was significantly related to overweight/obesity in children and adolescents. Milk consumption seems to have a protective effect against overweight/obesity, irrespective of yogurt or cheese consumption. Therefore, encouraging milk consumption is also important in protecting against obesity.

Comments Breakfast is commonly described as "the most important meal of the day." Skipping breakfast is common among children and adolescents. However, there is uncertainty regarding whether breakfast consumption contributes to or protects against overweight or obesity. A systematic review of 16 cross-sectional or cohort studies

involving more than 59,000 children/adolescents from Europe evaluated the evidence of the effects of breakfast consumption on body weight outcomes in children and adolescents in Europe. The results of this analysis suggested that eating breakfast is associated with a reduced risk of becoming overweight or obese and a reduction in the BMI in children and adolescents in Europe [13]. The same observation was reported in other studies that showed that skipping breakfast predicts a greater increase in BMI [14, 15] and association with increased risk of metabolic syndrome and other cardiometabolic factors in children and adolescents [16].

Previous studies also showed that dairy consumption was associated with lower adiposity and higher cardiorespiratory fitness in these adolescents [17]. A systematic review and meta-analysis of 10 prospective cohort studies comprising 46,011 children and adolescents with an average of 3-year follow-up suggested that dairy consumption was inversely and longitudinally associated with the risk of childhood overweight/obesity [18]. Milk (especially whey protein) that seems to have a protective effect against overweight/obesity, also stimulates insulin secretion that may directly affect food intake regulation by suppressing appetite.

The study limitations include: the cross-sectional design, element of reporting bias that cannot be excluded with the use of self-reported physical activity and dietary intake data.

One of the new aspect reported in this study was that children engaging in greater physical activity had higher body mass index values than others. Although it is well established that increasing purposeful or leisure-time physical activity is associated with reduced rates of obesity, recent evidence suggests that sedentary activities are associated with increasing obesity, independent of purposeful physical activity. Therefore, the effect of physical activity may be offset by other factors or habits and may not imply that more hours of exercise will lower BMI.

Yet, promoting the benefit of eating breakfast and increased diary consumption, especially milk, could be a simple and important implication to prevent obesity and its related comorbidities.

Fast food consumption and its associations with obesity and hypertension among children: results from the baseline data of the childhood obesity study in China mega-cities

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Background: Obesity and hypertension prevalence in China increased during the past decade, along with fast food consumption (FFC). This study investigated Chinese and Western FFC, risk factors associated with non-healthy food choices, maternal factors, and associations with health outcomes in Chinese children.

Methods: Data of 1626 children and adolescents aged 7–16 (11.6 ± 2.0) years and their parents from 4 big cities in China (Beijing, Shanghai, Nanjing, and Xi'an) were collected in the 2015 baseline survey of the "Childhood Obesity Study in China Mega-cities." Weight, height, waist circumference, and blood pressure were measured. Food intake was assessed using a questionnaire (FFC as times/week in the last 3 months). Mixed-effects models were fitted to investigate risk factors for FFC patterns and the association between FFC and health outcomes, adjusting for child factors (age, sex, and school location), and maternal factors (BMI and education level).

Results: Half (51.0%) of the children and adolescents were boys, 51.6% from primary schools and 48.4% from middle schools. The prevalence of overweight (including obesity) was 26.2%, obesity 11.1%, and central obesity 19.7%. The rates for boys were higher than those for girls (33.9, 15.2, and 27.4%, vs. 18.2, 6.9, and 11.7%, respectively, all *p* < 0.001). An elevated BP was found in 9.0% of participants, with no significant difference between genders. About half of children consumed Western (51.9%) and Chinese (43.6%) fast food during the past 3 months. Children with elementary school or below maternal education level were 49% more likely to consume Western fast food (OR and 95% CI 1.49 [1.10–2.03]) than children with college or above maternal education level. Chinese fast food consumption (FFC) rate increased by 12% with each year of child's age (OR and 95% CI 1.12 [1.02–1.23]). No significant associations between FFC and health outcomes were detected. Adjusting for Western FFC, children with lower maternal education were 71 and 43% more likely to have obesity and central obesity (ORs and 95% CIs 1.71 [1.12–2.61] and 1.43 [1.00–2.03], respectively), and maternal body mass index was positively associated with child obesity, central obesity, and hypertension (ORs and 95% CIs 1.11 [1.06–1.17], 1.12 [1.07–1.17], and 1.09 [1.03–1.15], respectively). Results were similar when Chinese FFC was adjusted.

Conclusions: The prevalence of obesity and hypertension and FFC is high in children from large cities in China. The obesity prevalence was much higher in boys, and the FFC and hypertension prevalence was higher in older children. Maternal factors affect child FFC and health outcomes: children of mothers with low education were more likely to consume FF, and with the increase in maternal BMI, children were more likely to be obese and/or have hypertension. Associations between FFC and obesity, central obesity, and hypertension were not detected.

| Comments | This well-designed study presents confirmatory data on childhood obesity from a rather small sample of elementary and high school children from 4 large Chinese cities. Interestingly, higher maternal education and lower maternal BMI seem to be protective in this cohort, indicating a strong social influence on the prevalence of obesity. The study has several limitations. Quite controversially, neither Western nor Chinese FFC was associated with child BMI. These may be due to the cross-sectional design of the study, which cannot assess causality. Additionally, FF bought from supermarket and ate at home was not detected, as modified food frequency questionnaires to estimate FFC instead of full 24 dietary recall was used. Also, the amount of FF or the percentage of total daily calories from FF was not captured. Therefore, the results must be interpreted with caution and cannot be generalized to the Chinese or other populations. |

Sweetened beverage intake in association to energy and sugar consumption and cardiometabolic markers in children

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Background: Sugar-sweetened beverages (SSBs) are major contributors of sugar and energy intake, providing 39% of total sugar intake in the US population, which is especially high in children and adolescents. Artificially sweetened beverages (ASBs) are publicized as healthier alternatives to SSBs for reducing sugar intake, but their effects on weight control and glycemia are controversial. The aims of this study were to investigate in a nationally representative sample of UK children and adolescents the associations between SSB and ASB consumption and: (a) energy and sugar intake, overall and from solid foods and beverages separately, and (b) body mass index (BMI), waist-to-hip ratio, blood glucose, and blood lipids.

Methods: Data from the National Diet and Nutrition Survey Rolling Program years 1–4 (2008/2009–2011/2012) were used. The sample of 1,687 children aged 4–18 years was randomly drawn from the UK Postcode Address File (56% response rate). Each participant or their guardian took part in a computer-assisted personal interview, completed a 4-day food diary, including weekends and weekdays, and had their weight and height measured. Two to 4 months later, all participants had a visit from a trained nurse collecting more detailed physical measurements and blood samples. Physical activity was assessed using an accelerometer for 7 days in children aged 4–15 years, and a self-completion physical activity questionnaire was used for children ≥16 years. Linear regression was used to examine the associations between SSBs, ASBs, energy and sugar, overall and from solid foods and beverages, and BMI, waist-to-hip ratio and blood parameters. Fixed effects linear regression tested within-person associations with energy and sugar.

Results: Several variables had incomplete data: income (13%), physical activity (47%), BMI (4%), waist-to-hip ratio (62%), glucose (76%), hemoglobin A1c (HbA1c), triglycerides, and total and HDL cholesterols (72%). About 43% of children consumed both SSBs and ASBs, while only 10% of participants did not consume any sweetened beverages (those from higher income group and consuming takeaway meals less frequently). Thirty percent of the children were consuming only SSBs (311.9 g/day) and 18% only ASBs (351.4 g/day). Compared with SSB consumers, ASB consumers were more likely to be younger and white, half were girls. Consumption of SSBs was associated with higher intakes of energy from beverages (91 kcal; 95% CI 54–129), overall sugar (6.1%; 95% CI 4.2–8.1), and sugar from beverages (5.4%; 95% CI 3.8–6.9) compared with non-consumers. Consumption of ASB was not associated with statistically significant higher overall sugar intake (1.4%; 95% CI 0.4–3.3), but ASB consumption was associated with higher sugar from solid foods (1.7%; 95% CI 0.5–2.9). Sensitivity analyses excluding children with obesity or on a weight loss diet attenuated the associations between ASBs and sugar from solid foods (1.3%; 95% CI 0.1–2.7), suggesting possible reverse causation. Comparing a day of non-consumption to a day of SSB consumption was associated with higher intakes of energy from all sources (89 kcal; 41, 138 for solid foods and 127 kcal; 107, 146 for beverages) and higher intakes of sugar overall (7.0%; 6.2, 7.8) and from beverages (7.4%; 6.8, 8.1). Comparing a day of non-consumption to a day of ASB consumption was associated with lower energy from beverages (–33 kcal; –54, –12), total sugar (–1.0%; –1.8, –0.1), and sugar from beverages (–1.0%; –1.7, –0.3). Adjusting for juice consumption attenuated these associations (e.g., for total sugar: –0.4%; –1.1, 0.4). SSB and ASB consumption was associated with higher glucose levels compared with non-consumption, also after correcting for energy and energy-adjusted food groups and BMI (SSB: 0.30 mmol/L; 0.11, 0.49 and ASB: 0.24 mmol/L; 0.06, 0.43).

Consumption of SSBs was associated with higher triglyceride levels (0.29 mmol/L; 0.13, 0.46), although associations were attenuated after adjustment for BMI (0.15 mmol/L; 0.00, 0.31). HbA1c, total cholesterol, and HDL cholesterol were not associated with SSB or ASB consumption.

Conclusions: The results confirm that reducing the SSB consumption should be a priority: the large effect size of the SSB and sugar intake association indicate that, in addition to social marketing and education techniques, more powerful actions are needed. SSBs contributed towards higher total sugar intake, while ASBs did not. However, both SSBs and ASBs were related to a less healthy cardiometabolic profile, indicating that minimizing the consumption of sweetened drinks and replacing them with unsweetened alternatives may represent the optimal strategy.

Comments	This study confirms the absolute priority of reducing the SSB consumption in an attempt to reduce the sugar intake, as suggested by several international and national guidelines. The data are cross-sectional and reverse causality cannot be ruled out. The time between collection of diaries and blood samples was at least 8 weeks, therefore comparisons between blood measurements and diet did not reveal a direct effect. Similarly, BMI cannot be explained by the 4-day food diary data, which could explain the lack of association between SSBs and BMI, contrary to the majority of the current literature. Moreover, the population number was quite small in some of the analyses due to missing values, particularly in the cardiometabolic and blood measurements data. Therefore, despite some possible detrimental consequences of ASB consumption, that were due to small numbers not clearly demonstrated in this study and were inferior in magnitude compared to SSB consumption, the focus should remain on reducing the consumption of SSB and sugar from other sources, including "natural" juices.

Sugar intake by type (added vs. naturally occurring) and physical form (liquid vs. solid) and its varying association with children's body weight, NHANES 2009–2014

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Background: Dietary guidelines discourage the consumption of sugar-sweetened beverages (SSBs), which tend to be high in glucose and fructose, and have been linked to excess energy intake, obesity, and heart disease risk. The consumption of whole fruits, many of which are also high in glucose and fructose, is encouraged for their fiber, vitamins, and minerals. Limits on consuming these same fruits in beverage form are advised given that fruit juices lack much of the whole fruit's beneficial fiber. On the contrary, lactose-containing dairy beverages are encouraged given the important nutrient they contain, particularly calcium. The contribution made to the total sugar intake and how the different types and forms of sugar associate with body weight is unclear.

The aim of this study was to describe the sugar intake among U.S. children, specifically to estimate the proportion, by age and weight status group, that is consumed as added sugars (AS) versus naturally occurring sugars (NOS) and form (solid versus liquid), and to determine if the independent association with children's weight varies by the type and form of sugars consumed.

Methods: Data, collected from children (*n* = 8,136) aged 2–19 years enrolled in the 2009–2014 cycles of National Health and Nutrition Examination Survey, were used for this study.

Cross-sectional dietary data (2 24-h recalls) from children were used to estimate the amount of each type and form of sugar by age and weight status. Linear regression models tested trends and the multivariate adjusted association between the different sugars and weight status.

Results: The mean age of participants was 10.6 years; 54.7% of them were non-Hispanic white.

The mean intake of total sugar, AS, and NOS was 118.1, 71.5, and 46.7 g, representing 25.3, 14.8, and 10.5% of the total energy consumed. Most sugars consumed were AS (57.3%). Nearly half of sugars were consumed as liquids. Non-dairy SSBs and 100% fruit juice contributed 6.0 and 2.4% of total energy, respectively.

Each % total energy increase from AS in non-dairy beverages was associated with a BMIz increase of +0.01 and each % total energy from AS in non-dairy foods was associated with a BMIz decrease of −0.03.

Conclusions: Dietary sugars contribute to a large proportion of the calories consumed by U.S. children, and the sugars consumed tend to be added rather than naturally occurring and consumed in beverages rather than foods. Heavier children consumed more of their total energy as AS in SSBs and less as AS in sugar-sweetened foods than their normal weight counterparts.

Comments	Previous studies reported that high intake of AS beverages in children is associated with poor eating habits and inadequate nutrient intake, as well as increased risk for developing childhood obesity [19, 20]. More than one-quarter of the calories children consume every day comes from sugars, most of which are added to foods and beverages rather than naturally occurring.
	Studies examining the role of satiety in weight control suggest that liquid calories are less likely to be compensated for, leading to an increased risk of overconsumption.
	The current study strengths include: the availability of demographic data and dietary data describing 2 full day's intake that allowed to examine sugar intake patterns as a proportion of total daily energy intake across multiple subgroups. Availability of data on race/ethnicity, income, age, sex, physical activity, and other dietary factors allowed to control for these potentially important confounding factors in the examination of sugar intake and weight status. Also, the availability of measured heights and weights provided a reliable and valid estimate of weight status.
	The study limitations include: the use of self-reported data, that can be biased by the type of recall and response that may differ by the weight status groups. In addition, the use of cross-sectional data that provide exposure and outcome data at a single time point limits the ability to make causal inferences about the form and types of sugar consumed and risk of obesity. Finally, we cannot be sure that this data that is relevant for the US children can be generalized to other populations.

Fructose replacement of glucose or sucrose in food or beverages lowers postprandial glucose and insulin without raising triglycerides: a systematic review and meta-analysis

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Background: In prediabetic and diabetic conditions, trauma on pancreatic beta-cells from high postprandial blood glucose concentrations may exacerbate oxidative stress and accelerate the evolution of type 2 diabetes. Conflicting data exist on the effects of fructose consumption in people with types 1 and 2 diabetes. No systematic review has addressed the effect of isoenergetic fructose replacement of glucose or sucrose on peak postprandial glucose, insulin, and triglyceride concentrations. Therefore, these were the aims of the present study.

Methods: The Cochrane Library, MEDLINE, EMBASE, the WHO International Clinical Trials Registry Platform Search Portal, and clinicaltrials.gov were searched till end of April 2016 for randomized controlled trials (RCTs) reporting peak postprandial glycemia after isoenergetic replacement of glucose, sucrose, or both with fructose in adults or children with or without diabetes. The risk of bias was assessed in all included studies. All procedures were performed by independent investigators. The main outcomes were peak postprandial blood glucose, insulin, and triglyceride concentrations. A random-effects model was used because the studies used different populations, different doses, and different food vehicles.

Results: From 154 full-text RCTs, 47 were included in the meta-analysis. Replacement of either glucose or sucrose by fructose resulted in significantly lowered peak postprandial blood glucose (–2.34 mmol/L [95% CI –2.62 to –2.06 mmol/L]), particularly in people with prediabetes and types 1 and 2 diabetes (type 2 diabetes: –4.66 mmol/L [95% CI –5.84 to –3.47 mmol/L], $p < 0.0001$ compared to those with normoglycemia). Both sugar replacements were associated with highly significant reductions in the blood glucose AUC (glucose replacement: $p < 0.00001$; sucrose replacement: $p = 0.003$). Similar results were obtained for insulin concentrations: in normoglycemic populations, the reduction in peak postprandial insulin was –45.15 IU/mL (95% CI –52.76 to –37.53 IU/mL), and in populations with impaired glucose tolerance the reduction in postprandial insulin was –60.13 IU/mL (95% CI –72.64 to –47.62 IU/mL); $p = 0.04$ compared to normoglycemic population. Peak postprandial blood triglyceride concentrations did not significantly increase.

Conclusions: This meta-analysis provided evidence that substituting glucose or sucrose with fructose in food or beverages lowered the peak postprandial blood glucose and insulin concentrations. This isoenergetic replacement did not result in a significant increase in blood triglyceride concentrations.

Comments	Results of this pedantically conducted meta-analysis look persuasive. Interestingly, the authors do not even mention the other side of the coin: as a result of its unique metabolic properties, fructose may be harmful, particularly to the liver. Diets high in fructose were associated with all of the key features of the metabolic syndrome [21]. A more balanced view may be difficult to compose as several reports seem to provide contradictive data. It may be that if the isoenergetic replacement of simple sugars by fructose does not result in an excessive daily fructose consumption, its meta-

Discouraging soft drink consumption reduces blood glucose and cholesterol of Brazilian elementary students: secondary analysis of a randomized controlled trial

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Background: Sugar-sweetened beverages (SSB) consumption that includes all beverages with added sugars, such as soft drinks, fruit juices, sport drinks, energy drinks, and tea, milk- and soya-based drinks, is higher in Latin America and the Caribbean. In 2005, a randomized controlled trial conducted in 7–12 year old children from Rio de Janeiro showed that reduction in soft drinks consumption significantly decreased their body mass index. This study investigated the influence of this same intervention on blood glucose and total cholesterol change from baseline to end of the 6 months follow-up.

Methods: A total of 478 children (238 in intervention and 240 in control group) had blood samples collected at either baseline or follow-up and were included in the analysis. Biochemical data for both baseline and the end of follow-up had 153 (64.3%) children in the intervention and 157 (65.4%) in the control group.

Results: Frequency of children who consumed soft drink at least once a day was higher among those with no blood samples (22.9%) compared to those with at least one blood sample (16.5%). At the end of follow-up, statistically significant differences in mean changes between intervention and control groups for both fasting glucose (–9.12 vs.+0.51 mg/dL; $p < 0.001$) and total cholesterol (–10.34 vs. +2.14 mg/dL; $p < 0.001$) was observed. A decrease in the prevalence of high glucose levels was detected in the intervention group (from 12.9 to 10.5%), with a concomitant increase in the control group (from 11.0 to 19.8%; $p = 0.04$ between groups). The prevalence of hypercholesterolemia decreased (from 39.1 to 29.1%) in the intervention group, and increased in the control group (from 26.0 to 28.7%; $p = 0.03$ between groups).

Conclusions: Reducing soft drink consumption among school children resulted in a decrease in both fasting glucose and total cholesterol in this RCT, suggesting that sweetened beverages may play a role in the progression of cardiometabolic risks in childhood.

Comments The importance of this study, which otherwise corroborate results from many observational studies, lies in the randomized controlled experimental design. Several confounders in observational studies often do not allow for clear separate analysis of the

effects of SSB consumption on metabolic risks. Clear-cut results from this and some other pediatric RCTs should serve as solid evidence for policy makers. Interestingly, a recent secondary analysis of another large pediatric RCT showed that healthy Dietary Approach to Stop Hypertension diet failed to modify the risk of dyslipidemia in adolescents [22]. The SSB consumption may therefore represent a considerably stronger risk, independent of the diet. The real challenge of course remains finding a successful strategy for long-term implementation of reducing daily SSB consumption in school children, particularly in socially underprivileged environments.

Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies

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Background: Nonnutritive sweeteners, such as aspartame, sucralose, and stevioside, are consumed by up to 30% of Western populations, yet their long-term health impact is unclear. A previous meta-analysis reported inconsistent evidence: randomized controlled trials (RCTs) indicated potential benefits (modest weight loss), whereas observational studies showed a small but significant association with increased body mass index (BMI). The present study combined evidence from prospective studies to determine whether routine consumption of nonnutritive sweeteners was associated with long-term adverse cardiometabolic effects.

Methods: MEDLINE, Embase, and Cochrane Library (inception to January 2016) were searched for RCTs testing nonnutritive sweeteners, and prospective cohort studies reporting on consumption of nonnutritive sweeteners among adolescents and adults. The primary outcome was BMI. Secondary outcomes included weight, obesity, and other cardiometabolic end points.

Results: Seven RCTs (1,003 participants; median follow-up 6 months) and 30 cohort studies (405,907 participants; median follow-up 10 years) were selected from 938 full-text studies and 11,774 citations. RCTs meta-analysis showed nonnutritive sweeteners had no significant effect on BMI (mean difference –0.37 kg/m^2; 95% CI –1.10 to 0.36; I^2 9%; 242 participants). No consistent effects on other reported measures of body composition were detected. Cohort studies meta-analysis demonstrated a modest increase in BMI (mean correlation 0.05, 95% CI 0.03–0.06; I^2 0%; 21,256 participants) associated with consumption of nonnutritive sweeteners. Additionally, it was associated with increases in weight and waist circumference, and higher incidence of obesity, hypertension, metabolic syndrome, type 2 diabetes, and cardiovascular events. Publication bias was indicated for studies with diabetes as an outcome.

Conclusions: Evidence from small RCTs with short follow-up (median 6 months) implicated that consumption of nonnutritive sweeteners was not consistently associated with decreases in body weight, BMI or waist circumference. In larger prospective cohort studies with longer follow-up periods (median 10 years), intake of nonnutritive sweeteners was significantly associated with modest long-term increases in each of these measures. Furthermore, consumption of nonnutritive sweet-

eners was associated with higher risks of obesity, hypertension, metabolic syndrome, type 2 diabetes, stroke and cardiovascular disease events; however, publication bias was indicated for type 2 diabetes. There are no data available from RCTs to confirm these observations.

Comments	This meta-analysis is well designed and conducted but the source data sets, particularly from the cohort studies, had several limitations. Observational cohort studies are also subject to confounding bias, particularly when the exposure (e.g., nonnutritive sweeteners) is a potential "treatment" for the outcomes under investigation. Consuming nonnutritive sweeteners on a regular basis may indicate a specific nutritional pattern with several associated poor food choices and sedentary life-style. Therefore, the observed associations in the prospective cohort studies cannot demonstrate causality between nonnutritive sweeteners consumption and an increase in BMI, other parameters of metabolic syndrome, and adverse cardiometabolic outcomes. Therefore, such meta-analyses, despite the best possible design and meticulous conduct, may add to the confusion related to the use of nonnutritive sweeteners rather than give firm answers. A sufficiently powered, multicenter, independent RCT of adequate duration is the only way to resolve the controversies.

The Intestinal Microbiota and their Relation to Metabolic Programming

Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity

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Background: The gut microbiota through a symbiotic relationship with the host, play a role in maintaining health and metabolic homeostasis, including the production of a diverse array of metabolites. Dysbiosis is associated with the promotion or aggravation of chronic metabolic diseases, as obesity and type 2 diabetes.
One trigger for metabolic disease relates to the gut microbiota's role whereby elevated circulating lipopolysaccharide (LPS), exacerbated by a high-fat or high-fructose diet, induces a low-grade inflammatory state.
The aim was to assess the effect of prebiotic supplementation on gut microbiota, fecal bile acids (FBA), and associated metabolic outcomes (body composition, serum inflammatory markers, lipid profile, and fasting glucose and insulin concentrations) in healthy children with overweight and obesity. The primary outcome was a change in the percentage of body fat from baseline to the end of the study.
Methods: This was a single-center, double-blind, placebo-controlled trial that included healthy children, 7–12 years old, with overweight or obesity (>85th percentile of body mass index). Par-

ticipants were randomly assigned to groups given either oligofructose-enriched inulin (OI; 8 g/day; $n = 22$) or maltodextrin placebo (isocaloric dose, controls; $n = 20$) once daily for 16 weeks.

Height, weight, and waist circumference were measured at baseline and every 4 weeks thereafter. Fat mass and lean mass were measured using dual-energy-X-ray absorptiometry.

Blood samples for lipids, cytokines, lipopolysaccharide, and insulin and fecal samples were collected at baseline and at 16 weeks. Bile acids were profiled using high-performance liquid chromatography, and the composition of the microbiota was analyzed by 16S rRNA sequencing and quantitative polymerase chain reaction (PCR).

Results: A total of 38 children, 20 in the prebiotic group and 18 in the control group, completed the study (90% retention), without significant differences in baseline characteristics between the groups.

After 16 weeks, children who consumed OI had significant decreases in body weight z-score (–3.1%), percent body fat (–2.4%), and percent trunk fat (–3.8%) compared to children given placebo (increase of 0.5%, increase of 0.05%, and –0.3%, respectively). Children who consumed OI had a significant reduction in serum triglycerides (–19%), and in interleukin (IL)-6 level from baseline (–15%) compared to the placebo group (increase of 25%).

Quantitative PCR showed a significant increase in *Bifidobacterium* spp. in the OI group compared to controls, with significant increases in species of the genus *Bifidobacterium* and decreases in *Bacteroides vulgatus* within the group who consumed OI revealed by 16S rRNA sequencing. In fecal samples, levels of primary bile acids increased in the placebo group but not in the OI group over the 16-week study period.

Conclusions: Supplementation with prebiotic improved obesity outcomes and serum level of IL-6 in children with overweight/obesity, with induction of specific gut bacterial shifts compared to placebo.

| Comments | As recently discovered, one of the most important risk factors affecting obesity is the influence of the gut microbiome [23]. Gut microbes ferment non-digestible polysaccharides, thereby producing short-chain fatty acids (SCFAs), which bind to receptors on gut epithelial cells and stimulate peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) production (1). PYY and GLP-1 are gut-derived hormones that attenuate gut motility and facilitate the aggregation of the constitutive flora to ferment more polysaccharides. These gut hormones also suppress appetite by delaying gastric emptying and centrally promoting satiation [24]. SCFAs also promote gut barrier integrity and antagonize local and systemic inflammations, which drive insulin resistance and lipogenesis [25]. Gut microbiota regulate energy metabolism by downregulating the expression of fasting-induced adipocyte factor from gut epithelial cells, thus resulting in the degradation of lipoproteins and the deposition of free fatty acids in adipose tissues [26]. |

The ability to engineer a favorable metabolic environment by dietary modulation makes the gut microbiome an attractive target in the treatment of obesity [27, 28]. Dietary modulation of the gut microbiome includes 3 kinds of foods: prebiotics, probiotics, and synbiotics. Prebiotics are nonviable food components associated with the favorable modulation of the gut microbiota, such as inulin, fructo-oligosaccharides, galacto-oligosaccharides, resistant starch, xylo-oligosaccharides, and arabinoxylan-oligosaccharides [29]. Probiotics are living microorganisms, such as Lactobacillus and Bifidobacterium, which, when ingested, provide health benefits, either directly or through interactions with the host or other microorganisms [30]. The combination of pre- and probiotics has been termed synbiotics.

A previous systematic review of the literature and a meta-analysis to assess the impact of prebiotics, probiotics, and synbiotics on body weight, body mass index (BMI), and

fat mass in adult human subjects showed that when the utilization of gut microbiome-modulating dietary agents was compared to placebo, there were significant decreases in BMI, weight, and fat mass [31].

The current study was the first randomized controlled study to assess the changes in gut microbial composition and FBAs with prebiotic intervention in children with overweight and obesity. The current study demonstrated that supplementation with prebiotic improved obesity outcomes in children with overweight/obesity, by induction of specific gut bacterial shifts compared with placebo.

The study limitations include: the small sample size of participants, inclusion of healthy overweight/obese children without metabolic dysfunction, and reduced generalizability of the findings because of the inclusion of middle-high socioeconomic status of the participants.

Prebiotics are inexpensive and non-invasive and, therefore, a plausible dietary intervention in the overweight and obese pediatric population.

The metabolic and microbial findings from this study provide a basis for larger clinical trials in the pediatric population to identify the ideal dose and duration of supplementation and to assess the durability of this effect.

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Term and Preterm Infants

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Introduction

It is well known that nutrition is fundamental not only for good health, growth and development during the early years of life, but it may have effects also on children's future growth as well as on their cognitive development. It is, therefore, of paramount importance to give children optimal nutrition during their early years.

In this chapter, we focus on 16 articles that shed light on the issue of feeding preterm and term infants. We hope the readers will find the comments interesting and that it will encourage them to further explore this field of feeding infants during the first months of their life.

Key articles reviewed for the chapter

Term infants

Prebiotics for the prevention of allergies: a systematic review and meta-analysis of randomized controlled trials

Cuello-Garcia C, Fiocchi A, Pawankar R, Yepes-Nunez JJ, Morgano GP, Zhang Y, Agarwal A, Gandhi S, Terracciano L, Schünemann HJ, Brozek JL

Clin Exp Allergy 2017; 47: 1468–1477

Infant formulae supplemented with prebiotics: are they better than unsupplemented formulae? An updated systematic review

Skorka A, Piescik-Lech M, Kołodziej M, Szajewska H

Br J Nutr 2018; 119: 8108–8125

Lactobacillus reuteri to treat infant colic: a meta-analysis

Sung V, D'Amico F, Cabana MD, Chau K, Koren G, Savino F, Szajewska H, Deshpande G, Dupont C, Indrio F, Mentula S, Partty A, Tancredi D

Pediatrics 2018; 141:e20171811

Young child formula: a position paper by the ESPGHAN committee on nutrition

Bell KA, Hojsak I, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, Hulst J, Indrio F, Lapillonne A, Mølgaard C, Vora R, Fewtrell M; ESPGHAN Committee on Nutrition

J Pediatr Gastroenterol Nutr 2018; 66: 177–185

Effect of a baby-led approach to complementary feeding on infant growth and overweight. A randomized clinical trial

Taylor RW, Williams SM, Fangupo LJ, Wheeler BJ, Taylor BJ, Daniels L, Fleming EA, McArthur J, Morison B, Erickson LW, Davies RC, Bacchus S, Cameron SL, Heath ALM

JAMA Pediatr 2017; 171: 838–846

Effect of hydrolyzed infant formula vs conventional formula on risk of type 1 diabetes. The TRIGR randomized clinical trial

Writing Group for the TRIGR Study Group; Knip M, Akerblom HK, Al Taji E; Becker D Bruining J, Castano L, Danne T, de Beaufort C, Dosch H-M, Dupre J, Fraser WD, Howard N, Ilonen J, Konrad D, Kordonouri O, Krischer JP, Lawson ML, Ludvigsson J, Madacsy L, Mahon JL, Ormisson A, Palmer JP, Pozzilli P, Savilahti E, Serrano-Rios M, Songini M, Taback S, Vaarala O, White NH, Virtanen SM, Wasikowa R

JAMA 2018; 319: 38–48

Modes of infant feeding and the risk of childhood asthma: a prospective birth cohort study

Klopp A, Vehling L, Becker AB, Subbarao P, Mandhane PJ, Turvey SE, Lefebvre DL, Sears MR, the CHILD Study Investigators, Azad MB

J Pediatr 2017; 190: 192–199

Associations of infant feeding with trajectories of body composition and growth

Bell KA, Wagner CL, Feldman HA, Shypailo RJ, Belfort MB

Am J Clin Nutr 2017; 106: 491–498

Preterm Infants

Growth

Head growth trajectory and neurodevelopmental outcomes in preterm neonates

Raghuram K, Yang J, Church PT, Cieslak Z, Synnes A, Mukerji A, Shah PS for the Canadian Neonatal Network; Canadian Neonatal Follow-Up Network Investigators

Pediatrics 2017; 140:e20170216

Parenteral Nutrition

Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: a randomized controlled trial

Najm S, Löfqvist C, Hellgren G, Engström E, Lundgren P, Hård AL, Lapillonne A, Sävman K, Nilsson AK, Andersson MX, Smith LEH, Hellström A

Clin Nutr ESPEN 2017; 20: 17–23

Human Milk

A systematic review and meta-a of human milk feeding and morbidity in very low birth weight infants

Miller J, Tonkin E, Damarell RA, McPhee AJ, Suganuma M, Suganuma H, Middleton PF, Makrides M, Collins CT

Nutrients 2018; 10:E707

Exosomal microRNAs in milk from mothers delivering preterm infants survive in vitro digestion and are taken up by human intestinal cells

Kahn S, Liao Y, Du X, Xu W, Li J, Lönnerdal B

Mol Nutr Food Res 2018; 62:e1701050

Cost-effectiveness of supplemental donor milk versus formula for very low birth weight infants

Trang S, Zupancic JAF, Unger S, Kiss A, Bando N, Wong S, Gibbins S, O'Connor DL; GTA DoMINO Feeding Group

Pediatrics 2018; 141:pii:e20170737

Miscellaneous

Early energy and protein intakes and associations with growth, BPD, and ROP in extremely preterm infants

Klevebro S, Westin V, Stoltz Sjöström E, Norman M, Domellöf M, Edstedt Bonamy AK, Hallberg B

Clin Nutr 2018;pii:S0261-5614(18)30197-3. https://doi.org/10.1016/j.clnu.2018.05.012

The impact of routine evaluation of gastric residual volumes on the time to achieve full enteral feeding in preterm infants

Riskin A, Cohen K, Kugelman A, Toropine A, Said W, Bader D

J Pediatr 2017; 189: 128–134

Nutritional strategies and gut microbiota composition as risk factors for necrotizing enterocolitis in very-preterm infants

Rozé JC, Ancel PY, Lepage P, Martin-Marchand L, Al Nabhani Z, Delannoy J, Picaud JC, Lapillonne A, Aires J, Durox M, Darmaun D, Neu J, Butel MJ for the Nutrition EPIPAGE 2 study group and the EPIFLORE Study Group

Am J Clin Nutr 2017; 106: 821–830

Term Infants

Prebiotics for the prevention of allergies: a systematic review and meta-analysis of randomized controlled trials

Cuello-Garcia C[1], Fiocchi A[2], Pawankar R[3], Yepes-Nunez JJ[1,4], Morgano GP[1], Zhang Y[1], Agarwal A[5], Gandhi S[5], Terracciano L[6], Schünemann HJ[1], Brozek JL[1]

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Clin Exp Allergy 2017;47:1468–1477

Background: Allergies are a major health problem for patients and an important economic burden for health care systems. The prevalence of various allergies ranges between 2 and 40%. Current evidence shows that gut microbiota is involved in the modulation of immune response in early life. Therefore, interventions that alter the microbiota (e.g., probiotics or prebiotics) have been suggested as preventive strategies. Supplementation of prebiotics has been regarded as a promising intervention for the prevention of allergies. The aim of the study was to assess the impact of supplementing prebiotics on the development of allergy among pregnant or lactating women and in infants.
Methods: A systematic review of studies assessing the effects of prebiotic supplementation with an intention to prevent the development of allergy was performed.
Results: Out of 446 records published in Cochrane, MEDLINE, and EMBASE until November 2016, 22 studies fulfilled a priori specified criteria. There were no studies of prebiotics given to pregnant or lactating women. Three studies assessed infants at high risk of allergy, 16 with average risk, while 3 did not provide enough information. Most studies (19 of 22) used fructo-oligosaccharides (FOS) with galacto-oligosaccharides (GOS) while three studies used a combination of inulin and polydextrose with FOS/GOS. The included studies used formula ($n = 16$), hypoallergenic formula ($n = 3$), cereal ($n = 2$), or capsule ($n = 1$) to deliver prebiotics. Prebiotic supple-

mentation in infants, compared to placebo, had the following effects: risk of developing eczema (RR 0.68, 95% CI 0.40–1.15), wheezing/asthma (RR 0.37; 95% CI 0.17–0.80), and food allergy (RR 0.28, 95% CI 0.08–1.00). There was no increased risk of adverse effects (RR 1.01, 95% CI 0.92–1.10). Prebiotic supplementation had little influence on the growth rate (MD: 0.92 g per day faster with prebiotics, 95% CI 0–1.84) and the final infant weight (MD: 100 g higher with prebiotics, 95% CI 90–290).

Conclusion: The current evidence from randomized trials shows a possible effect of prebiotic supplementation in infants on the reduction in the risk of asthma or wheezing. However, the certainty of that effect is very low. Additional randomized trials are likely to substantially contribute the certainty of the effects.

Comments	There is ongoing controversy as to whether the addition of prebiotics to infant foods may decrease the risk of allergic diseases/disorders [1]. This paper summarizes the available evidence. No conclusion can be drawn on the use of prebiotics in pregnant or lactating women due to the lack of studies. There was insufficient evidence from randomized or observational studies to support a beneficial effect of prebiotics in infants. There was some evidence suggesting that prebiotics may reduce the risk of recurrent wheezing in infants; however, the certainty of these estimates is very low due to risk of bias, indirectness of the evidence, and imprecision of the results due to the low number of events.
	Randomized clinical trials did not show an increased risk of adverse effects of prebiotics when compared to placebo. Nutritional status as the composite of the final weight at 12 months, mean weight gain, or the adjusted increase in weight from baseline improved at one to 12 months of follow-up. However, the difference was unlikely to be biologically relevant (differences of a few grams between groups in most studies). The authors mention the limitations of their review, emphasizing that 18 of the 22 studies (82%) were funded by the manufacturer and that the populations studied were mostly infants who were not breastfed. Therefore, the results might be different in other settings where breastfeeding is common.
	To summarize, this systematic review and meta-analysis are very much welcome when communication from the industry on infant formula supplemented with prebiotics is likely to suggest health care providers and parents that some prebiotics are able to decrease the risk of developing allergy in at-risk infants. This paper allows to conclude that is currently not the case.

Infant formulae supplemented with prebiotics: are they better than unsupplemented formulae? An updated systematic review

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Background: In 2011, the Committee on Nutrition (CoN) of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) reviewed published evidence related to the safety and health effects of the administration of formula supplemented with pro- and/or prebiotics, and concluded that there was no evidence to support the routine use of prebiotic-supplemented formulae in infants. The aim of this review was to update the evidence on the effects of the

administration of prebiotic-supplemented infant formulae (IF), and to find out whether there was a need to revise the current recommendations.

Methods: A search of 5 databases (Cochrane Library, MEDLINE, EMBASE, Web of science and CINAHL) for randomized controlled trials (RCTs) up to March 2017 was done.

Results: A total of 41 publications were identified, including 25 new publications. Giving currently evaluated prebiotic supplemented formulae to healthy infants does not raise safety concerns with regard to growth and adverse effects. However, some favorable clinical effects which may be beneficial in some infants are possible, such as stool softening.

Conclusion: In line with the 2011 ESPGHAN document, the available data suggest that the administration of currently prebiotic-supplemented formulae to healthy infants does not raise safety concerns with regard to growth and adverse effects. Some favorable clinical effects are possible, which may be beneficial in some infants. Nevertheless, currently, there is no existing robust evidence to recommend the routine use of prebiotic-supplemented formulae. The efficacy and safety should be considered for each prebiotic(s)-supplemented formula.

Comments	This study provides an additional piece of information on the effect of prebiotics in infants. Only RCTs were eligible for inclusion. Participants had to be healthy term infants. Only studies that compared infant formula or follow-on formula supplemented with prebiotics (with prebiotic specification) during the manufacturing process with unsupplemented formula were included. Studies in which prebiotics were not administered during the manufacturing process, but thereafter, for example, in capsules, the contents of which were supplemented to infant formula or feeds, were not considered. Studies in which synthetic human milk oligosaccharides were used were also excluded as well as trials evaluating fermented, acidified, and partially or extensively hydrolyzed formulae supplemented with prebiotics. The studies varied in the types of prebiotics used. As previously reported by the ESPGHAN CoN [2], the most commonly studied prebiotic was a 9:1 mixture of short-chain galacto-oligosaccharides (GOS) and long-chain fructo-oligosaccharides (FOS; GOS/FOS). There were many other prebiotics studied: (a) GOS; (b) acidic oligosaccharides (AOS); (c) FOS; (d) GOS/FOS/AOS; (e) oligofructose plus inulin (SYN-1); and (g) polydextrose (PDX) plus GOS with lactulose (PDX + GOS + LOS) or without lactulose (PDX + GOS). The doses of prebiotics ranged from 0.1 to 0.8 g/100 mL, and the duration of the intervention ranged from 2 weeks to 12 months. All but 5 RCTs reported the prebiotic supplementation of an infant formula. In these 5 trials, prebiotics were used to supplement follow-on formula. The quality of the included RCTs varied. Almost all of the included trials had a number of methodological limitations. The most common problems were a lack of description of randomization procedures and/or allocation concealment and/or blinding. The methodological quality of the included studies was generally moderate to low, which increases the risk of bias. Some of the prebiotics were evaluated in single trials only. The included studies were likely to be underpowered for addressing some outcomes (also adverse events). An important strength of this systematic review is the use of rigorous methodology developed by the Cochrane Collaboration. The majority of included studies were industry-supported trials. It is well known that there is bias associated with study funding sources. Compared with non-industry-sponsored studies, industry-sponsored studies tend to have more favorable effectiveness and harm findings, and more favorable conclusions. Funding of research by manufacturers of IF may be considered even more controversial because of the need for protection and promotion of breast-feeding. However, in the case of studies involving infant formulae, industry involvement is unavoidable, as investigators obviously lack the means to manufacture quality infant products.

The use of prebiotic-supplemented formulae in infants can be considered as safe and is associated with adequate growth. Very few can be expected from their use with respect to clinical outcomes including gastrointestinal infections/diarrhea, respiratory infections, allergic manifestations, frequency of antibiotic treatment. In other words, they are not better than unsupplemented formulae. Prebiotic-supplemented formulae have a stool softening effect that may be of help in infants presenting with hard stools. The conclusions of this systematic review are very much in line with those of the 2011 ESPGHAN CoN paper. The same research group also concluded in a recent paper that the addition of probiotics to infant formulae was also safe with respect to growth and adverse effects but was not associated with health benefits [3].

Lactobacillus reuteri to treat infant colic: a meta-analysis

Sung V[1], D'Amico F[2,3], Cabana MD[4], Chau K[5], Koren G[5], Savino F[6], Szajewska H[7], Deshpande G[8], Dupont C[9], Indrio F[10], Mentula S[11], Partty A[12], Tancredi D[13]

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Background: Infant colic is a burdensome condition, affecting about 20% of infants <3 months old. Numerous studies have demonstrated the differences in gut microbiota between infants with and without colic. The role of probiotics in colic has come into focus with randomized controlled trials (RCTs) indicating *Lactobacillus reuteri* DSM17938 to show promise in managing colic. However, results have been conflicting. The aim of the study was to determine if *L. reuteri* DSM17938 effectively reduces crying and/or fussing time in infants with colic and whether effects vary by feeding type.
Methods: Databases (PubMed, MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature, the Database of Abstracts of Reviews of Effects, and Cochrane), e-abstracts, and clinical trial registries were used through an individual participant data meta-analysis. The analyzed data was based on double-blind RCTs (published by June 2017) of *L. reuteri* DSM17398 versus a placebo, delivered orally to infants with colic, with outcomes of infant crying and/or fussing duration and treatment success at 21 days. Individual participant raw data were collected from included studies modeled simultaneously in multi-level, generalized, linear mixed-effects regression models.
Results: Four double-blind trials involving infants with colic (174 probiotic and 171 placebo) were included. The probiotic group averaged less crying and/or fussing time than the placebo group at all time points. The probiotic group was almost twice as likely as the placebo group to experience

treatment success at all time points (day 21 adjusted incidence ratio 1.7 [95% CI 1.4–2.2]). Intervention effects were dramatic in breastfed infants (number needed to treat for day 21 success 2.6 [95% CI 2.0–3.6]) but were insignificant in formula-fed infants.

Conclusion: The pooled data suggest that *L. reuteri* DSM17938 effectively reduces crying and/or fussing in breastfed infants with colic. Although the results of this study help clarify the debate on the usefulness of *L. reuteri* DSM 17938 in improving colic symptoms in breastfed infants, its role in formula-fed infants with colic needs further clarification.

Comments   Infant colic, that is, "excessive crying" of unknown cause, is a frequent condition affecting around 20% of infants <3 months old, and management options are limited. Although infant colic usually self-resolves beyond the first 3–4 months of life, it is associated with potentially significant adverse effects, such as maternal depression, child abuse, and early cessation of breast feeding. There is also some evidence of long-term adverse outcomes, such as behavior and sleep problems. The etiology of infant colic is multifactorial and related to feeding disorders, dysmotility, hormone alterations, or behavioral factors. The differences in gut microbiota between infants with and without colic have been shown, thereby suggesting that the use of probiotics could be of help.

L. reuteri DSM 17938 is the daughter strain of *L. reuteri* ATCC 55730. The latter was originally isolated from the breast milk of a Peruvian mother, and it may be present in normal humans on the mucosa of the gastric corpus and antrum, duodenum, and ileum. *L. reuteri* strains produce reuterin, a broad-spectrum antibacterial substance, which is capable of inhibiting the growth of a wide spectrum of microorganisms such as gram-positive or negative bacteria, yeast, fungi, or parasites [4]. *L. reuteri* strains may also regulate immune responses. It was demonstrated that *L. reuteri* strain DSM 17938 improved LPS-induced intestinal morphological damage, including villus length and density and reduced intestinal inflammation in an experimental model of necrotizing enterocolitis via inhibiting a toll-like receptor-4 signaling pathway that leads to cytokine expression. *L. reuteri* has been granted GRAS (generally recognized as safe) status by FDA and QPS (qualified presumption of safety) status by EFSA.

The results of RCTs with *L. reuteri* DSM17938 were initially promising before being controversial. Three studies of breastfed infants with colic demonstrated the probiotic to be effective. In contrast, one study of both breastfed and formula-fed infants with colic, showed it was ineffective even for the breastfed infants. The main strength of this meta-analysis is the large sample size from the pooling of data from existing studies, which provides enough power to detect treatment effects and subgroup differences. All included studies were of high methodological quality. The intervention groups in all 4 studies received the same probiotic (*L. reuteri* DSM17398) manufactured by the same company in the same dose, with the control groups all receiving the same placebo (maltodextrin in oil suspension). The main limitation of the study is the use of different definitions of infant colic and measured outcomes. No conclusion could be drawn with respect to the effectiveness of the probiotic for formula-fed infants with colic because only one study included a limited number of formula-fed infants. The authors did not succeed in determining if the probiotic's effects differed according to proton pump inhibitor exposure, hypoallergenic formula exposure, or maternal dairy elimination diets. Breastfed and formula-fed infants have different gut microbiota compositions, with Bifidobacteria dominating in breastfed infants, whereas formula-fed infants have more diverse gut microbiota. The unique composition of breast milk or possibly the direct effects of microbes or oligosaccharides in breast milk may contribute to the differences in the effects of *L. reuteri* DSM17938 on breastfed as

compared with formula-fed infants with colic. The main take home message from this study is that a positive effect of an intervention in breastfed infants cannot be generalized to the whole population of infants whatever their type of feeding. Therefore, there is no evidence for advising parents and health care providers to use a formula supplemented with *L. reuteri* DSM17938 in non-breastfed infants presenting with colic. There is no concern on the safety of the use of this probiotic in young infants.

Young child formula: a position paper by the ESPGHAN committee on nutrition

Hojsak I[1], Bronsky J[2], Campoy C[3], Domellöf M[4], Embleton N[5], Fidler Mis N[6], Hulst J[7], Indrio F[8], Lapillonne A[9], Mølgaard C[10], Vora R[11], Fewtrell M[12]; ESPGHAN Committee on Nutrition

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Background: Young child formulae (YCF) are milk-based drinks or plant protein–based formulae intended to partially satisfy the nutritional requirements of young children aged 1–3 years. There is no international legal definition or compositional criteria for YCF, and the composition of currently available YCFs on the European market differs significantly. The aim of this study was to perform a systematic review of the literature by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition (CoN) and to review the composition of YCF and evaluate their role in the diet of young children.
Methods: The databases MEDLINE (via PubMed) and Cochrane were searched for publications on YCF up to January 2017. The searches were limited to human studies performed in children, limited to English language manuscripts and only published data were considered. Outcomes that may identify possible beneficial effect of YCF were determined, and available data on the composition of YCF were reviewed.
Results: The article presents critical literature review on the role of YCF for nutrition in children. The review identified that YCF have a highly variable composition, which in some cases is inappropriate with very high protein and carbohydrate content and even high amounts of added sugars. Based on the available evidence, ESPGHAN CoN suggests that the nutrient composition of YCF should be similar to that of follow-on formulae with regards to energy and nutrients that may be deficient in the diets of European young children such as iron, vitamin D, and polyunsaturated fatty acids (n-3 PUFAs), whereas the protein content should aim towards the lower end of the permitted range of follow-on formulae if animal protein is used. YCF may increase intakes of vitamin D, iron, and n-3 PUFAs. However, these nutrients can also be provided via regular and/or fortified foods or supplements.
Conclusion: ESPGHAN CoN does not recommend the routine use of YCF in children from 1 to 3 years of life. They can, however, be used as part of a strategy to increase the intake of iron, vitamin

D, and polyunsaturated fatty acid and decrease the intake of protein compared with unfortified cow's milk. Follow-on formulae can be used for the same purpose.

Comments The aim of this ESPGHAN CoN position paper is to critically review the available evidence on the role of YCF for nutrition in children, to consider existing recommendations for their content, and to propose recommendations for European children. The previously so-called "growing-up milk" or "toddlers' milk" are formulae intended specifically for young children (1–3 years). There is no international legal definition or compositional criteria for these products and their availability and regulation differs between countries. No compositional criteria have been laid down in the legislation of the European Union (EU). YCF may or may not be based on milk. The European Food Safety Authority (EFSA) proposed in 2013 not to use the term "growing-up milk" because this would imply a particular effect on growth [5]. EFSA also proposed not use the term "toddlers' milk" because it considered that a young child is better defined by age. "Young-child formula" was therefore the term proposed by EFSA for formulae intended for young children. This would include also formulae based on protein sources other than cow's milk, i.e. other animal or plant protein.

YCF have been available in Europe for more than 2 decades and their use is increasing. The EFSA report published in 2013 mentioned that there were more than two hundred YCFs present in the EU market, with the highest number in France ($n = 34$), Spain ($n = 32$), and Italy ($n = 24$), and the lowest in Scandinavian countries, Sweden ($n = 2$), and Denmark ($n = 0$).

There are no published adverse effects associated with the use of YCF. The concern is the significant differences in the composition of YCF. Some of those available on the European market have a high protein content, added sweeteners, taste modifiers, and are without long-chain PUFAs. The available information on the health benefits of YCF is scarce. The main interest of YCF is to prevent the occurrence of the few nutritional deficits that have been described in Europe, that is, iron, vitamin D, n-3 PUFAs, and in some countries, iodine.

In line with the conclusions of the 2013 EFSA Scientific Opinion, ESPGHAN CoN emphasizes that YCF is one of several means to increase n-3 PUFAs, iron, vitamin D, and iodine intakes in infants and young children living in Europe with inadequate or at risk of inadequate status of these nutrients. However, other means, such as fortified cow milk, fortified cereals and cereal-based foods, supplements or the early introduction of meat and fish into complementary feeding and their continued regular consumption, are efficient alternatives to increase intakes of these nutrients. The selection of the appropriate form and vehicle through which these nutrients are provided in the diet will depend on national dietary habits, health authorities, the regulatory context, and caregivers' preferences. No unique role of YCF with respect to the provision of critical nutrients in the diet of infants and young children living in Europe can be identified, so that they cannot be considered as a necessity to satisfy the nutritional requirements of young children when compared to other foods that may be included in the normal diet of young children (such as breast milk, infant formulae, follow-on formulae, and cow's milk). Follow-on formulae can be used for the same purpose as YCF. ESPGHAN advocates the need for a specific regulation of YCF to avoid inappropriate composition. However, ESPGHAN CoN also mentions that based on the limited data, there is no evidence to recommend a composition of YCF that differs from that of follow-on formula for energy, iron, vitamin D, n-3 PUFA, whereas the protein content should aim towards the lower end of the permitted range if animal protein is used. Indeed, many member states ask the YCF manufacturers to apply to YCF the

compositional requirements for FOF laid down in the EU regulation. Finally, ESPGHAN CoN stipulates that the marketing of YCF should be separated from infant and follow-on formula and the use of similar branding (whether images or text) on these different product categories should be avoided.

Effect of a baby-led approach to complementary feeding on infant growth and overweight. A randomized clinical trial

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Background: Baby-led weaning (BLW) is an alternative approach to introducing solid foods in which infants feed themselves all their food from the start of complementary feeding. Proposed advantages include: improved energy self-regulation (ability to respond appropriately to appetite and satiety cues), leading to improved body weight, and reduced food fussiness. However, concerns have been raised that children may not eat enough, particularly if self-feeding skills are poor. The aim of this trial was to determine whether allowing infants to control their own food intake by feeding themselves solid foods using a baby-led approach to complementary feeding results in differences in body mass index (BMI) z scores and in energy self-regulation, eating behaviors (assessed with questionnaires), and energy intake (assessed with 3-day weighed diet records) at 12 and 24 months of age compared with traditional spoon-feeding.
Methods: The 2-year Baby-Led Introduction to Solids (BLISS) randomized clinical trial recruited women in late pregnancy ($n = 206$) as part of a community intervention in Dunedin, New Zealand. Women were randomized to a control condition ($n = 101$) or the BLISS intervention ($n = 105$) after stratification for parity and education. All outcomes were collected by staff blinded to group randomization, and no participants withdrew due to an adverse event. Data were analyzed based on intention to treat. Mothers in the BLISS group received lactation consultant support (≥ 5 contacts) to extend exclusive breastfeeding and delay introduction of complementary foods until 6 months of age and 3 personalized face-to-face contacts.
Results: Among the 206 participants, 166 were available for analysis at 24 months (retention, 80.5%). The mean (SD) BMI z score was not significantly different at 12 months (control group, 0.20 [0.89]; BLISS group, 0.44 [1.13]; adjusted difference, 0.21; 95% CI –0.07 to 0.48) or at 24 months (control group, 0.24 [1.01]; BLISS group, 0.39 [1.04]; adjusted difference, 0.16; 95% CI –0.13 to 0.45). At 24 months, 5 of 78 infants (6.4%) were overweight (BMI $\geq$95th percentile) in the control group compared with 9 of 87 (10.3%) in the BLISS group (relative risk, 1.8; 95% CI 0.6–5.7). Lower satiety responsiveness was observed in BLISS infants at 24 months (adjusted difference, –0.24; 95% CI –0.41 to –0.07). Parents also reported less food fussiness (adjusted difference, –0.33; 95% CI –0.51 to –0.14) and greater enjoyment of food (adjusted difference, 0.25; 95% CI, 0.07–0.43) at 12 months in BLISS infants. Estimated differences in energy intake were 13 kcal (95% CI –68 to 95 kJ) at 12 months and 34 kcal (95% CI –58 to 126) at 24 months.
Conclusion: A baby-led approach to complementary feeding does not appear to result in healthier growth or a reduced risk for overweight compared with traditional feeding practices, although some

benefits may accrue in attitudes toward food, including reduced food fussiness. Additional research is required to determine the extent to which these findings apply to infants who are using a baby-led approach without the modifications and additional support provided by the BLISS intervention.

Comments   Over the last century, tradition has been to introduce infants to solid foods using spoon-feeding of specially prepared infant foods. However, over the last 10–15 years, an alternative approach known as BLW has become more and more popular among parents. BLW is a method of introducing solid food into a baby's diet by allowing them to feed themselves family foods in their whole form, as opposed to being spoon-fed [6]. The emphasis is on allowing infants to choose what, and how much, they eat and for the infant to be part of family mealtimes. BLW is supposed to facilitate self-regulation of energy intake, and as a consequence decrease the risk of obesity. However, concerns have been raised that BLW may increase the risks for infant undernutrition and choking. Studies on BLW performed so far were only observational. Any information on the nutritional adequacy of BLW is therefore welcome. The feasibility of BLW as an approach to infant feeding can only be determined in a randomized controlled trial (RCT). The results of the BLISS RCT clearly show that BLW is safe with no group differences in energy intake, growth faltering, or iron-deficient anemia. There were also no differences in the numbers of self-limiting or more serious choking events. Nevertheless, there was no benefit of BLW on the obesity risk. More research is needed on the benefits/risks associated with BLW.

Effect of hydrolyzed infant formula vs conventional formula on risk of type 1 diabetes. The TRIGR randomized clinical trial

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Background: Accumulating evidence suggests that β-cell autoimmunity emerges early in life. Accordingly, any measure aimed at primary prevention of type 1 diabetes (T1D) has to be initiated in infancy. Epidemiological and immunological studies suggest that exposure to complex foreign proteins in early infancy may increase the risk of β-cell autoimmunity and T1D in genetically susceptible individuals. The aim of this study was to evaluate the intervention effect of weaning to an extensively hydrolyzed formula on the incidence of T1D by 11.5 years of age in the TRIGR (Trial to Reduce Insulin-Dependent Diabetes Mellitus in the Genetically at Risk) Study.

Methods: An international double-blind randomized clinical trial of infants (n = 2,159) with Human Leukocyte Antigen (HLA) disease susceptibility and a first-degree relative with T1D recruited between 2002 and 2007 in 78 study centers in 15 countries; patients were randomized to be weaned to the extensively hydrolyzed casein formula (n = 1,081) and to a conventional adapted cow's milk formula supplemented with 20% of the casein hydrolysate (n = 1,078). The primary outcome was T1D diagnosed according to WHO criteria, and secondary outcomes included: age at T1D diagnosis and safety.

Results: Among 2,159 newborn infants who were randomized, 1,744 (80.8%) completed the trial, with a median observation time of 11.5 years (quartile [Q] 1-Q3: 10.2–12.8). In this trial, weaning to a hydrolyzed formula compared with a conventional formula did not significantly decrease the cumulative incidence of T1D (8.4 vs. 7.6%). The hazard ratio for T1D adjusted for HLA risk group, duration of breastfeeding, duration of study formula consumption, sex, and region while treating study center as a random effect was 1.1 (95% CI 0.8–1.5; p = 0.46). The median age at diagnosis of T1D was similar in both groups (6.0 years [Q1–Q3, 3.1–8.9] vs. 5.8 years [Q1–Q3, 2.6–9.1]; difference, 0.2 years [95% CI –0.9 to 1.2]).

Conclusion: Weaning to a hydrolyzed formula did not reduce the risk of T1D in children with an increased risk for T1D. These findings do not support a need to revise the dietary recommendations for infants at risk for T1D.

Comments	Overt diabetes is preceded by an asymptomatic period during which diabetes-associated autoantibodies appear in the peripheral circulation as markers of emerging β-cell autoimmunity. Several disease-related autoantibodies predict the clinical manifestation of T1D: islet-cell antibodies, insulin autoantibodies, autoantibodies to glutamic acid decarboxylase, tyrosine phosphatase-related insulinoma-associated 2 molecule, and zinc transporter 8. Positivity for two or more antibodies is associated with a risk of 50–100% for the development of T1D over a 5- to 10-year period. Some epidemiological and immunological studies suggest that exposure to complex foreign proteins in early infancy, including cow's milk proteins, may increase the risk of β-cell autoimmunity in genetically susceptible individuals [7], although others do not [8]. Data from the same research group indicated that among children at increased risk for T1D, weaning to a highly hydrolyzed formula was associated with a decrease in the cumulative incidence of islet-cell antibodies and the cumulative incidence of at least one autoantibody by the age of 7.5 years. The present study is of paramount importance for health care providers interested in decreasing not only the occurrence of markers of β-cell autoimmunity but more importantly the occurrence of T1D in at risk infants. This is the first study assessing whether eliminating the exposure to foreign intact protein in the infant diet could prevent T1D in a genetically high-risk population. This trial strongly suggests that cow's milk can be acquitted of any responsibility in the development of T1D. Consequently, there is no rationale for using hydrolyzed infant formula in non-breastfed infants at risk for T1D. However, the authors underline 2 limitations of their study: (1) the results may not be valid for the general population since participants were selected based on a positive family history for T1D and an HLA genotype conferring risk for type 1 diabetes; (2) the outcome is not necessarily applicable to children with other HLA genotypes.

Modes of infant feeding and the risk of childhood asthma: a prospective birth cohort study

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Background: The importance of breastfeeding is well-recognized for infants' short-term health with respect to growth, immune function, and gastrointestinal health. Although several studies have found that breastfeeding is protective against asthma, a recent meta-analysis found that evidence for this association was inconsistent across studies, with high heterogeneity. The aim of the current study was to determine the association of infant feeding modes in the first 3 months of life with asthma development by 3 years of age.

Methods: A total of 3,296 children in the Canadian Healthy Infant Longitudinal Development birth cohort were studied. The primary exposure was infant feeding mode at 3 months, reported by mothers and categorized as direct breastfeeding only, breastfeeding with some expressed breast milk, breast milk and formula, or formula only. The primary outcome was asthma at 3 years of age, diagnosed by trained health care professionals.

Results: At 3 months of age, the distribution of feeding modes was 27% direct breastfeeding, 32% breastfeeding with some expressed breast milk, 26% breast milk and formula, and 15% formula only. At 3 years of age, 12% of children were diagnosed with possible or probable asthma. Infant feeding mode was associated significantly with possible or probable asthma diagnosis at 3 years of age. Compared with direct breastfeeding, any mode of infant feeding that included expressed milk or formula was associated with an increased risk of possible or probable asthma diagnosis. The lowest prevalence (8.8%) was observed among infants who received direct breast milk only. Prevalence was higher among infants receiving some expressed breast milk (12.5%) or breast milk and formula (14.9%), and was highest among exclusively formula-fed infants (15.8%). These associations persisted after adjusting for maternal asthma, ethnicity, method of birth, infant sex, gestational age, and daycare attendance (some expressed breast milk: aOR 1.64, 95% CI 1.12–2.39; breast milk and formula, aOR 1.73, 95% CI 1.17–2.57; formula only: aOR 2.14, 95% CI 1.37–3.35). Sensitivity analyses adjusting for frequent respiratory infections yielded similar results, while adjustment for total breastfeeding duration resulted in slightly attenuated associations.

Conclusion: Modes of infant feeding in the first 3 months of life are associated with asthma development by 3 years of age. Compared with formula feeding, direct breastfeeding seems to be most protective, whereas expressed breast milk may confer intermediate levels of protection. Further research is warranted to confirm and explain the differential effects of direct breastfeeding and expressed breast milk. Policies that facilitate and promote direct breastfeeding could have a significant impact on the primary prevention of asthma.

Comments Breastfeeding has many established health benefits, but its impact on asthma development is uncertain. While most studies have found a protective effect of breastfeeding on allergic diseases, several others have found no association or even an increased

risk of childhood asthma for subsets of individuals. Differences in methodological quality and design may account for some of these discrepancies, but it is also likely that the true association is dependent on a combination of factors which have been inconsistently assessed between studies. These include duration of breastfeeding, timing of the introduction of solids, characteristics and cultural practices of the population of interest and exact definitions including ages for the various allergic outcomes. Variations in human milk composition may also contribute to the conflicting results obtained from breastfeeding studies in different settings and populations. Human milk is complex and personalized, containing micro- and macronutrients, oligosaccharides, cytokines, enzymes, growth factors, immune cells, and microbes. There is emerging evidence that human milk fatty acids, oligosaccharides, and TGF-beta may influence immunological outcomes in breastfed infants [9]. The concentration of these and other bioactive factors in human milk is highly variable, and can be affected by multiple genetic and environmental factors that differ at the individual and population levels, including ethnicity, diet, body composition, smoking, immunization history, health status (e.g., asthma, allergies), geographic location, and method of delivery. Mechanistic studies examining human milk bioactives and their impact on lung health and asthma development are beginning to emerge, and these will be important in establishing the causality and mechanistic basis of the observed associations between breastfeeding and asthma.

The present study shows that any mode of infant feeding other than direct breastfeeding is associated with an increased likelihood of possible or probable asthma by 3 years of age. Compared with infants who received direct breast milk only, those who received some expressed milk had 43% increased odds of this diagnosis, and those who received only formula had 79% increased odds. These associations were independent of established maternal, socioeconomic, and environmental risk factors.

Although several studies have examined the association between infant feeding and asthma, this study uniquely distinguishes between direct breastfeeding and expressed breast milk. Feeding mode differences could help explain the apparently inconsistent results observed in "breastfeeding" studies across different populations and settings. It adds to recent evidence that feeding expressed breast milk is associated with increased odds of otitis media and rapid infant weight gain, compared with direct breastfeeding [10]. There are several possible explanations for the apparently differential effects of direct breastfeeding and expressed breast milk. One involves the alteration of breast milk components, such as immune cells, cytokines, and microbiota, during the expression and storage of breast milk. For example, freezing or processing human milk has been shown to diminish its antioxidative properties, decrease vitamin levels, and reduce immunoglobulin A activity. In addition to the bioactive factors in breast milk, the physical act of breastfeeding may also play a role in asthma prevention. There is increasing evidence that commensal bacteria are essential to health, and the direct skin-to-skin contact during breastfeeding provides a source of potentially protective maternal microbes to the nursing infant. Programs of breastfeeding promotion should emphasize that direct breastfeeding seems to be more appropriate than feeding expressed breast milk in a bottle, at least for optimizing the beneficial role of breastfeeding in the prevention of asthma.

Associations of infant feeding with trajectories of body composition and growth

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Background: The extent to which breastfeeding in infancy exerts a protective effect against later obesity is still a subject of much debate. Understanding the relation between breastfeeding and the accrual of adiposity during infancy may provide insight into the link between breastfeeding and a reduced risk of later-life obesity and its comorbidities. The aim of the study was to analyze differences in body composition trajectories between formula-fed and breastfed healthy infants during the first 7 months of life.

Methods: A total of 276 participants from a previous study of maternal vitamin D supplementation during lactation were studied. Mothers used monthly feeding diaries to report the extent of breastfeeding. Infants' anthropometrics were measured and dual-energy X-ray absorptiometry was used to assess the body composition at 1, 4, and 7 months. A comparison of changes in infant size (z scores for weight, length, and body mass index [BMI (in kg/m^2)]) and body composition (fat and lean mass, body fat percentage) between predominantly breastfed and formula-fed infants, adjusting in linear regression for sex, gestational age, race/ethnicity, maternal BMI, study site, and socioeconomic status was made.

Results: Among included infants in the breastfed group ($n = 214$), 149 (70%) were exclusively breastfed for 6 months, and only 28 (13%) completely discontinued breastfeeding before 6 months. No infant in the formula-fed group received any breastmilk. Most breastfed infants (87%) were occasionally fed expressed milk from a bottle. Formula-fed infants had significantly lower birth-weight z scores (mean: –0.22 vs. 0.16), were more likely to be African American or Hispanic rather than white, and were more likely to be covered by public insurance or no insurance (compared with private insurance) than were breastfed infants. Mothers of formula-fed infants had attained less education and had a higher pre-pregnancy BMI than mothers of breastfed infants. At age 7 months, formula-fed infants had weight z scores that were 0.37 U (95% CI 0.04–0.71 U) and BMI z scores that were 0.35 U (95% CI 0–0.69 U) higher than breastfed infants, although length z scores were similar between the 2 groups (difference: 0.05; 95% CI −0.24 to 0.34). The extra weight in formula-fed infants was almost entirely attributable to having more lean mass, whereas fat mass and body fat percentages were not different between feeding groups. Weight and BMI z score trajectories differed between breastfed and formula-fed infants. Specifically, weight z scores of breastfed infants decreased slightly over 7 months (–0.03 U/months; $p = 0.004$), whereas weight z scores of formula-fed infants increased by 0.07 U/months ($p = 0.001$). BMI z scores also increased by 0.08 U/months ($p < 0.001$) in formula-fed infants, whereas BMI z scores of breastfed infants remained constant (–0.005 U/months; $p = 0.71$). Length z score trajectories were not statistically different between the 2 groups. Both breastfed and formula-fed infants gained fat mass at a similar rate, and body fat percentages also remained similar between the 2 groups.

Conclusion: Exclusively formula-fed infants gained lean mass (but not fat mass) more rapidly than predominantly breastfed infants over the first 7 months of life. These findings suggest that differences in fat accumulation during infancy are unlikely to explain the previously observed association between infant feeding and future obesity risk.

Comments The extent to which breastfeeding in infancy is associated with a decreased risk for obesity later in life remains highly controversial. In the present study, weight gain in formula-fed infants was more rapid than in breastfed infants. The original findings of this study are that excess weight gain was not due to an excess gain in fat mass but in lean body mass. Greater lean body mass in formula-fed infants is biologically plausible. Indeed, formula-fed infants have a higher protein intake than breastfed infants in the first semester of life, and it is well known that a greater protein intake is associated with greater lean body mass accretion in infancy. These results may support the protein hypothesis whereby a higher protein intake in early infancy may be associated with a higher risk of overweight and obesity later in life [11].

Preterm Infants

Growth

Head growth trajectory and neurodevelopmental outcomes in preterm neonates

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Background: The authors evaluated the association between head growth (HG) during neonatal and post-discharge periods and neurodevelopmental outcomes of preterm neonates of <29 weeks gestational age.

Methods: A retrospective cohort study of infants <29 weeks gestational age admitted between 2009 and 2011 was conducted in Canada. Differences in head circumference (ΔHC) z score were calculated and divided into 3 time periods. These periods included admission to discharge, discharge to follow-up at 16–36 months, and admission to follow-up. The differences were categorized in 1 reference group (ΔHC z score between –1 and +1) and 4 study groups (ΔHC z score of <–2, between –2 to –1, +1 to +2, and >+2). Neurodevelopmental outcomes were compared with the created reference group.

Results: A total of 1973 infants met the inclusion criteria. Poor HG occurred frequently during the NICU admission (ΔHC z score <–2 in 24% infants versus 2% infants post-discharge). Significant neurodevelopmental impairment was higher in infants with the poorest HG from admission to follow-up (adjusted odds ratio 2.18, 95% CI 1.50–3.15), specifically cognitive and motor delays. Infants with poor initial HG and catch-up post-discharge have a lower adjusted odds ratio of significant neurodevelopmental impairment (0.35, 95% CI 0.16–0.74). Infants with poor HG received a longer duration of parenteral nutrition and mechanical ventilation and had poor weight gain.

Conclusion: Poor HG during the neonatal and post-discharge periods was associated with motor and cognitive delays at 16–36 months.

| Comments | Consecutive measurements of head circumference growth remain a concrete way of predicting later outcome. It is cheap, and with proper training it can be used in all settings. Although many may advocate that more advanced imaging like term MRI is necessary, recent data do not support that view [12]. Obviously, a significant cost and burden can be established by abolishing these MRI's at term equivalent age. Nutritional management can influence the head circumference growth [13]. A nice example is the SCAMP trial [14] where early postnatal head growth failure in preterm infants could be ameliorated by optimizing parenteral nutrition. On the contrary, a recent Cochrane review could not confirm that, for instance, a higher amino acid intake was associated with improved neurocognitive outcomes [15]. That review concludes that very low-quality evidence suggests that higher AA intake reduces the incidence of postnatal growth failure. However, evidence was insufficient to show an effect on neurodevelopment, so more studies are needed to address the issue. Altogether these data suggest that there might be something to gain by improving direct postnatal management, and putting effort in improving the skills to measure head circumference precisely. |

Parenteral Nutrition

Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: a randomized controlled trial

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Background: Theoretically, a deficit of omega-3 LCPUFA might hamper visual and neurodevelopment. Hence, many studies examine the effect of adding either LC-PUFA to enteral nutrition or providing fish-based lipid emulsions during parenteral nutrition. The purpose of this study was to compare the effects of the parenteral emulsion SMOFlipid®, with 15% fish oil, with Clinoleic® on retinopathy of prematurity (ROP) and other morbidities and growth. Retinopathy of prematurity, other morbidity and growth were correlated with each parenteral lipid supplement.
Methods: The authors randomized 90 infants born at gestational age <28 weeks who were randomized to treatment with SMOFlipid® or Clinoleic®. Two thirds (66%) of the infants received paren-

teral nutrition for up to 14 days after birth (median 8, range 2–14 days), and additional 25% of the infants received for up to 28 days after birth (median 21, range 15–28 days). Treatment groups were compared with regard to ROP, bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus sepsis, and growth between birth and 36 weeks.

Results: Infants on SMOFlipid® had higher fractions of omega-3 LCPUFA eicosapentaenoic acid and slightly higher omega-3 LCPUFA docosahexaenoic acid (DHA) fraction and a decreased arachidonic acid (AA) to DHA ratio from one week after birth up to 32 postmenstrual weeks compared to infants on Clinoleic®. Treatment groups did not differ in morbidities or growth.

Conclusion: Supplementation with SMOFlipid® containing 15% fish oil during parenteral nutrition did not reduce morbidity or affect growth. Since extremely preterm infants accumulate a large deficit of DHA and AA, studies on more prolonged or different levels of DHA and AA supplementation are warranted.

Comments	Multiple studies have addressed possible benefits of omega-3 LCPUFA containing lipid emulsions when compared to either pure soybean-based emulsions or mixtures with either MCT oils or olive oils. Despite theoretical advantages hardly any benefit is observed, which might be attributed to the relatively low number of days on total parenteral nutrition and the increasing use of human milk that contains omega-3 LCPUFA as well. The only difference might be in the prevalence of (severe) Retinopathy of Prematurity [16], although the present study did not show any direction towards a reduction of ROP.

Human Milk

A systematic review and meta-analysis of human milk feeding and morbidity in very low birth weight infants

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Background: This systematic review and meta-analysis synthesized the post-1990 literature examining the effect of human milk on specific neonatal morbidities and neurodevelopment in infants born ≤28 weeks' gestation and/or publications with reported infant mean birth weight of ≤1,500 g.

Methods: The well-known online databases were searched, and comparisons were grouped as follows: exclusive human milk versus exclusive preterm formula (EPTF), any human milk (HM) versus EPTF, higher versus lower dose HM, and unpasteurized versus pasteurized HM. Experimental and observational studies were pooled separately in meta-analyses.

Results: After excluding several papers for various reasons, 44 papers were included in the meta-analyses. HM provided a clear protective effect against NEC, with an approximate 4% reduction in incidence. HM also provided a possible reduction in LOS, severe ROP, and severe NEC. Particularly for NEC, any volume of HM is better than EPTF, and the higher the dose the greater the pro-

tection. Evidence regarding pasteurization is inconclusive, but it appears to have no effect on some outcomes.

Conclusion: The authors conclude that improving the intake of mother's own milk and/or donor HM results in small improvements in morbidity in the small neonates studied.

Comments	More and more manuscripts are published that show an association of the use (and also with the volume ingested) and a reduction in neonatal morbidities (e.g., [17, 18]). Major criticism towards those studies is that they are neither blinded nor randomized as this is impossible to do. And on average mothers who provide own mothers' milk to their prematurely born children are highly educated and of higher socioeconomic status, that may already in itself result in other outcomes. Prospective and adequate blinding is possible in studies using pasteurized human donor milk, although the handling has a distinct effect on several important and possible beneficial properties of own mothers and raw milk. A recent meta-analysis revealed that even pasteurized donor milk has a significant effect on the incidence of necrotizing enterocolitis [19]. Consequently, the advice of the ESPGHAN Committee on Nutrition and invited experts provided in 2013 holds true [20]; fresh own mother's milk is the first choice in preterm infant feeding and strong efforts should be made to promote lactation. When own mother's milk is not available, donor HM is the recommended alternative. When neither own mother's milk nor donor human milk is available, preterm formula should be used.

Exosomal MicroRNAs in milk from mothers delivering preterm infants survive in vitro digestion and are taken up by human intestinal cells

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Background: Milk exosomes encapsulate various types of nutrients, for example, proteins, mRNAs, microRNAs (miRNA), and protect them against enzymatic and non-enzymatic degradation. The ability of preterm milk exosomes to survive gastric/pancreatic digestion, internalization by intestinal epithelia, and the miRNAs contents is studied here.

Methods: Milk is collected from mothers who delivered preterm and term infants ($n = 10$) at an infant's age of approximately 2 weeks. Milk is exposed to conditions simulating infant gut digestion. Exosomes are isolated and lysed, and the exposed miRNAs are sequenced.

Results: Preterm milk exosomes survive in vitro digestion, and can be taken up by intestinal epithelia. Three hundred and thirty miRNAs are identified as preterm milk exosome miRNAs. Digestion does not have a pronounced effect on their expression when measured in vitro. The abundant miRNAs in preterm milk exosomes are similar to those from term milk. Twenty-one low abundance miRNAs are specifically expressed in preterm milk exosomes compared to early term milk in the current study and what was previously found in mature term milk.

Conclusion: These results for the first time reveal the survivability of preterm milk exosomes following simulated gastric/pancreatic digestion. The authors demonstrate the richness of the miRNAs content in these exosomes. The results improve the knowledge of preterm milk biology and

the molecular basis by which exosome miRNAs may uniquely affect preterm infants during early development.

Comments The major question why breastmilk has so many advantages on the well-being of preterm infants is not clearly understood. Most likely many different factors may contribute. Exposure to the immunologic factors found in maternal breast milk has been shown to compensate for the immature immune system that characterizes the preterm infant. Bioactive molecules found in human milk may cause an anti-inflammatory effect. The present paper adds new insight into the mechanism of how human milk may exert its effect. Milk exosomes are regarded as most important signal molecules mediating cellular communication between the mother and her infant [21]. In analogy to a viral infection, milk provides virus-sized exosomes equipped with abundant miRNAs that modify the gene expression of receptor cells. Current infant formulas are highly deficient in milk-derived miRNAs [22], a deficit that may have negative effects on long-term immunological and metabolic programming of the infant [23]. Signaling information through highly conserved miRNAs that modify transcription and epigenetic regulation to promote infant's anabolism and growth can be a very plausible explanation of the differences found in human milk-fed infants as compared to formula-fed infants [24].

Cost-effectiveness of supplemental donor milk versus formula for very low birth weight infants

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Background: To determine the cost-effectiveness of supplemental donor human milk (DHM) versus preterm formula (PTF) for very low birth weight (VLBW, <1,500 g) infants from a societal perspective to 18 months' corrected age.
Methods: This prospective cost-effectiveness analysis of 363 VLBW infants was conducted for a randomized control trial, where infants received donor milk or formula if own mother's milk was not available. The authors obtained formal health care costs for initial hospitalization and readmissions from standardized cost-accounting systems and physician fees in Canada. Informal and non-health care sector costs (e.g., caregiver transportation, labor market earnings) were calculated from parent reports.
Methods: The mean infant birth weight was 996 (SD, 272) g. Incidence of necrotizing enterocolitis (NEC) differed between groups (all stages 3.9% DHM, 11.0% PTF; $p = 0.01$), but neurocognitive outcome at 18 months of age was not significantly different. Costs to 18 months did not differ with a mean (95% CI) of 217,624 (197,697–237,551) and 217,245 (196,494–237,995) 2015 Canadian dollars in the DHM and PTF groups. Post-discharge costs were lower in the DHM (46,440 [40,648–

52,233]) than in the PTF group (55,102 [48,269–61,934]; *p* = 0.04), driven by loss of wages by parent. DHM cost an additional USD 5,328 per case of averted NEC.

Conclusion: In a high mother's milk use setting, total costs from a societal perspective to 18 months of providing supplemental DHM versus PTF to VLBW infants did not differ, although post-discharge costs were lower in the DHM group. Although supplemental DHM was not cost-saving, it reduced NEC supporting its use over PTF.

Comments	In preterm and LBW infants, feeding with formula compared with donor breast milk, either as a supplement to maternal expressed breast milk or as a sole diet, results in higher rates of weight gain, linear growth, and head growth and a higher risk of developing necrotizing enterocolitis. However, no effect on all-cause mortality, or on long-term growth or neurodevelopment is observed in the latest Cochrane review on this topic [19]. Nonetheless, the reduction in NEC will most likely result in a switch towards using more donor human milk as compared to formula. Estimates of the incremental length of stay associated with NEC were ~18 days for medical NEC and 50 days for surgical NEC [25]. Costs of donor human milk are highly variable due to different regulations in different countries. Cultures of milk before and after pasteurization, transportation costs, track and trace procedure, and storage contribute to the overall costs, salaries for staff contribute most. Costs in Europe range from EUR 100 to -500 per liter, charged by nonprofit organizations usually connected to the NICU [26, 27]. A few more trials are either just closed or still in progress. Those will provide additional data that can help in the consideration whether one should use donor milk instead of formula.

Miscellaneous

Early energy and protein intakes and associations with growth, BPD, and ROP in extremely preterm infants

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Background: The authors aimed to examine the associations of early nutritional intakes on growth and risks of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) in a high-risk population.

Methods: This population-based cohort study included infants born before 27 0/7 weeks of gestational age without severe malformations and surviving ≥10 days. Intakes of energy and protein on postnatal days 4–6 and association with weight standard deviation score (WSDS) from birth to day

7, as well as intakes of energy and protein on postnatal days 4–6 and 7–27, respectively, and association with composite outcome of death and BPD and separate outcomes of BPD and ROP were examined. As expected the authors adjusted for potential confounders.

Results: In total, the cohort consisted of 296 infants with a median gestational age of 25 3/7 weeks. Expressed as daily intakes, every additional 10 kcal/kg/day of energy during days 4–6 was associated with 0.08 higher WSDS on day 7 (95% CI 0.06–0.11; $p < 0.001$). Between days 7 and 27, every 10 kcal/kg/day increase in energy intake was associated with a reduced risk of BPD of 9% (95% CI 1–16; $p = 0.029$) and any grade of ROP with a reduced risk of 6% (95% CI 2–9; $p = 0.005$) in multivariable models. This association was statistically significant in infants with ≤10 days of mechanical ventilation. In infants with >10 days of mechanical ventilation, a combined higher intake of energy and protein was associated with a reduced risk of BPD.

Conclusion: Early provision of energy and protein may reduce the postnatal weight loss and risk of morbidity in extremely preterm infants.

Comments	In this retrospective, observational trial, the authors show that energy intake in combination with protein intake had a positive impact on initial weight development. Higher energy intake during postnatal days 7–27 was associated with a lower risk of BPD and ROP. This study also indicates an association between higher protein intake and reduced risk of BPD, provided there was sufficient energy intake. The findings suggest that energy and protein supply to extremely preterm infants is important despite critical illness. They did not demonstrate any statistically significant associations between energy or protein intake during the first postnatal week and subsequent risk of BPD or ROP, similar to what has been described by 2 recent randomized clinical trials. However other studies do indicate that first week management is also important. Earlier in this paper we discussed the results of a randomized trial on additional parenteral nutrition on head circumference growth rates [14], and also Ehrenkranz showed an association between early nutritional intake and the risk of adverse outcomes [28].
	So, all in all, mostly observational studies show an association with suboptimal nutritional intake and adverse outcomes, whereas interventional trials are lacking. As studies in older pediatric intensive care patients are showing detrimental results of too much nutrition in the first phase of admission [29, 30], a large randomized trial in preterm infants is needed.

The impact of routine evaluation of gastric residual volumes on the time to achieve full enteral feeding in preterm infants

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Background: The authors evaluated the time to full enteral feedings in preterm infants after a practice change from routine evaluation of gastric residual volume before each feeding to selective evaluation of gastric residual volume, and also evaluated the impact of this change on the incidence of necrotizing enterocolitis (NEC).

Methods: In this large retrospective study, data were collected on all gavage-fed infants born at ≤34 weeks gestational age (GA) for 2 years before ($n = 239$) and 2 years after the change ($n = 233$).

Results: The median GA was 32.0 (interquartile range 29.7–33.0) weeks before and 32.4 (30.4–33.4) weeks after the change ($p = 0.02$). Compared with historic controls, infants with selective evaluations of gastric residual volumes weaned from parenteral nutrition 1 day earlier ($p < 0.001$) and achieved full enteral feedings (150 mL/kg/day) 1 day earlier ($p = 0.002$). The time to full oral feedings and lengths of stay were similar. The rate of NEC (stage ≥2) was 1.7% in the selective gastric residual volume evaluation group compared with 3.3% in the historic control group ($p = 0.4$). Multiple regression analyses showed that the strongest predictor of time to full enteral feedings was GA. Routine evaluation of gastric residual volume and increasing time on noninvasive ventilation both prolonged the attainment of full enteral feedings. Findings were consistent in the subgroup with birth weights of <1,500 g. Increased weight at discharge was most strongly associated with advancing postmenstrual age, but avoidance of routine evaluations of gastric residual volume also was a significant factor.
Conclusions: Avoiding routine evaluation of gastric residual volume before every feeding was associated with earlier attainment of full enteral feedings without increasing the risk for NEC.

Comments	Evaluation of gastric residuals has gained much attention in recent years. The association of volume, color or frequency of residuals with the incidence of necrotizing enterocolitis in the absence of suspicious clinical signs has been questioned. Abandoning routine gastric residual volume evaluation has been advised [31], although this practice is still widespread [32]. The present retrospective study is one that shows an association with an earlier achievement of full enteral feeding. No randomized controlled trials, which are needed before the abandoning of this practice can be really implemented, are published.

Nutritional strategies and gut microbiota composition as risk factors for necrotizing enterocolitis in very-preterm infants

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Background: The pathophysiology of necrotizing enterocolitis (NEC) remains poorly understood. As the microbiome might influence the development and prevention of NEC, these authors assessed the relation between feeding strategies, intestinal microbiota composition, and the development of NEC.
Methods: Data from a prospective nationwide population-based study, EPIPAGE 2 including preterm infants born at <32 weeks of gestation in France in 2011 were used. From individual characteristics observed during the first week of life, the authors calculated a propensity score for the risk

of NEC (Bell's stage 2 or 3) after day 7 of life. They analyzed the relation between neonatal intensive care unit (NICU) strategies concerning the rate of progression of enteral feeding, the direct-breast-feeding policy, and the onset of NEC using general linear mixed models to account for clustering by the NICU. An ancillary propensity-matched case-control study, EPIFLORE, in 20 of the 64 NICUs, analyzed the intestinal microbiota by culture and 16S ribosomal RNA gene sequencing.

Results: Among the 3,161 enrolled preterm infants, 106 (3.4%; 95% CI 2.8–4.0) developed NEC. Individual characteristics were significantly associated with NEC. Slower and intermediate rates of progression of enteral feeding strategies were associated with a higher risk of NEC, with an adjusted OR of 2.3 (95% CI 1.2–4.5; $p = 0.01$) and 2.0 (95% CI 1.1–3.5; $p = 0.02$), respectively. Less favorable and intermediate direct-breastfeeding policies were associated with higher NEC risk as well, with an adjusted OR of 2.5 (95% CI 1.1–5.8; $p = 0.03$) and 2.3 (95% CI 1.1–4.8; $p = 0.02$), respectively. Microbiota analysis performed in 16 cases and 78 controls showed an association between *Clostridium neonatale* and *Staphylococcus aureus* with NEC ($p = 0.001$ and $p = 0.002$).

Conclusions: A slow rate of progression of enteral feeding and a less favorable direct-breastfeeding policy are associated with an increased risk of developing NEC. For a given level of risk assessed by propensity score, colonization by *C. neonatale* and/or *S. aureus* is significantly associated with NEC.

Comments This well-organized observational study identifies several important issues. Again, NICUs with a less stringent breastfeeding policy show higher rates of NEC, whereas a high rate of advancement of feeding does not influence the incidence of NEC, as shown before [33]. We know that the implementation of the quality-improvement initiatives reduced the NEC rate, and as I do not expect that many countries differ in the implementations strategies, it is wise to bring this issue at the highest level of NICU management [34].

Several studies suggest that NEC is associated with both unusual intestinal microbial species and an overall reduction in the diversity of the microbiota [35, 36]. Fecal microbiota diversity in preterm infants born at a gestational age of <32 weeks, who are at the highest risk of NEC, increases much more slowly than in more mature infants, and their composition is dominated by staphylococci, enterobacteria, and enterococci, with a very low abundance of anaerobes except clostridia [37]. Clostridial involvement in NEC onset is supported by the fact that the main clinical signs in definite NEC, that is, intestinal necrosis and pneumatosis, are consistent with clostridial infection and a strong association between clostridia and NEC was observed after adjustment for individual risk factors and NICU strategies in the present study. However, Gammaproteobacteria (Enterobacteriaceae) can be involved as well. Pathogenic characteristics leading to NEC injuries can be shared by various bacterial strains, as recently shown in a meta-analysis [38].

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Cognition

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Introduction

The role of nutrition in pregnancy and during early life is today recognized as critical for infants' and children's neurodevelopment, in both well-developed and developing countries in economic transition.

This chapter presents a selection of recent articles that have been published in the area of cognition and nutrition between July 1, 2017 and June 30, 2018. The topics explored in the articles fall into 4 categories: fatty acids, micronutrients, microbiome, and miscellanea.

The majority of the studies presented, specifically those concerning fatty acids and micronutrients, are based on large populations of mother-child pairs. It follows a greater statistical power of these analyses compared to previously published studies. More harmonized methods and larger population samples are expected to suggest more meaningful interventions in the forthcoming years towards improving children's cognitive function, universally considered a fundamental goal for public health.

Individual comments following the abstracts and/or summaries of the individual papers are included for each of the four sections, together with an overall summary at the end.

Key articles reviewed for the chapter

Fatty Acids

Associations between maternal long-chain polyunsaturated fatty acid concentrations and child cognition at 7 years of age: the MEFAB birth cohort

Brouwer-Brolsmaa EM, van de Resta O, Godschalkb R, Zeegersb MPA, Gielenb M, de Grootb RHM

Prostaglandins Leukot Essent Fatty Acids 2017; 126: 92–97

Docosahexaenoic acid for reading, working memory and behavior in UK children aged 7–9: a randomized controlled trial for replication (the DOLAB II study)

Montgomery P, Spreckelsen TF, Burton A, Burton JR, Richardson AJ

PLoS One 2018; 13:e0192909

Maternal dietary intake of polyunsaturated fatty acids modifies association between prenatal DDT exposure and child neurodevelopment: a cohort study

Ogaz-González R, Mérida-Ortega Á, Torres-Sánchez L, Schnaas L, Hernández-Alcaraz C, Cebrián ME, Rothenberg SJ, García-Hernández RM, López-Carrillo L

Environ Pollut 2018; 238: 698–705

Maternal nutritional determinants of colostrum fatty acids in the EDEN mother-child cohort

Armand M, Bernard JY, Forhan A, Heude B, Charles MA; the EDEN mother-child cohort study group

Clin Nutr 2018; 37: 2127–2136

Mendelian randomization shows sex-specific associations between long-chain PUFA-related genotypes and cognitive performance in Danish schoolchildren

Lauritzen L, Sørensen LB, Harsløf LB, Ritz C, Stark KD, Astrup A, Dyssegaard CB, Egelund N, Michaelsen KF, Damsgaard CT

Am J Clin Nutr 2017; 106: 88–95

Micronutrients and Pregnancy

Preconception maternal iodine status is positively associated with IQ but not with measures of executive function in childhood

Robinson SM, Crozier SR, Miles EA, Gale CR, Calder PC, Cooper C, Inskip HM, Godfrey KM

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Role of iodine-containing multivitamins during pregnancy for children's brain function: protocol of an ongoing randomised controlled trial: the SWIDDICH study

Manousou S, Johansson B, Chmielewska A, Eriksson J, Gutefeldt K, Tornhage CJ, Eggertsen R, Malmgren H, Hulthen L, Domellöf M, Nystrom Filipsson H

BMJ Open 2018; 8:e019945

Association between maternal vitamin D status in pregnancy and neurodevelopmental outcomes in childhood; results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

Darling AL, Rayman MP, Steer CD, Golding J, Lanham-New SA, Bath SC

Br J Nutr 2017; 117: 1682–1692

Maternal prenatal blood mercury is not adversely associated with offspring IQ at 8 years provided the mother eats fish: a British prebirth cohort study

Golding J, Hibbeln JR, Gregory SM, Iles-Caven Y, Emond A, Taylor CM

Int J Hyg Environ Health 2017; 220: 1161–1167

The impacts of maternal iron deficiency and being overweight during pregnancy on neurodevelopment of the offspring

Berglund SK, Torres-Espínola FJ, García-Valdés L, Sequra MT, Martinez-Zaldívar C, Padilla C, Rueda R, Pérez García M, McArdle HJ, Campoy C

Br J Nutr 2017; 118: 533–540

Effect of maternal high dosages of folic acid supplements on neurocognitive development in children at 4–5 y of age: the prospective birth cohort Infancia y Medio Ambiente (INMA) study

Valera-Gran D, Navarrete-Muñoz EM, Garcia de la Hera M, Fernández-Somoano A, Tardón A, Ibarluzea J, Balluerka N, Murcia M, González-Safont L, Romaguera D, Julvez J, Vioque J; INMA Project

Am J Clin Nutr 2017; 106: 878–887

Effects of fortified milk on cognitive abilities in school-aged children: results from a randomized-controlled trial

Petrova D, Bernabeu Litrán MA, García-Mármol E, Rodriguez-Rodriguez M, Cueto-Martín B, López-Huertas E, Catena A, Fonollá J

Eur J Nutr 2018, Epub ahead of print. https://doi.org/10.1007/s00394-018-1734-x

Microbiome

Infant gut microbiome associated with cognitive development

Carlson AL, Xia K, Azcarate-Peril MA, Goldman BD, Ahn M, Styner MA, Thompson AL, Geng X, Gilmore JH, Knickmeyer RC

Biological Psychiatry 2018; 83: 148–159

The brain-gut-microbiome axis

Martin CR, Osadchiy V, Amir Kalani A, Mayer EA

Cell Mol Gastroenterol Hepatol 2018; 6: 133–148

Miscellanea

Impact of early-life weight status on cognitive abilities in children

Li N, Yolton K, Lanphear BP, Chen A, Kalkwarf HJ, Braun JM

Obesity 2018; 26: 1088–1095

Fatty Acids

Associations between maternal long-chain polyunsaturated fatty acid concentrations and child cognition at 7 years of age: the MEFAB birth cohort

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Background: Maternal fatty acid status during pregnancy may have a link with offspring brain growth and function. Dutch women present with generally low circulating levels of n-3 long-chain polyunsaturated fatty acids (LCPUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Since during pregnancy high concentrations of these fatty acids are incorporated into fetal brain, low maternal EPA and DHA concentrations may adversely affect fetal brain accretion and subsequently infants' neurodevelopment. Within the available literature, arachidonic acid (AA) levels could substitute for n-3 LCPUFA either in circulating pools or in the brain. The aim of this study was to assess the potential relationship between maternal fatty acid levels and child cognition. ***Methods:*** Data from the Maastricht Essential Fatty Acid Birth cohort (MEFAB) were used, and 292 Dutch mother-child pairs were enrolled in this study. The Kaufman Assessment Battery for Children was used to assess children developmental achievement (sequential, simultaneous and mental processing composite scores).

Cognition

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Results: Maternal DHA:AA ratio has no associations with brain growth and function at age 7 years. Only 2% of the children performed more than one SD below the mental processing composite norm score.

Conclusions: Although cognition and school performance are related, the inconsistent data described here cannot confirm that low maternal EPA and DHA levels during gestation may have adverse consequences on cognitive performance in Dutch children at 7 years of age.

Comments	Authors considered the MEFAB, established in 1989, to study the changes in fatty acid concentration during pregnancy and how these relate to the fatty acid concentrations of the neonate. The original sample contains data from 1,203 subjects. Findings do not support the potential role of maternal fatty acids concentration on the offspring cognitive outcomes. Even if the results seem "negative", readers should consider that, on the whole, surveys on this issue give either positive or NO associations, but very rarely (if any) inverse associations. Accordingly, these results should be better considered as "neutral" (that is, a confirmation of the "null" hypothesis on the potential associations between circulating pools of n-3 LCPUFA and brain functional development).

Docosahexaenoic acid for reading, working memory and behavior in UK children aged 7–9: a randomized controlled trial for replication (the DOLAB II study)

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Background: The objectives of this study was to confirm the results obtained in the DHA-Oxford-Learning-and-Behavior (DOLAB I) study that found beneficial effects of the long-chain omega-3 docosahexaenoic acid (DHA) supplementation on the school performance of healthy children.

Methods: A total of 376 healthy children attending mainstream UK primary schools, aged 7 ± 9 years, were enrolled. The study was a parallel group, fixed-dose, randomized, double-blind placebo-controlled trial (RCT) with 2 treatment groups. The intervention consisted of administration of a fixed dose of 600 mg/day DHA from algal oil and placebo for 16 weeks. Learning and behavioral outcomes of schoolchildren have been assessed at baseline and at 16-week follow-up through specific tests and scales.

Results: Reading, working memory, and behavioral scores showed no consistent differences between the intervention and the placebo groups, respectively. Some behavioral subscales showed minor between-group differences.

Conclusions: No positive associations for the intervention group have been obtained. Replication of the previous study was not successful, probably due to the complexity of the interventions.

Comments	This RCT named DOLAB II, was aimed at replicating the DOLAB I study. The previous investigation, carried out in 2012, showed the beneficial effects of a dietary supplementation with DHA on the reading, working memory, and behavior of healthy schoolchildren. The DOLAB II did not show the expected results. Accordingly, authors do not actually recommend PUFA supplementation in UK children because of no conclusive evidences on the matter. The report is a rare example of a replication study, a fundamental step in the pyramid of evidence, often neglected.

Maternal dietary intake of polyunsaturated fatty acids modifies association between prenatal DDT exposure and child neurodevelopment: a cohort study

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Background: To study the potential positive role of n-3 and n-6 fatty acids on the connection between maternal 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE), the main metabolite of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), exposure during pregnancy and child neurodevelopment.
Methods: From a total of 271 Mexican mother-child pairs remaining after 5 years of follow-up, 142 children were included in multivariate analysis. The maternal fatty acid intake during gestation was evaluated by using questionnaires, maternal DDE serum levels measured using electron capture gas chromatography while children cognition was estimated by means of the McCarthy scales.
Results: Data showed lower motor development and memory component scores associated with maternal DDT exposure among children whose mothers had lower DHA and AA intakes during gestation.
Conclusions: Low maternal DHA and AA intakes may correlate with a more unfavorable child neurodevelopment associated with maternal DDT exposure during pregnancy.

Comments	DDT is an environmental persistent compound, with a half-life of approximately 10 years and it has been widely used in Mexico. Maternal serum concentrations of DDE during the third trimester of pregnancy are negatively linked with cognitive indices, as well as the numerical, verbal, and memory components of the specific scales in Mexican children at 42 and 60 months of age. The authors have demonstrated possible beneficial effects of DHA and AA intakes, as protective factors towards DDT exposure of pregnant women, on children's brain growth and function. This survey supports the hypothesis of a neuroprotective role of DHA, that is, n-3 LCPUFA could have an independent protective role on functionally-related biomechanisms of the neural cells towards pollutants and neurotoxicants, separate from a positive and primitive, direct, neurofunctional effect.

Maternal nutritional determinants of colostrum fatty acids in the EDEN mother-child cohort

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Background: Human milk is the best food for the proper neurodevelopment of the fetus and the infant. It naturally contains polyunsaturated fatty acids (PUFAs), and specifically contains n-6 and n-3 long-chain forms (LC-PUFA). PUFAs content in human milk is quite variable and sensitive to mother's diet, lactation period, and maternal overweight. Colostrum, the early milk, provides the initial supply of PUFA to the newborns during breastfeeding. Systematic reviews and observational studies have been inconclusive or limited. This study aimed to obtain a better comprehension of maternal and pregnancy factors related with colostrum PUFA levels.
Methods: Data collected from the French Etude des Déterminants pré- et postnatals précoces du développement et de la santé de l'Enfant (EDEN) mother-child cohort, enrolling 934 mother-child pairs. Colostrum samples were collected between 2 and 5 days after delivery and were analyzed by gas chromatography. To analyze the eating habits and nutrient intakes of pregnant women, a food-frequency questionnaire (FFQ) was completed during the third trimester of pregnancy.
Results: The ratio between linoleic acid (LA) and alpha linolenic acid (ALA) was positively associated with the degree of maternal obesity while the AA/DHA and total n-6/total n-3 PUFA ratios followed a u-shaped association with mother's BMI. Colostrum of women with high pre-pregnancy BMI contained the highest level of LA and AA and the lowest levels of ALA and DHA. Other maternal factors were found independently associated with ALA, DHA, LA or AA levels in colostrum (such as primiparous status and mother's age). AA levels in colostrum were not related to dietary intake as opposed to what concerned DHA levels, depending on the daily consumption through the diet.
Conclusions: Data obtained from this study are consistent and reliable because of the large sample of mother-child pairs (EDEN cohort) used. Several maternal factors may influence the variability of PUFA levels in colostrum.

Comments	Newer well-designed studies should be performed to investigate fatty acids composition in human milk at various stages and the association with offspring outcomes. Available data show the importance of accurate nutritional counseling before and during pregnancy. To improve the PUFA status in early milk, it seems appropriate to ensure, before gestation, a normal mother's BMI and an adequate consumption of food rich in unsaturated fats. The study supports the hypothesis of a direct dependence of DHA status in human milk from diet, different than AA. The observation has been already described, and is consistent with similar findings for DHA and AA in blood as well as in nervous and brain membranes. Since AA is essential for life (while DHA more on the quality of life) these observations are consistent and biologically plausible.

Mendelian randomization shows sex-specific associations between long-chain PUFA–related genotypes and cognitive performance in Danish schoolchildren

Lauritzen L[1], Sørensen LB[1], Harsløf LB[1], Ritz C[1], Stark KD[2], Astrup A[1], Dyssegaard CB[3], Egelund N[3], Michaelsen KF[1], Damsgaard CT[1]

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Background: Since findings on the hypothetical positive effect of LCPUFAs on child neurodevelopment remain inconclusive, further investigative steps on the genetic polymorphisms of fatty acid desaturases (FADS) and their functional associations are needed. Single-nucleotide polymorphisms (SNPs) rs1535 and rs174448 in the FADS gene cluster may have contrasting roles on erythrocyte LCPUFAs at 9 months. The aim of this Mendelian randomized study was to assess the potential association between selected gene polymorphisms of FADS and elongases (ELOVL) with gender-related performance in Danish schoolchildren.

Methods: This cross-sectional study is based on data from the OPUS School Meal Study. Parameters of good cognitive performance have been collected (low test of attention error%, high concentration performance, and high reading scores) in 834 children aged 8–11 years from the third and fourth grades of nine Danish schools enrolled in the study from May 2011 to October 2011.

Results: Associations between single nucleotide polymorphisms (SNP) in FADS and ELOVL genes and child cognition were found. Sex interactions were identified in 50% of the SNP performance sets. The associations with cognitive outcomes were consistent in opposite directions in girls and boys.

Conclusions: The present findings suggest sex-specificity in the association between LCPUFA-related SNPs and cognitive outcomes in a large sample of Danish children.

Comments This interesting study analyzed two original aspects: (1) selected gene polymorphisms of fatty acids and sex-specificity, and (2) the association with children's cognitive performance. Accordingly, newer studies aimed at investigating the effects of n-3 LCPUFA interventions on child cognition should ideally consider sex differences, together with genetic polymorphisms in the pathways leading to LCPUFA synthesis. Different genetic patterns, environment, diet, and gender seem to contribute to the puzzling picture connecting LCPUFA status to neurodevelopment, neurocognition, and neuroprotection through the lifespan.

Preconception maternal iodine status is positively associated with IQ but not with measures of executive function in childhood

Robinson SM[1, 3], Crozier SR[1], Miles EA[2], Gale CR[1, 4], Calder PC[2, 3], Cooper C[1, 3, 5], Inskip HM[1, 3], Godfrey KM[1, 3]

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Role of iodine-containing multivitamins during pregnancy for children's brain function: protocol of an ongoing randomised controlled trial: the SWIDDICH study

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Background: It is widely agreed that an adequate iodine status is important for early-life neurodevelopment. Dietary deficiency of iodine is an often unknown, unrecognized dietary issue, associated with poorer neuro-intellectual outcomes. Two recent documents (a survey and the protocol of a study design, here reported, respectively), are aimed at exploring the relationships between maternal iodine status during pregnancy and the offspring cognitive function.
Methods: In the first prospective study (The Southampton Women's Survey), pregnant women and their children were assessed. Data about mother's iodine status were collected through the iodine:creatinine concentration (I/Cr) ratio in urine spot sample analyses. Furthermore, the Wechsler Abbreviated Scale of Intelligence and tests from the Cambridge Neuropsychological Test

Automated Battery (CANTAB) were used to assess children's cognitive function at 6–7 years of age. The second publication is the protocol of an ongoing randomized controlled trial: the SWIDDICH study. A total of 1,275 Swedish mother-child pairs will be enrolled and mothers will be randomly assigned to receive iodine supplementation or placebo, every day, during pregnancy. Children will be followed up to 14 years of age. Maternal variables will be measured and children outcomes assessed by using specific developmental scales and tests (for instance, the Wechsler Intelligence Scale for Children-V).

Results: In the first study, the I/Cr ratio collected before conception, was positively associated with offspring IQ, before and after adjustment for potential confounders, while no associations with the executive function outcomes assessed via CANTAB, were found.

Conclusions: Previous studies reported the relationship between iodine status of women before conception and their offspring IQ. Robinson et al. (page 78) confirmed this connection even if they found no association with measures of executive function. A new promising protocol has been issued to more clearly disentangle the associations between maternal iodine status in pregnancy and children's neurofunctional outcomes.

Comments	Dietary iodine intake is required for the production of thyroid hormones that are essential for the development of the central nervous system. It is widely agreed that an adequate iodine status is important for early-life neurodevelopment.
	Children's cognitive outcomes appear to be dependent on their mothers' nutritional iodine status and low iodine levels in women before conception seems to be related to a poorer intellectual performance in their children at primary school age. Newer studies should be designed to explore the role of an optimal maternal iodine status as a goal for public health. One should mention that dietary iodine may be suboptimal in the first years of life, even in some areas of Europe. Fish is an excellent source of iodine (and also Vitamin D, see the next paper), and not just n-3 LCPUFA. Disentangling the independent role of these components on the later neurodevelopmental outcome is opportune to issue correct dietary recommendations.

Association between maternal vitamin D status in pregnancy and neurodevelopmental outcomes in childhood; results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

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Background: There is a positive association between fish consumption during gestation and children's brain growth and function, but the potential correlation between high content of vitamin D in fish oil and cognitive outcomes is not well understood.

Methods: A total of 7,065 mother-child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort were recruited in this study. The cohort had data for both serum total 25(OH)D concentration in pregnancy and at least one measure of offspring neurodevelopment (pre-school development at 6–42 months; "Strengths and Difficulties Questionnaire" scores at 7 years; IQ at 8 years; reading ability at 9 years).

Results: Low vitamin D levels in pregnant women (<50.0 nmol/L) may negatively affect children's motor and social development under 4 years of age but not cognitive outcomes, including IQ, at older ages.

Conclusions: Maternal vitamin D deficiency prevention should be recommended to prevent suboptimal neurodevelopmental steps through the earlier years of life.

Comments	Vitamin D has an important role in early life, and multiple lines of evidence suggest that this vitamin is actually a neuroactive steroid that acts on brain development. Vitamin D deficiency is considered one of the most common nutritional deficiencies and a commonly undiagnosed medical condition widespread throughout the world. Since some early neurodevelopmental steps may be suboptimal if maternal vitamin D levels are low in pregnancy, an adequate maternal consumption to reach adequate circulating levels in pregnancy is recommended. Dietary fish may be a source of vitamin D in addition to UVB exposure.

Maternal prenatal blood mercury is not adversely associated with offspring IQ at 8 years provided the mother eats fish: a British prebirth cohort study

Golding J[1], Hibbeln JR[2], Gregory SM[1], Iles-Caven Y[1], Emond A[1], Taylor CM[1]

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Background: The relationship of the mercury levels of pregnant women and the cognitive performance of their children are not clear. The aim of this study is to disentangle aspects of this topic on a British pre birth cohort.

Methods: Authors enrolled 14,541 mother-child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, with delivery between April 1991 and December 1992. Self-completion questionnaires have been administered to mothers to collect some pregnancy-related information. At 8 years of age, 2,062 offsprings were investigated to assess their cognitive function through the Wechsler Intelligence Scale for Children WISC-III.

Results: After adjustment, data obtained show no negative influence of prenatal mercury levels on brain function, in case of maternal seafood consumption, while an adverse effect may exist if mothers do not consume fish.

Conclusions: Seafood consumption should be recommended during pregnancy in spite of the intrauterine exposure to mercury, due to the positive associations with children's cognitive skills.

Comments	Available data do not provide strong evidence that blood mercury levels are associated with a poorer neurobehavioral performance, provided the mothers consume fish. On the contrary, the intrauterine exposure to mercury through maternal fish consumption seems to have a beneficial effect on children's IQ. The beneficial role of maternal fish consumption may reflect the presence of several nutrients in fish, such as n-3 LCPUFAs (mainly DHA), iodine, and vitamin D. All these compounds, mentioned in the chapter, might independently promote the functional development of brain and/or act as neuroprotective agents from external compounds and toxicants, including mercury.

The impacts of maternal iron deficiency and being overweight during pregnancy on neurodevelopment of the offspring

Berglund SK[1, 2], Torres-Espínola FJ[1], García-Valdés L[1], Sequra MT[1], Martinez-Zaldívar C[1], Padilla C[3], Rueda R[4], Pérez García M[5], McArdle HJ[6], Campoy C[1, 7, 8]

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Background: Maternal overweight (OW) or obese (Ob) status and inadequate iron (Fe) serum levels may play a negative role on children's neurodevelopment. The associations between these two conditions and the underlying factors need clarifications.

Methods: A total of 331 pregnant Spanish women from a prospective observational study (PRE-OBE) were enrolled. Iron blood levels were measured at 34 weeks and at delivery. Bayley III scales were used to assess neurodevelopment at 18 months in infants.

Results: Results show a relationship between maternal iron deficiency (ID, Hb below 110 g/L) at 34 weeks and lower offspring composite motor scores at 18 months of age. In addition, lower maternal iron blood levels at delivery was related to babies with lower cognitive, receptive, expressive, composite, and language scores. Similar negative associations have been found between maternal pre-gestational Ow/Ob and lower gross motor scores in the offspring. Negative associations with the ID status persisted even after adjusting for the OW condition.

Conclusions: Maternal ID and pre-gestational Ow/Ob are both negatively associated with Bayley scores, but show independent associations with different subscales of the Bayley scores, in infants at 18 months of age.

Comments	ID represents the main worldwide nutritional disorders. An adequate level of prenatal iron may be essential for the correct child neurodevelopment but this association has been poorly investigated. Obesity in turn is considered a risk factor for ID, most likely caused by an increased inflammatory status and a subsequent hyper-induction of the Fe-regulatory protein hepcidin causing depletion of extracellular iron [1]. Accordingly, low iron levels may negatively affect the neurodevelopment of infants born to women with obesity and ID, with different independent mechanisms. The debate on the opportunity of iron supplementation during pregnancy is still open when considering pregnant women in general and obese pregnant women in particular, considering the overall effect balance.

Effect of maternal high dosages of folic acid supplements on neurocognitive development in children at 4–5 y of age: the prospective birth cohort Infancia y Medio Ambiente (INMA) study

Valera-Gran D[1,2], Navarrete-Muñoz EM[1,2], Garcia de la Hera M[1,2], Fernández-Somoano A[2,3], Tardón A[2,3], Ibarluzea J[2,4], Balluerka N[2,5], Murcia M[2,6], González-Safont L[2,6], Romaguera D[7–9], Julvez J[2,8], Vioque J[1,2]; INMA Project

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Background: It is well established that folic acid deficiency (absolute or relative) is a predisposing factor for neural tube defects, with myelomeningocele as its maximal expression. Supplements with folic acid (FASs) during the embryonic development reduce the risk of neural tube defects. However, little is known about the effects of excessive doses of FAS, that is, over the Tolerable Upper Intake Level (UL) of 1,000 μg/day. This study aimed at understanding the connection between the use of high dosages of FASs during gestation and brain growth and function in children at ages 4–5 years.

Design: A total of 1,682 Spanish mother-child pairs from the Infancia y Medio Ambiente (INMA) Project (a Spanish multicenter prospective mother-child cohort study) were enrolled between 2003 and 2008.

Validated questionnaires were administered to pregnant women to evaluate FASs during pregnancy. McCarthy Scales of Children's Abilities have been used to assess neurodevelopment in children at 4–5 years of age.

Results: High dosages of FAS (>1,000 μg/day) during the periconceptional period have negative influences on cognitive scores in children (measured as global verbal, verbal memory, cognitive function of posterior cortex, and cognitive function of left posterior cortex).

Conclusions: During sensitive and critical periods, such as pre-conception and gestation, women's FAS should be carefully planned and followed up to prevent negative outcomes in the offspring.

Comments Several randomized controlled trials showed that folic acid is an essential factor for the prevention of neural tube defects**.** Its protective effect has led to recommendations for daily FAS starting preconceptionally in women planning to become pregnant. At the same time, FAS dosages over 1,000 μg/day are recommended. The recommendation is consistent with another recent review suggesting that daily doses over 1,000 μg/day may not be any more effective than lower doses for the prevention of recurrent neural tube defects [2].

Agostoni · Bettocchi

Effects of fortified milk on cognitive abilities in school-aged children: results from a randomized-controlled trial

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Background: It is largely accepted that micronutrients and n-3 LCPUFAs are crucial for early-life neurodevelopment. The aim of this study was to examine the effects of fortified milk on child neurocognitive development and function.

Methods: Authors performed a randomized, controlled double-blind study with a fortified group and a control group. The fortified milk contained high levels of various added micronutrients (vitamins A, B complex, C, D and E, calcium, phosphorus, zinc) and n-3 LCPUFA (DHA + EPA), and it was compared to not fortified milk. A total 119 children were enrolled in the study and consumed 0.6 L/day of either milk for 5 months. Anthropometric measures, blood samples, and cognitive tests were collected and analyzed at the start and the end of the study.

Results: Serum DHA and 25OH-vitamin D levels increased following the intake of the enriched milk. The fortified milk showed a positive influence on children's working memory, and an indirect association with processing speed at one of two tests used to explore this domain.

Conclusions: Consumption of milk with the supplementation of micronutrients and n-3 LCPUFA may improve children's neurodevelopment at school age.

Comments The results of this RCT study suggest that a micronutrient fortified milk-based drink reduces the risk of deficiencies of certain micronutrients in apparently healthy children and may play a beneficial role in child cognition. However, the observation remains scattered while requiring larger confirmations from different settings. It is likely that we need to identify who could benefit from supplemented micronutrients based on an individualized dietary approach.

Infant gut microbiome associated with cognitive development

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Background: The first postnatal years of life represents a crucial time for both human gastrointestinal trait colonization and brain development. Diverse and complex community of microbes (gut microbiota) established in this trait through evolutionary processes that begin at childbirth may contribute to the developmental programming of many tissues and functions of the body. A detailed knowledge of the patterns of gut microbial colonization and the mechanisms by which they may influence the psycho-neuro-immunological pathways, is crucial to improve the quality of life and ensure a healthy status of infants and children.

Methods: A total of 89 infants at 1 year of age from 2 prospective longitudinal studies of early brain development at the University of North Carolina were enrolled. Fecal samples were collected from infants, and the microbial community was characterized by 16S ribosomal RNA amplicon sequencing. Authors used the Mullen Scales of Early Learning to evaluate the association between gut microbiota with (a) cognitive outcomes of infants at 1 year of age, and (b) brain volumes at 1 and 2 years of age through structural magnetic resonance imaging.

Results: Three groups of infants with different microbial composition have been identified. Analysis of the change in Mullen scores for receptive language and expressive language from 1 to 2 years of age were significantly different between clusters. Furthermore, alpha diversity was negatively correlated with cognitive scores at 2 years of age, and secondary analyses showed a negative association of expressive language with alpha diversity. Accordingly, the human gut microbiota at 1 year of age may predict cognitive performance at 2 years of age. Results also suggest a potential effect of gut microbiome on regional gray matter volumes.

Conclusions: The gut microbial community may play an important role in the neurodevelopment during early life. Newer studies incorporating other neuroimaging techniques should be performed to investigate neural circuits involved in the microbiome-gut-brain axis.

Comments This observation connects the diversity of the intestinal microbiome with not only functional differences in various domains of infants' brain so early as at 12 months of age, but even brain anatomical volumes. Apart from observations, suggesting hypotheses, trials should become available to distinguish causality, reverse causality, collinearity, and causality.

The brain-gut-microbiome axis

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Review: The authors provide an overview of the "microbiome-gut-brain axis" and the factors that may influence microbiome composition. It is widely agreed that gut microbiota play an important role in brain's regulation but only recently the presence of three bidirectional pathways (immunological, endocrine, and neural) connecting brain and gut microbiome has been clarified. Preclinical and clinical studies have shown associations between perturbations of this axis and the pathogenesis and pathophysiology of irritable bowel syndrome, obesity, and several psychiatric and neurologic disorders.

Overall commentary of the 2 papers

The microbiome represents the last and promising frontier of the connection between nutrition and neurodevelopment. Inadequate colonization during the early stages of life may increase the risk of several adverse outcomes related to neurodevelopment and motor activities. Recent findings suggest possible microbiome-based interventions to treat disorders of the gastrointestinal trait and other adverse medical symptoms related to cognition and physical as well as emotional wellbeing. Dietary gut microbiome manipulations may have the power to exert physical and psychological health benefits. These nutritional interventions may improve the general health population status and may also be investigated as a treatment option for individuals with diverse conditions such as irritable bowel syndrome, anxiety, depression, and Alzheimer's disease. Considering either the ecological associations described in the first paper and the second overview, we still recommend a prudent approach. The pyramid of the evidence requires a careful and step-wise approach, so nutritionists, pediatricians, and the scientific community as a whole are requested to keep calm before undue claims are expressed, even in cases (as described here) where the expectations may easily translate into wishful thinking.

Impact of early-life weight status on cognitive abilities in children

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Background: The global prevalence of childhood overweight and obesity has increased substantially since the 1990s and an early excess adiposity in children is associated with a higher risk to be overweight or obese in later childhood and in adulthood too. In adults, obesity relates to lower cognitive abilities. This study investigated the possible connection between weight status during early-life and cognitive performance in children.

Methods: The authors analyzed data from a longitudinal cohort of 233 mother-child pairs enrolled in the Health Outcomes and Measures of the Environment (HOME) Study (2003–2006). SD (= z) scores were calculated to assess the weight status of children, and several specific tests were used to assess cognitive abilities at 5 and 8 years of age, respectively.

Results: Intelligence quotient scores decreased with a 1-unit increase in weight-for-height (WH) z score. Early-life weight-for-length/WH z score may be inversely associated with full-scale intelligence quotient, perceptual reasoning index, and working memory index scores after adjusting for potential confounders. Early-life WH z was also suggestively associated with higher reaction time T-scores on the Conners' Kiddie Continuous Performance Test and Conners' Continuous Performance Test-II at ages 5 and 8 years, respectively.

Conclusions: Available results showed that overweight status during the first years of life may be inversely associated with full-scale IQ, perceptual reasoning scores, and working memory scores (boys only) and associated with longer reaction times among school-aged children.

Comments Within a well-developed setting, weight development (as an indicator of adiposity) in the first 2 years of life was associated with an array of cognitive abilities in school-age children at 5 and 8 years, respectively. Accordingly, the authors hypothesize that the biologic plausibility could be carried out by the production of pro-inflammatory compounds negatively affecting children's neurodevelopment. Data are now needed to explore this type of association with pathologic conditions such as attention-hyperactivity disorders and learning disabilities.

The negative influence of adiposity extends to intraindividual variability in cognitive control among preadolescent children

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Background: Mechanisms underlying the associations between adiposity and children's cognition connected with fitness have been poorly explored so far. The aim of the present study was to investigate the influence of adiposity on brain function using measures of central tendency and intraindividual variability, taking into account demographical factors and aerobic fitness.
Methods: Authors enrolled 233 children at 7–9 years of age from the east-central Illinois region as part of the FITKids2 study, a randomized controlled trial, performed between 2013 and 2017, that tried to assess the role of daily exercise on cognitive performance in pre-adolescent children. Assessment of children's intelligence quotient, pubertal stage, cardiorespiratory values, and attentional inhibition were determined through Woodcock Johnson Test of Cognitive Abilities, modified Tanner Staging scales, maximal oxygen consumption test, and a modified flanker task, respectively. Furthermore, children's anthropometric measurements and whole body and visceral adiposity data were collected.
Results: The excess fat mass acts negatively on markers of cognitive function, as observed in children with greater adiposity who exhibited higher markers of cognitive impairment (IIV). These results were further confirmed by analyzing the weight status of different groups of children.
Conclusions: Further randomized controlled and longitudinal trials should be performed to study the negative influence of adiposity, accounting specific markers of obesity-related decrements in cognitive control in children as dispersion measures. To obtain a better cognitive achievement, children should reach and maintain their healthy weight status.

Comments The authors describe in a setting – similar to the one described in the study previously reported (well-developed, US-based) – a direct association between body composition and a neurodevelopmental task, both measured at the same time (primary school, 7–9 years). The report represents, therefore, a complementary finding. A poorer aerobic performance is hypothesized in this case as a plausible biologic possibility. Once more, these associations should be explored more in depth in developed countries.

Overall commentary of the 2 papers

The relationships between weight status and cognitive performance in children have been infrequently analyzed and are still poorly understood. Some reports have shown associations of childhood obesity on bad cognitive control, after analysis of cognition skills and their influencing factors. Additional studies are needed to confirm these results and to understand the potential associations between adiposity, weight status, and cognitive outcomes. We need more information on the associations in these conditions from both the developed and developing countries, since different settings may result in different outcomes and/or spurious associations.

Flynn effect and its reversal are both environmentally caused

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Background: The Flynn Effect represents the rising IQ scores in high-income nations over the 20th century, indicating historical increases in mental abilities in these countries. During the last years, a slowdown of this phenomenon has been observed in several settings.
Methods: Hypothetic causal factors were identified through the analysis of administrative register data with information on family relationships and cognitive ability scores from military conscription testing. Data were collected for three decades (1962–1991) from a cohort of Norwegian males at 18–19 years of age.
Results: Available data show that the trend of the Flynn Effect (increase, turning point, and decline) may be recovered from within-family alterations in cognitive performance. The authors note that the observed changes are not related to parents perturbation, but seemingly to environmental factors and may vary within families, while remaining unable to recognize the causal agents.
Conclusions: The results obtained are coherent with several hypothetic factor that may influence IQ decline in recent years, including dietary factors.

Comments	The Flynn Effect represents an established phenomenon in many developed (and also less developed) countries. Recently, evidence has shown that the Flynn Effect has gone into reverse, switching towards the so-called "Negative Flynn Effect." Several possible explanations may underlie this negative trend. In the presented study, the authors discuss the probable causes, such as mutations in education levels, unbalanced diet ("worsening nutrition") or aggravation of some health conditions, and social consequences due to immigration. By incident, the switch of the Flynn Effect copes with the increased availability of video screens of any type (from TV to PC and iPad or iPhone) at any age in any part of the world, theoretically leading to a more widespread access to any type of information.

Effect of childhood nutrition counselling on intelligence in adolescence: a 15-year follow-up of a cluster-randomised trial

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Background: The authors performed a single-blind, cluster-randomized trial to study the possible influence of a nutrition counselling, during early childhood, on adolescents' IQ.

Methods: In 1998, 424 mothers of children aged 18 months or younger were recruited in a nutrition counseling intervention study. Doctors provided nutritional counselling to mothers, encouraging also to give their children 5 meals/day at least. Counseling included promotion of exclusive breast-feeding until 6 months of age and continued breast-feeding supplemented by protein-, lipid- and carbohydrate-rich foods after age 6 months up to age 2 years. The control group received routine feeding advice. Children were closely monitored at 8, 45, and 180 days after the intervention. The last round of follow-up took place in 2013. The Wechsler Adult Intelligence Scale (WAIS-III) was used to assess children's IQ.

Results: At the end of the recruitment, 363 participants were divided into 2 groups (183 intervention group, 180 control group). Of these, 339 adolescents completed the WAIS-III. No significant differences were found between groups. Data obtained from the 2 groups resulted in similar outcomes for mental disorders, school failure, smoking habits, and alcohol use.

Conclusions: This clinical trial showed no impact of a nutrition counseling intervention in early years on cognitive performance in adolescents at 15–16 years of age.

Comments	The role of nutritional interventions, during gestation and early years, on the cognitive development of children and adolescents, has been investigated in several countries, particularly in the transition/developing world. Some studies showed associations between an adequate nutrition during early-childhood and neurodevelopment. In any case, studies and results from similar designs give heterogeneous and contrasting results, underlying the role of different environmental conditions. For instance, children from the intervention group of the described study had lower family income, social class and maternal schooling, probably influencing the observations in adolescence.

Overall Summary

The overall summary last year ended with an (almost) frustrating sentence as follows, If studies and research in the field do not evolve further, it is hard that in the next years we could evolve from the present status, where many single studies suggest mild effects of intervention (if any) and systematic reviews and meta analyses end with the frustrating sentence on "more well-designed studies are needed."

This year, even if the main arguments still relate to the world of n-3 LCPUFA, breastfeeding, micronutrients (iodine first, close to iron, and folic acid), and the microbiome, the methodology shows some progress: out of 18 pertinent papers, several papers deal with the maternal-infant pairs in exploring the associations between maternal nutrition and the development of the offspring numerosity, and sample sizes are adequately consistent in observational studies, safety issues are prominent (from folic acid high dosages to methylmercury and the possible neuroprotective roles offered by some compounds), methodology shows a trend towards a higher degree of harmonization, even if different scales and subscales to test intelligence quotient score are used, for instance by identifying specific ages at early and long-term assessment, long-term effects and replication of study designs have been considered, showing results in contrast with those previously published either in the same population (long-term effects) or different subjects (data replication).

Some black holes still remain. For instance, the number of studies from rich, well-developed countries is still exceeding compared to results from developing and transition countries. In some areas (i.e., the microbiome-brain association), reviews and hypotheses exceeds clinical observations, but some new direct observations in humans are now available. Looking forward, we expect to approach a methodological reform of Nutrition Research, which is more objective and less biased [3].

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Nutrition and Growth in Chronic Disease

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Introduction

Growth failure is common in children with chronic diseases. The pathophysiology of growth failure in children with chronic conditions is multifactorial and includes disease-related higher energy needs, increased energy loss, poor or selective intake, hormonal disturbances, and the action of inflammatory cytokines. Additional metabolic and pathophysiologic abnormalities, characteristic of each and different chronic disease further leads to significant malnutrition and growth failure. The presence of malnutrition represents an aggravating element, further escalating the challenges faced by these children. For these disorders, treatment of disease-specific abnormalities is not enough and we should also address the energy and protein deficits, correction of vitamin and mineral deficiencies as well as metabolic and endocrine abnormalities. Long-term monitoring of weight and growth and individualized, age-appropriate nutrition intervention will minimize the malnutrition and growth failure seen in children with chronic diseases. The present chapter is a selection of the last year publications on the advances on the pathophysiology, investigations and treatment of growth failure that affect some of the chronic diseases of childhood.

Key articles reviewed for the chapter

Inflammatory Bowel Disease

Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate Crohn's disease: results from the growth CD study

Cohen-Dolev N, Sladek M, Hussey S, Turner D, Veres G, Koletzko S, Martin de Carpi J, Staiano A, Shaoul R, Lionetti P, Amil Dias J, Paerregaard A, Nuti F, Pfeffer Gik T, Ziv-Baran T, Ben Avraham Shulman S, Sarbagili Shabat C, Sigall Boneh R, Russell RK, Levine A

J Crohns Colitis 2018; 12: 306–312

Dietary therapy with the Crohn's disease exclusion diet is a successful strategy for induction of remission in children and adults failing biological therapy

Sigall Boneh R, Sarbagili Shabat C, Yanai H, Chermesh I, Ben Avraham S, Boaz M, Levine A

J Crohns Colitis 2017; 11: 1205–1212

Nutritional adequacy of the specific carbohydrate diet in pediatric inflammatory bowel disease

Braly K, Williamson N, Shaffer ML, Lee D, Wahbeh G, Klein J, Giefer M, Suskind DL

J Pediatr Gastroenterol Nutr 2017; 65: 533–538

Cystic Fibrosis

Nutritional status in the first 2 years of life in cystic fibrosis diagnosed by newborn screening

Munck A, Boulkedid R, Weiss L, Foucaud P, Wizla-Derambure N, Reix P, Bremont F, Derelle J, Schroedt J, Alberti C; Gastroenterology and Nutrition Société française de la Mucoviscidose (SFM) Working Group and the ALIMUDE Study Group

J Pediatr Gastroenterol Nutr 2018; 67: 123–130

The relationship between energy intake and body-growth in children with cystic fibrosis

Woestenenk JW, Dalmeijer GW, van der Ent CK, Houwen RH

Clin Nutr 2018 (in Press) https://doi.org/10/1016/j/clnv/2018/02.005

Celiac Disease

Risk of fractures in youths with celiac disease - a population-based study

Canova C, Pitter G, Zanier L, Simonato L, Michaelsson K, Ludvigsson JF

J Pediatr 2018; 198: 117–120

E-healthcare for celiac disease – a multicenter randomized controlled trial

Vriezinga S, Borghorst A, van den Akker-van Marle E, Benninga M, George E, Hendriks D, Hopman E, de Meij T, van der Meulen-de Jong A, Putter H, Rings E, Schaart M, Schweizer J, Smit M, Tabbers M, Weijerman M, Wessels M, Mearin ML

J Pediatr 2018; 195: 154–160

Chronic Liver Disease

Body composition predicts growth in infants and toddlers with chronic liver disease

Hurtado-López EF, Vásquez-Garibay EM, Trujillo X, Larrosa-Haro A

J Pediatr Gastroenterol Nutr 2017; 65:e117–e119

Preoperative nutritional status and its impact on cholangitis after Kasai portoenterostomy in biliary atresia patients

Li D, Chen X, Fu K, Yang J, Feng J

Pediatr Surg Int 2017; 33: 901–906

Effect of preoperative growth status on clinical outcomes after living-donor liver transplantation in infants

Lu Y, Xia Q, Yang Y, Wan P, Hou J, Wang Y, Qiu B, Feng M, He K, Huang M, Ren X, Gao L, Zhang J

Transplant Proc 2017; 49: 1848–1854

Human Immunodeficiency Virus Infection

Dietary inadequacies in HIV-infected and uninfected school-aged children in Johannesburg, South Africa

Shiau S, Webber A, Strehlau R, Patel F, Coovadia A, Kozakowski S, Brodlie S, Yin MT, Kuhn L, Arpadi SM

J Pediatr Gastroenterol Nutr 2017; 65: 332–337

Dyslipidemia, chronic inflammation, and subclinical atherosclerosis in children and adolescents infected with HIV: the positHIVe health study

Augustemak de Lima LR, Petroski EL, Moreno YMF, Silva DAS, Trindade EBMS, Carvalho AP, Back IC

PLoS One 2018; 13:e0190785

Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate Crohn's disease: results from the GROWTH CD study

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Background: Exclusive enteral nutrition (EEN) has been established as the first choice for the induction of remission in pediatric patients with Crohn's disease (CD). EEN has equivalent remission rates not only compared to corticosteroids (CS) but also compared to anti-TNF-α treatment. However, the role of EEN in delaying disease relapse or prevention of early complications is unclear. The present study used an inception cohort from the GROWTH CD study, treated with either EEN or CS, to evaluate if the early use of EEN might reduce early complication rates and improve growth.
Methods: The Growth Relapse and Outcomes With THerapy CD (GROWTH CD) study is a prospective inception cohort that follows newly diagnosed treatment-naive children with CD. The study was conducted in 17 sites in Europe and Israel, by members of the Pediatric Inflammatory Bowel Disease Porto Group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and supported by the European Crohn's Colitis Organization. The patient population of the present research consists of consecutive patients with mild-to-moderate disease, enrolled in the prospective GROWTH CD study. This framework study was designed to evaluate and prognosticate different early adverse outcomes, such as growth retardation, relapse, complicated disease behavior, and requirement for surgery and to evaluate the role of treatment choices on these outcomes. This study was planned a priori to evaluate the effect of initial therapy on these outcomes, and to evaluate relapse by 78 weeks (early relapse) and complications, including surgery, by 104 weeks (early complications).
Results: Among the 285 children with long-term follow-up, 147 with mild-to-moderate disease received either EEN (*n* = 60) or CS (*n* = 87) for the induction of remission. EEN was significantly

superior to CS for the induction of remission: EEN 38/60 (63%); CS 41/87 (47%); $p = 0.036$. Relapse rates by 78 weeks were similar between CS (43/87, 49%) and EEN (27/60, 45%); $p = 0.552$. The median time to relapse by 78 weeks was similar for either group, in CS-treated patients 14.39 ± 1 month, in EEN group 16.05 ± 1.1 months, $p = 0.283$. New complications by 2 years were not statistically significant between groups, CS 12/87 (13.7%); EEN 7/60 (11.7%); $p = 0.29$. Surgical procedures for complications were performed in 9.2% (8/87) among CS, and 3.3% (2/60) among EEN-treated patients, $p = 0.164$. Use of biologics between weeks 12 and 104 was significantly higher among patients treated with CS compared with those treated initially with EEN, CS 16/87 (18.4%); EEN 4/60 (6.7%); $p = 0.042$.

Using the propensity score, 46 matched pairs were selected. EEN was superior for achieving remission 29/46 (63%), relative to CS 19/46 (41%); $p = 0.05$. Baseline height Z score did not differ between groups (CS -0.62 ± 1.3; EEN -0.25 ± 1.1; $p = 0.156$); however, height Z score in the CS group decreased over time whereas it remained stable for the EEN group. By week 78, there was a nearly significant trend towards significance, with higher Z scores favoring the EEN group (CS -0.763 ± 1.3 SD; EEN -0.226 ± 1 SD; $p = 0.055$). Relapse by week 78 (CS 24/46 [52.2%]; EEN 24/46 [43.5%]), complications (CS 12/46 [26.1%]; EEN 9/46 [19.6%]), and surgery (CS 4/46 [8.7%]; EEN 2/46 [4.3%]) by week 104 did not differ ($p = 0.541, 0.648, 0.688$, respectively) between treatment types.

Conclusions: As already shown by other studies, compared to CS, EEN was associated with superior clinical remission rates even after correcting for confounders, such as baseline severity and use of immunomodulators. In spite of superior remission rate, EEN was not followed by lower relapse, complication rates, or biologics' use. However, use of EEN conferred participants' the benefit of preservation of long-term linear growth, as use of CS was associated with a significant decline in height Z scores, whereas EEN was associated with stable height Z scores over time.

Comments The efficacy of EEN for the induction of remission in pediatric patients with CD is well established and comparable to the efficacy of CS. Recently, the efficacy of EEN has also been confirmed in comparison to biological therapy [1]. Considering the benefits of EEN and taking into account the adverse effects of steroids, EEN has been recommended as the first-line therapy for the induction of remission in pediatric luminal CD [2]. EEN is particularly suited for malnourished children and adolescents with CD and poor growth. All studies investigating weight change during EEN treatment reported positive effect of EEN on weight. Some studies also showed an increase in lean body mass. Effect of EEN on height is, however, conflicting. Some studies reported that height velocity increased immediately after the EEN treatment, others found no significant long-term improvement in height z-score. Control studies which compared EEN and CS found either improved growth rate on EEN or no difference [3]. The participants on EEN in the present cohort maintained growth, whereas CS-treated participants' experienced decreased linear growth. Thus, the study reinforces the concept that EEN or biologics might be preferable in children with CD and faltering growth.

Dietary therapy with the Crohn's disease exclusion diet is a successful strategy for induction of remission in children and adults failing biological therapy

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Background: Several dietary interventions either providing specific nutrients or dietary restrictions have been developed lately as alternative therapeutic strategy in IBD. "Crohn's Disease Exclusion Diet" (CDED) is one of the new specialized dietary interventions that has been shown to assist in the achievement of remission in small series in children and adults with Crohn's disease (CD). The present study reports on the use of CDED in patients with loss of response (LoR) to infliximab or adalimumab.

Methods: The study was a retrospective analysis of patients using CDED therapy after LoR to biologics. Patients with LoR to a biologic agent (either infliximab or adalimumab) were given partial enteral nutrition (PEN) with a polymeric formula and the CDED for 12 weeks. Pediatric patients with severe relapse received at first 14 days of EEN followed by PEN + CDED. Harvey Bradshaw Index (HBI), C-reactive protein, and albumin were recorded. Remission was defined as HBI <5 at week 6.

Results: The analysis included 21 patients, mean age 22.2 ± 8.9 years (11 adults, 10 children) with CD, mean disease duration of 7.6 years. At the end of 12 weeks, clinical response was obtained in 19/21 (90.4%) patients, and remission in 13/21 (62%). Improvement of previously elevated inflammatory markers occurred in 17/21 (81%) patients. Among the 4 patients who used the CDED alone without any liquid formula supplementation, 3 entered clinical remission. Isolated ileal disease had the highest remission rate (5/6, 83.3%), whereas isolated colitis had the lowest remission rate (3/6, 50%). Ten of 13 patients in clinical remission at week 6 continued successfully with their biologic therapy through follow-up.

Conclusion: LoR to biologic agents represent a significant challenge when treating patients with CD. Use of specific, feasible dietary strategies may play a pivotal role in regaining remission among patients failing medical therapy with biologics without further escalation of immunosuppression or change of therapy.

Comments Crohn's disease (CD) and ulcerative colitis (UC) – are relapsing and remitting diseases characterized by chronic inflammation of the gastrointestinal tract. The general scheme of IBD etiopathogenesis is believed to stem from interactions between individuals' genetic susceptibility, intestinal microbiome, and environmental triggers. Since nutrients play a key role in shaping the intestinal microbiome and may in themselves modify the inflammatory response, diet has emerged as a potential factor that can influence IBD pathogenesis and activity. Several epidemiological studies have reported on the associations between the intake of specific dietary components (excess or deficiency) or dietary patterns and the risk of developing IBD [4]. Besides being a risk factor, recent studies have investigated the possible role of diet as a therapeutic intervention, primarily in CD. There are multiple mechanisms through which dietary components may work in IBD, from antigenicity of the foods to influence on gut microbiota composition and activity, and nutrient repletion. Several dietary interven-

tions involving elimination of certain foods or inclusion of food components that can target the underlying pathophysiology of IBD have been intensively studied. However, data on diet and IBD is full of contradictions and is sparse in terms of good quality clinical trials.

The largest body of literature on the use of diet as a specific therapy for IBD/CD is on exclusive enteral nutrition (EEN). EEN is a formula-based, complete exclusion diet of 6–12 weeks duration during which 100% of the daily caloric intake is provided through formulas rather than from table foods. EEN has been shown to improve clinical symptoms and nutritional status and induce mucosal healing in children with CD, with remission rates equivalent to CS. Furthermore, higher rates of mucosal healing and safety profile make EEN the first line of therapy for the induction of remission in children with luminal CD [5].

The Specific Carbohydrate Diet (SCD) is a dietary regime initially developed by the gastroenterologist Sidney Haas in 1951 and later popularized by Elaine Gottschall in the book "Breaking the Vicious Cycle: Intestinal Health Through Diet" [6]. The diet is based on the principle that specifically selected carbohydrates, requiring minimal digestive processes are absorbed and leave virtually none to be used for further microbial growth in the intestine. The SCD allows intake of monosaccharides only and complete avoidance of disaccharides and polysaccharides based on the assumption that carbohydrates have the greatest influence on the intestinal microbiota's maintenance and growth. So far, several case-series, many in pediatric patients, suggest that SCD may be effective in IBD. In a clinical study, children with CD under this diet for 12 and 52 weeks had remarkably reduced mucosal damage and improved clinical symptoms [7]. In a recent prospective multicenter study of the SCD in pediatric subjects with mild-to-moderate CD or UC, 8 out of 12 subjects (aged 10–17 years) followed for 12 weeks demonstrated clinical remission, 2 out of 12 subjects did not improve, whereas 2 out of 12 individuals were unable to maintain the diet. A recent retrospective study in 26 children with IBD indicated that the use of a SCD is potentially helpful in maintaining remission, as highlighted by a marked drop in disease activity scores. It is important to mention that most patients remained on maintenance drug therapy and only half of the patients were on strict SCD [8]. There is mounting evidence of the role of mucosal healing in changing the natural history and improving outcome in children and adults with IBD. However, mucosal healing, has not been consistently reported in patients on SCD [9].

The low FODMAP diet specifically limits fructose, lactose, fructans, galactans, and polyols, and has been shown to be effective in improving IBS symptoms. The theory behind the low FODMAP diet is partially similar to that of the SCD; exclusion of poorly absorbed short-chain carbohydrates that can be fermented by intestinal bacteria, leading to bloating, abdominal cramping discomfort, and diarrhea. A recent meta-analysis including 2 randomized controlled trials and 4 before – after studies, with a total of 319 patients with IBD, reported an overall improvement in gastrointestinal symptoms such as diarrhea, abdominal bloating, fatigue, and nausea [10].

The IBD-anti-inflammatory diet (IBD-AID) was developed by a group at University of Massachusetts Medical School, and is derived from the SCD. It encourages the use of omega-3 fatty acids, utilizes food-based prebiotics and probiotics, and uses a graded approach of food introduction based on food textures. In a small, retrospective case-series of 11 adult subjects with CD and UC adherent to the IBD-AID diet for at least 4 weeks, all demonstrated improvement in clinical symptoms and reportedly all subjects were able to discontinue at least one prior IBD medication [11]. To date, there is a paucity of prospective data or application of IBD-AID in the pediatric population.

The CD exclusion diet (CDED), which is the topic of the current paper, designed and evaluated by a group in Israel, led by Arie Levine, focuses primarily on excluding processed foods, specifically gluten, dairy, animal fat, processed meats, products containing emulsifiers, and all canned or processed foods. In the first publication in 2014, in a prospective cohort of 47/33 pediatric and young adults with mild-to-moderate CD, Sigall-Boneh et al. [12] were successful in achieving induction of clinical remission in 70% of patients. This included a reduction in inflammatory markers. Mucosal healing was also reported among patients who achieved remission and were evaluated during the maintenance phase of the diet [12].

The present study investigated the effect of CDED in patients who lost response or relapsed while on treatment with biologic agents (anti-TNFα). Clinical response occurred in 19/21 patients (90.4%) and remission in 13/21 patients (62%). Improvement and normalization in inflammatory markers occurred in 17/21 (81%) and 9/21 (40.9%) patients, respectively. Although not easy to implement and follow, CDED could be less demanding than EEN and therefore may be used in some situations in exchange to the more challenging EEN. In the present study, this strategy allowed patients to regain remission and successfully continue previous therapy, thus avoiding addition of more immunosuppression or treatment switches which decreases possible/future therapeutic options. It must be noted, however, that most patients continued to consume partial EN, and the lack of a control group lowers the level of the observed outcome.

There are many other diets described in the medical literature and lay press for IBD: the IgG-4 guided exclusion diet, the semi-vegetarian diet, the low-fat, fiber-limited exclusion diet, the paleolithic diet, the maker's diet, the vegan diet, and the low-carbohydrate diet. Some diets have been described only in the lay press with some associated anecdotal success, but no clinical trials or case reports have been published in peer-reviewed medical journals.

In summary, we are witnessing rapid development and improved understanding of the role of gene-environment interactions in the onset and development of IBD. Targeted nutrition, taking into account individual genetic make-up, epigenetics, and microbiota composition may represent a novel strategy for successful prevention and disease control. However, more work is required to evaluate the role of individual food compounds and complex nutritional interactions with potential to decrease inflammation, manipulate modulatory epigenetic traits, and maintain intestinal microbial balance as a means of prevention and management of IBD.

Finally, despite the above, based on available evidence, none of the diets can be suggested as a way to induce remission in IBD patients [3].

Nutritional adequacy of the specific carbohydrate diet in pediatric inflammatory bowel disease

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Background: In light of the increasing interests in specialized diets, concern has been raised whether restrictive diets, such as the Specific Carbohydrate Diet (SCD), have the potential to induce nutritional deficiencies. The present study aimed to evaluate the nutritional adequacy of the SCD by comparing nutrient intake of pediatric patients with IBD following the SCD, to dietary reference intake (DRI) levels and population-based intake for key nutrients.

Methods: Intake of 20 key nutrients of 8 children with IBD following SCD was compared to DRI levels and nutrient intake data of similarly aged children from The National Health and Nutrition Examination Survey National Youth Fitness Survey (NYFS) 2012.

Results: The mean energy intake in the study group ranged from 88 to 145% of the recommended dietary allowances (RDA). Protein intake was significantly higher than the NYFS reference population and approximately 3 times the RDA. The majority of participants' daily intakes met or exceeded the RDA for vitamins B2 (82%), B3 (67%), B5 (70%), B6 (90%), B7 (74%), B12 (82%), C (76%), A (92%), E (55%). In 71% participants, daily intakes were below the RDA for vitamins B1 and 67% for B9. All patients had daily intakes of vitamin D below the RDA. Only 56% of participants met the recommended RDA for vitamin K. Daily intakes exceeded RDA for iron in 91% and for selenium in 74%. RDA intakes for zinc, magnesium, and phosphorus were met in 48, 42, and 45% patients respectively. Daily intake of calcium was less than RDI in 75% of children. The upper limit (UL) was met or exceeded for magnesium in 42% of participants on average and in 66% of participants for vitamin A. The average vitamin A intake in patients was significantly greater than the UL ($p = 0.01$).

Conclusions: The results of this study show that in a very small cohort of pediatric patients with active IBD, intake of 20 key nutrients (energy, protein, minerals, and vitamins) in children following SCD was comparable to that of healthy peers in the NNYFS. Vitamin D intake was below RDA in all children on SCD, and average vitamin A intake was significantly greater than the UL compared to NYFS data.

Comments	The increased widespread use of "special" diets among patients with IBD makes essential the evaluation of nutritional adequacy of these diets. In the presence of malnutrition and growth failure, and especially in the pediatric age, the adequacy of food intake becomes an integral aspect of IBD care. Whether on regular or special diets, patients with IBD should be checked for intake adequacy and nutritional deficiencies on a regular basis and deficits should be appropriately corrected. Intake adequacy as well as nutritional deficiencies have been reported in several studies in children and adolescents with IBD, and they were shown to be different compared to their peer or RDI in several components/aspects [13]. The DRI provide reference values for energy and nutrient intake in healthy individuals and are used for assessing diets for individuals and groups. The disadvantage with using DRI is the lack of reference values for individuals with chronic disease or malabsorptive states. This may underestimate the true needs in this patient

population. As there is no standard criteria for nutrient adequacy in pediatric IBD, many studies use either age and gender matched healthy controls or DRI as comparison.

The intake of patients on SCD reported in this study was comparable to DRI and intake data from the NYFS. This is good news, however, anthropometry and growth status, body composition and selected blood chemistries are the truthful indices of nutritional adequacy and this type of data is essential when assessing peculiar diets' adequacy in children and adolescents with IBD.

Cystic Fibrosis

Nutritional status in the first 2 years of life in cystic fibrosis diagnosed by newborn screening

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Aims: To evaluate the nutritional status and respiratory outcomes in a French cohort of children with cystic fibrosis (CF) diagnosed by newborn screening (NBS).

Methods: ALIMUDE study (Alimentation Mucoviscidose Depistage) is a prospective study of 24 months duration, conducted at 30 French CF centers at university hospitals from April 2010 to September 2011. The diagnosis of CF relied on the identification of 2 CF transmembrane receptor (CFTR)-causing mutations and/or a sweat chloride (SC) value >60 mmol/L. The cohort was observational and there was no interference with centers' clinical management. The data collected included: demographic data, age at first visit, SC, CFTR genotype, CF-related initial symptoms, exocrine pancreatic insufficiency (EPI) or sufficiency (EPS), anthropometry, type of feedings, biochemistries, and pulmonary outcomes.

Results: The study enrolled 105 infants, EPI ($n = 86$) and EPS ($n = 19$), 99/105 completed the 2-year study.

In the whole cohort, infants with weight z-score "at risk," defined as weight-for-age less than –1SD at month 3 (57/104, 55%), were no more undernourished at month 24 than those "not at risk" (9/54, 17% vs. 4/44, 9%, $p = 0.27$). However, with a length z-score "at risk," defined as length-for-age less than –1SD at month 3 (45/103), stunting was more frequent (15/44, 34% vs. 6/52, 12%, $p = 0.01$). In the EPI cohort, 14/87 (16%) were undernourished at 12 months and showed no weight improve-

ment at 24 months (13/87, 15%). Stunting was even more common in EPI (25/85, 29% and 21/86, 24%, respectively) at 12 and 24 months.

EPI cohort had also lower birth weight z-scores and higher prevalence of initial symptoms ($p = 0.01$ and $p < 0.01$, respectively). At the initial visit, 47% of the EPI cohort was BF; BF was less common in the EPS cohort (28%). Compared with the EPS cohort, the EPI cohort consumed more calories (expressed in %EER): 129 (109; 145) versus 113 (97; 139), and more infants ingested >110% EER calorie intake (73 vs. 54%).

After introduction of pancreatic enzymes replacement therapy, the percentage of infants with EPI receiving >110% EER calorie intake fluctuated from 55 to 82%. Nearly all infants (93–100%) received salt and fat-soluble vitamin supplementation.

Both cohorts, EPI and EPS, had high isolation rates of methicillin-sensitive *Staphylococcus aureus* and rates of acquisition of *Pseudomonas aeruginosa,* 28% (24/87) and 25% (3/12), respectively.

The logistic regression model found a positive association between both weight and length z-scores "at risk" at month 24, and initial pulmonary symptoms (odds ratio [OR] 0.06, $p < 0.01$ and OR 0.08, $p < 0.01$, respectively). *Staphylococcus aureus* (OR 0.05, $p = 0.01$ and OR 0.17, $p < 0.01$) colonization was also associated with stunting. Pulmonary symptoms were less frequent when age at first visit was earlier than 1.2 months (33 vs. 67%, $p = 0.02$). Pulmonary outcome did not differ according to pancreatic status. Breast-feeding for at least 3 months delayed the first acquisition of *P. aeruginosa.* Despite sodium and fat-soluble vitamin supplementation, half of both cohorts had low urinary sodium output and half of the EPI cohort had low vitamin D levels.

Conclusions: ALIMUDE study is the first national prospective study in Europe on nutritional status in a CF cohort diagnosed by NBS. The study showed that, compared with the EPS, the EPI cohort had a significantly poorer growth pattern. Modalities of feeding (breast vs formula feeding) were not associated with nutritional status but BF up to 3 months delayed acquisition of *P. aeruginosa* beyond 12 months. Infants consuming high calorie density intake for some duration tended to have lower median weight z-scores at month 24, suggesting a "need-driven" intervention. There was no correlation between lipase dosages and weight z-scores, and no difference in dosages between infants with weight z-scores, "at risk" or not.

Comments on this manuscript are incorporated into the comments of the following one (Woestenenk et al, page 103).

The relationship between energy intake and body-growth in children with cystic fibrosis

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Background: International CF guidelines recommend a high-energy diet, with intakes between 110 and 200% of gender- and age-specific estimated average requirement (EAR). To date, very few details on the actual relation between routine dietary intake and the nutritional status are known. The study aimed to investigate the long-term effect of energy intake on body-growth in pediatric CF patients, aged 2–10 years.

Methods: This retrospective study included 2–10 years' old children born between 1988 and 2012 and diagnosed with CF and exocrine pancreatic insufficiency (EPI), who received medical care at the CF-centre of the University Medical Centre Utrecht, Holland. Yearly, weight and height were measured during routine clinical care visit, and dietary data were collected through 3-day dietary food records in clinical stable patients.

Results: The study investigated 191 children with proven CF (98% Caucasian, 98 boys). The mean follow-up period was 4.7 ± 2.3 years. At the initiation of the study, the z-scores weight-for-age (WFA), height-for age-adjusted-for-target height (HFA/TH) or body mass index (BMI) were below 0 in 125/191 (65%), 131/188 (70%), and 106/191 (55%) of children, and below –1 in 43/191 (23%), 55/188 (29%), and 31/191 (16%) of children, respectively.

The EAR was $\geq$110% in 457/969 (47%) of the food intake measurements. A linear regression analysis was used to calculate the association between baseline measurement of WFA, HFA/TH or BMI, and energy intake, expressed as absolute caloric intake.

Boys with a higher caloric intake had also a higher WFA, HFA/TH, and BMI (all $p < 0.05$). Each 100 calories increase in intake resulted in a 0.07 increase in WFA, a 0.05 unit increase in both HFA/TH and BMI. However, the caloric intake explained no more than 18, 6 or 7% of variation in WFA, HFA/TH or BMI, respectively. Longitudinally, in boys, the caloric intake was associated with WFA and BMI but not with HFA/TH. Each time a boy increased his intake by 100 calories, the z-score WFA would increase by 0.02 (95% CI 0.01–0.04), and z-score BMI increased 0.03 (95% CI 0.01–0.05).

Girls with a higher caloric intake had also a significantly higher WFA ($p < 0.05$). Each 100 calories increase in intake resulted in a 0.06 increase in z-score WFA. The caloric intake accounted only for 6% of the variation in WFA ($R^2 = 0.06$). However, there was no significant association between HFA/TH or BMI and caloric intake in girls. Longitudinally, in girls, the caloric intake was associated with WFA but not with HFA/TH and BMI. Each time a girl increased her intake with 100 calories, the z-score WFA would increase with 0.01 (95% CI 0.00–0.03).

Furthermore, the contribution of protein, fat, and carbohydrates, expressed as a percentage of the total energy intake, was not associated with WFA, or HFA/TH or BMI.

Conclusions: The present study showed that dietary intake was >110% EAR in less than half of intake evaluations. A positive impact of increasing energy intake on WFA was demonstrated, but not on HFA/TH (ideal growth). The caloric intake explained less than 18, 6 or 7% of variation in WFA, HFA/TH or BMI respectively, suggesting that other factors besides caloric intake are important and affect growth of children with CF.

Comments The ALIMUDE cohort is the second prospective study in children with CF diagnosed by NBS.

The first study was the Baby Observational and Nutrition Study (BONUS) published the previous year, which was a prospective multicenter study of infants with CF diagnosed by NBS in United States with a follow-up of 12 months [14]. The prevalence of undernutrition (13.3%) and stunting (23.9%) in the BONUS study was similar to that in ALIMUDE study. Similarly, EPI had a negative impact on the nutritional status, but not on the feeding type. Nutritional status in BONUS study was poorer in males and *P. aeruginosa* infection had negative influence on weight.

The landscape of CF has changed dramatically in the last decade due to the incorporation of new technologies for the diagnosis and treatment of the disease, starting with the implementation of CF NBS in many countries around the world [15]. CF diagnosis by NBS was shown to confer nutritional benefits, improved pulmonary outcome, and survival. Early diagnosis affords the opportunity to improve long-term outcomes through close monitoring and appropriate interventions beginning before severe nutritional deficits or irreversible airway damage have occurred. This is even more significant, especially now in the era of CFTR-targeted therapies.

Although significant progress was reported in weight gain of infants with CF, stunting is still common and affects mainly EPI children. In this group, neither increased caloric intake or pancreatic enzymes replacement therapy or addition of PPI seem to improve the growth status. Linear growth is a complex process with inflammatory, anabolic, and catabolic interactions. The pathophysiology of growth failure in children with CF is poorly understood. Besides malnutrition and chronic inflammation, impact of CFTR genotype on growth hormone-insulin-like growth factor 1 axis and essential fatty acids deficiency (reported in children with CF) have also been implied [16]. BF did not confer nutritional advantages but delayed the age of *P. aeruginosa* acquisition beyond 12 months, making it still the desirable feeding modality in infants with CF.

This study of Woestenenk et al. reported that absolute caloric intake in children with CF increased with age. However, when the caloric intake was expressed as EAR, it exceeded the EAR for healthy referents in the young, but stayed below the recommended intake for children with CF. In the older age groups, the intake was even below the EAR for healthy children.

Both cross-sectional and longitudinal evaluation showed that a higher caloric intake has an impact on weight (gain). Nevertheless, the variation in body growth, explained by caloric intake was restricted. Longitudinally, the magnitude of the association appeared relatively small, however, if repeated, possibly these effects may cumulate to a clinically significant effect on weight gain.

Nutritional status/growth and lung disease are closely interrelated. Several studies have shown that pulmonary function, pulmonary exacerbations, and bacterial colonization are all related in a way or other with the nutritional status of infants and children with CF. Furthermore, growth status is the cornerstone for clinical outcomes, including overall survival, into adulthood. Intensive monitoring and treatment, medical therapies, nutritional supplementation, and behavioral interventions may improve the chance of reaching these goals.

Risk of fractures in youths with celiac disease: a population-based study

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Aims: This study aimed to assess the risk of any fracture in a cohort of individuals with celiac disease (CeD), diagnosed in childhood or adolescence compared with matched reference individuals.
Methods: The study examined 213,635 individuals born and residing in the region of Friuli Venezia-Giulia Region in northern Italy between 1989 and 2011. For each patient with CeD, 5 reference individuals, matched for gender and birth year, were selected from the Medical Birth Register. Follow-up began on the date of CeD diagnosis until the end of the study, death, migration out of the area, or first hospital admission with any fracture, whichever occurred first.
Results: The study included 1,233 subjects with CeD and 6,167 matched references. Biopsy confirmation was available for 883 (72%) of the individuals with CeD, and 933 (76%) were identified by at least 2 data sources. The median age at CeD diagnosis was 6 years (range 0–17 years); 60% the study participants were females.
During follow-up until maximum age of 23 years, there were 22 hospital admissions/records for fractures in individuals with CeD compared with 128 in matched references, corresponding to incidence rates of 234 and 271 per 100,000 person-years, (HR 0.87; 95% CI 0.55–1.37). HR was similar after adjustment for vitamin D supplementation or maternal education. Risk of fractures occurring before the age of 18 years remained not significant (HR 0.95; 95% CI 0.59–1.51). There was no increased risk of fractures by gender, age or period at CeD diagnosis.
Conclusions: In this population-based, longitudinal record linkage study conducted in Northeast Italy, the hospital records of fractures in individuals with CeD were independent of CeD status, and not significantly higher than in the reference population. Neither the risk of fracture preceding or following CeD diagnosis was statistically significant.

Comments CeD is a systemic immune-mediated disease that develops in genetically predisposed individuals, upon ingestion of gluten, the major storage protein in wheat, barley, and rye. The clinical picture of malabsorption dominated by diarrhea and weight loss (classical CeD) is less seen these days. The more common, non-classical symptoms include iron deficiency, bloating, constipation, chronic fatigue, headache, abdominal pain, and osteoporosis. With the exception of osteopenia or osteoporosis identified by dual X-ray absorptiometry (DXA), other manifestations (bone pain, rickets, tetany) are rarely the presenting signs and symptoms of CeD in children [17].
Bone strength, the product of bone quality and mineralization, is largely determined by the maximum bone mass achieved during childhood and adolescence. In individu-

als with CeD, low bone mineral density (BMD) is the result of a combination of malabsorption, hypogonadism, and inflammation. Furthermore, adequate bone acquisition relies on optimal vitamin D and calcium intake, nutritional status, and exercise.

Low BMD has been described at diagnosis of CeD and may persist in some. In one study, 22% of children with CeD had BMD z scores between –2 and –1 z scores and up to 13% had BMD z scores less than –2 [18]. Fracture risk in patients with CeD is variable. Some studies report no increased fracture rates [19]. Currently, there are no consistent guidelines regarding when or with what frequency to assess BMD in newly diagnosed CeD or in those with subclinical disease. The International Society for Clinical Densitometry (ISCD) does not recommend routine evaluation of BMD in CeD [20]. Guidelines from the United Kingdom, however, recommend testing in all patients at the time of diagnosis [21]. Expert recommendations for the management of CeD in children, published from 2016, outlined the guidelines for bone status evaluation in children at diagnosis of CeD and during follow-up [22].

Routine screening for phosphorus, alkaline phosphatase, ± parathyroid hormone is not recommended. Similarly, DXA is not routinely recommended in children with a short duration of symptoms, as bone density recovers rapidly and completely on gluten-free diet (GFD) [22, 23].

Abnormalities of bone density are more likely to occur with presentations that are associated with severe malabsorption, prolonged delay in diagnosis, or clinical presentations suggestive of bone disease, including fractures. In selected patients with CeD who do not adhere to GFD, reduction in bone density and increased fracture risk may occur. In these situations, BMD is the test of choice. If abnormalities in BMD are identified, besides instructions on GFD, dietary counseling should include advice on vitamin D and calcium intake and supplementation, with calcium supplementation dependent on the lack of hypercalciuria. BMD testing is to be repeated after 1–2 years following GFD and calcium/vitamin D supplementation.

Last year, the NHANES-based study of Kamycheva reported a significant association between CeD autoimmunity and reduced BMD in both children and adults. Furthermore, in men aged ≥40 years, CeD autoimmunity was significantly associated with high FRAX hip fracture score and borderline significantly associated with FRAX major fracture score [24]. Two earlier population-based studies also reported a moderate increase in both the absolute and relative fracture risks in adult individuals with CeD [25, 26].

The present population-based study found a similar risk of fractures in children and young adults with CeD as the general population. However, the study was limited to hospital admission records of fractures, eventually ignoring the fractures diagnosed at the emergency rooms and discharged home after treatment or the children treated at the community clinics. Other limitations include lack of data on potential confounders besides vitamin D and maternal education as well as the short follow-up into adulthood.

Precise estimates of the excess fracture risk experienced by people with CeD in comparison with the general population is difficult and limited by several shortcoming, such as population size, prospective/retrospective collection of data, criteria used for the definition of CeD diagnosis, ability to adjust for multiple potential confounders, and most important of all – adherence to GFD, and duration of follow-up.

E-healthcare for celiac disease: a multicenter randomized controlled trial

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Background: Medical care for patients with celiac disease (CeD) after diagnosis consists of regular assessment of health, growth, gluten-free diet (GFD) adherence, and CeD-serology. Although important, the process is time consuming and many patients do not keep up with regular CeD follow-up. The present study investigated the (cost-) effectiveness of an online consultation use as a substitute for an outpatient consultation, in the follow-up of patients with CeD.

Methods: This multicenter, randomized, clinical trial recruited children and young adults ≤25 years diagnosed CeD for ≥1 year, from 7 academic and non-academic hospitals in The Netherlands. The study collected sociodemographic and growth data, symptom questionnaire, CeD-specific IgA antitransglutaminase-type-2 antibodies (TG2A) evaluated by a point-of-care (POC) testing, GFD adherence, CeD-specific health-related quality of life (HRQOL), and parents' and/or patients' satisfaction with the online consultation. The physician-researcher discussed the results with the participants/parents over the telephone, and sent a copy of the results to their physician. In case of abnormalities, an outpatient consultation was scheduled. The control group received traditional care at the outpatient clinic with their own physician. The primary outcome was disease control 6 months after the participant had finished the online or outpatient consultation, defined as negative TG2A using the POC test. Secondary outcomes were detection of health problems, evaluation of dietary adherence as well as CD-specific HRQOL, patient satisfaction, and costs 6 months after the online or outpatient consultation.

Results: In total, 304 participants were randomized to online ($n = 156$) or control ($n = 148$) groups. At baseline, there were significantly more controls with positive TG2A than online participants: 13/145 (mean titer of 21.5 U/mL; range 8–56) versus 2/153 (POC test; $p = 0.003$). In the control group, significantly fewer POC tests were positive than laboratory tests at baseline (1/134 vs. 13/145; $p = 0.012$). Six months later, the number of positive POC tests in the online group was similar to baseline (5/148 vs. 2/153; $p = 0.25$).

Abdominal pain, lassitude, and increased appetite were reported significantly more frequently by the online group. Growth status was not statistically different in either group. The self-reported dietary adherence was described as "strict" by 142 of 156 online participants and by 128 of 148 controls (91 vs. 87%; $p = 0.297$). Positive TG2A measured with the POC test or by conventional ELISA test did not correlate with self-reported gluten consumption (K = 0.001 and K = –0.024 respectively). At baseline consultation, participants' overall CeD-specific HRQOL was similar in both groups (neutral to bad). Upon reassessment approximately 6 months later, a statistically significant improvement was observed in the overall score of the online group ($p = 0.013$) but not in the overall score of the controls ($p = 0.810$). The improvement included the subscales of communication and diet. The mean satisfaction was significantly higher in controls than in the online group, both at

baseline (mean grade, 8.16 [range 5–10] vs. 7.65 [range 2–10]; $p < 0.001$) as well as 6 months later (mean grade, 8.01 [range 4–10] vs. 7.58 [range 3–10]; $p = 0.001$). However, 48% of the online participants ($n = 75$) regarded the online consultation to be as good as outpatient care. Six months after the intervention, the POC test was preferred to the conventional venipuncture by 80% of the online participants and by 81% of the controls.

Extra follow-up consultations because of detected abnormalities at the baseline consultation were similarly required among the online ($n = 29$) and the control ($n = 17$) groups ($p = 0.06$).

The mean total costs in the online group were EUR 202 lower per participant during the study period (medical savings of EUR 138; nonmedical savings of EUR 64).

Conclusions: Because the performance of the POC test was unreliable, the primary outcome of the study (negative TG2A at follow-up using the POC) could not be assessed. However, the study secondary end-points suggest that online consultations for children and young adults with CeD saved costs, increased CeD-specific HRQOL, and are satisfactory for the majority of participants.

Comments	The only treatment currently available for individuals with CeD is a strict, lifelong GFD, which is burdensome, restrictive, and challenging to adhere to. Yearly follow-up including general health assessment, GFD adherence, and CeD serology are recommended by both pediatric and adult gastroenterology associations [27, 28]. Several studies on follow-up in children with CeD after diagnosis have reported that many patients are lost to follow-up, GFD adherence is variable, and many patients and families have difficulties in coping with the requirements/challenges of GFD as reflected by poorer HRQOL reported by these patients [29].
	This study investigated the performance of online consultation in patients with CeD diagnosed at least one year before. Unfortunately, the study could not test the primary study outcome, negative TG2A serology (by POC test) at follow-up, due to high POC false-negative results. The POC tests were initially designed for primary clinical screening in patients suspected of CeD. Performance of POC tests in these circumstances was shown to be good with high diagnostic accuracy when compared to serologic laboratory-based tests: TG2A and anti-endomysial antibody [30]. As low antibody titers, close to cutoff of normality, are expected in patients with CeD on GFD and occasionally dietary transgressions, this group requires a very sensitive POC. Otherwise, only laboratory-based serology tests will suit for patients' follow-up after the initiation of GFD, although even these tests' sensitivity has been found to be lower compared to detailed dietary interview or duodenal biopsies [31, 32].
	The online consultation detected more symptoms than traditional care, probably because of the use of multiple choice questionnaire compared to limited time spent at office physicians'. The vast majority of the participants favored a POC self-test rather than the conventional venipuncture (80%), implying that they would welcome its implementation in their health care. Furthermore, online consultation increases the CD-specific HRQOL while saving costs. Participants' satisfaction with the online consultation in this study was not associated with age or disease duration, suggesting that the optimal combination of online and outpatient should be adapted to each patient/family based on personal characteristics.
	Patients with abnormalities at baseline or follow-up consultations were appointed for extra/office consultations, suggesting that the online consultations are more appropriate as a supplement, not substitute for office/outpatient consultations.
	A previous online intervention in adults with CeD successfully achieved increased GFD adherence and knowledge in Australian patients with CeD, which may represent a more reasonable and achievable goal for online consultations, especially for individuals struggling to achieve or maintain adequate GFD adherence [33].

Body composition predicts growth in infants and toddlers with chronic liver disease

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Background: Malnutrition and growth failure are frequently reported in infants and children with chronic liver diseases (CLD). Body composition (BC) in these patients is notoriously abnormal, and not accurately reflected by the typical anthropometry evaluations (weight, length/height, body mass index). The aims of the present study were to validate arm anthropometric measures to estimate the BC of infants and toddlers with CLD, using dual X-ray absorptiometry (DXA) as the standard criterion, and to determine BC predictors of linear growth.

Methods: This cross-sectional study investigated 15 infants and toddlers with CLD. Patients after liver transplantation or with associated metabolic, genetic, or systemic diseases were excluded. DXA (pediatric software) was the standard investigation for the validation of anthropometric indicators. The variables recorded using DXA were fat mass (FM), free-fat mass (FFM), and bone mineral content (BMC). The anthropometric measurements included weight, length, head circumference, mid-upper arm circumference, triceps, and subscapular skinfolds thickness (SFT). Arm fat and muscle areas were calculated according to the published formulas. Z scores of length-for-age and body mass index (BMI) were calculated with the WHO 2006 reference pattern. Z scores of arm anthropometric indicators were calculated using references. The severity of liver disease was estimated with the Pediatric End-Stage Liver Disease Score.

Results: The patients' median age was 14 months (4–28 months), 11/15 were younger than 18 months.

Twelve of the 15 children had biliary atresia, 7/12 after portoenterostomy.

DXA: According to Fomon's reference standard, 12 patients (80%) had low FFM (median <80%) and 10 patients (67%) had decreased FM (median <80%). According to Butte references, 53.3% ($n = 8$) had FM depletion (z score <–2 SD). BMC was <–2 standard deviation (SD) in all cases (–5.4 SD ± 1.9).

Anthropometric indicators: With the exception of BMI and subscapular skinfold, all the investigated parameters (weight, length, head and arm circumference) were below –2 SD.

DXA/anthropometry correlations: FM had a positive and significant correlation with all the anthropometric indicators except subscapular SFT and BMI. FFM had a significant correlation and could be predicted by arm circumference, arm total area, and arm muscle area. BMC showed significant correlation with arm circumference, arm areas, length, and head circumference.

Hartman · Shamir

Prediction models of length and head circumference from BC: FM plus FFM explained 88% of length and FFM plus BMC explained 91% of length. FM and FFM predicted head circumference (81%).

Conclusions: The use of BMI to assess the nutritional status of children with CLD grossly underestimated the rate and severity of malnutrition in these children. With the exception of BMI and subscapular skinfold, all the other anthropometry measures were able to disclose the severe nutritional status of the children evaluated in this study. In contrast to BMI and subscapular skinfold, arm anthropometry showed a good correlation with BC indicators, which makes it a useful tool for nutritional assessment of patients with CLD.

Comments on this manuscript as well as the following one (Li et al) are incorporated into the comments of the manuscript of Lu et al (page 111).

Preoperative nutritional status and its impact on cholangitis after Kasai portoenterostomy in biliary atresia patients

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Background: The current therapeutic approach for biliary atresia (BA) consists of restoring the bile flow using Kasai portoenterostomy (KPE). Cholangitis is the most common and serious complication following KPE in patients with BA and leads to increased risk of morbidity and mortality in BA patients. The present study evaluated the effects of preoperative nutritional status on cholangitis after KPE in infants with BA.

Methods: This retrospective study investigated the data of 106/133 infants with type III BA who underwent KPE from 2010 to 2014 at the Department of Pediatric Surgery, Tongji Hospital.

The following data were recorded: demographic, anthropometry, and biochemistry before and after KPE, incidence of cholangitis, ratio of jaundice clearance, and 2-year survival with the native liver. Cholangitis was defined according to conventional criteria; early cholangitis was defined as episodes of cholangitis within 3 months after KPE.

The Screening Tool for Risk on Nutritional status and Growth (STRONGkids) questionnaire was used to evaluate infants' nutritional status. This nutritional risk screening questionnaire consists of 4 items, including subjective clinical assessment (1 point), high-risk disease (2 points), nutritional intake and losses (1 point), and weight loss or poor weight gain (1 point). Patients with STRONGkids score 0 were classified as having low nutritional risk (LNR), a score of 1–3 classified them at moderate nutritional risk (MNR), and a score of 4–5 classified patients at high nutritional risk (HNR).

Results: STRONGkids results preoperatively were as follows: 0/106 patients were at LNR, 49/106 patients were at MNR (46.2%), and 57/106 infants were at HNR (53.8%).

No significant differences in gender, birth weight, preoperative weight, age at surgery or biochemistry existed between the 2 groups. The serum albumin was higher (44.3 ± 3.4 vs. 37.8 ± 5.0 g/L, $p = 0.009$) and postoperative length of hospital stay was shorter (13.35 ± 5.47 vs. 17.79 ± 5.57 days, $p = 0.023$) in MNR compared to HNR. No significant differences in the preoperative total bilirubin levels ($p = 0.819$) or the percentage decrease in bilirubin levels 2 weeks after surgery ($p = 0.298$) were observed between the MNR group and the HNR group.

Early cholangitis (within 3 months after KPE) was diagnosed in 8 cases (16.3%) in the MNR group and in 20 cases (35.1%) in the HNR group ($p = 0.029$). In the first 12 months after surgery, MNR patients had 1.8 episodes per patient, whereas HNR group had 2.6 episodes per patient ($p = 0.031$). During the entire follow-up, 29/49 (59.2%) of cholangitis episodes occurred in the MNR and 39/57 (68.4%) episodes in the HNR group, ($p = 0.263$).

At the end of the 6-month follow-up, 30 cases in MNR group and 22 cases in HNR group exhibited total serum bilirubin levels less than 20 mmol/L, ($p = 0.02$). Furthermore, 2-year survival with the native liver was 36.7% in the MNR group and 21% in the HNR group ($p < 0.05$).

Conclusions: All patients with BA reported in this study were at nutritional risk. Poor nutritional status in children with BA after KPE was closely associated with an increased prevalence of cholangitis and increased need for liver transplantation or death by 24 months of age.

Effect of preoperative growth status on clinical outcomes after living-donor liver transplantation in infants

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Background: Children with chronic liver diseases (CLD) have a high prevalence of growth retardation, and nutritional status has been shown to significantly affect prognosis of children with CLD. The present study investigated the impact of growth status on clinical outcomes of living-donor liver transplantation (LDLT).

Methods: The study evaluated 131 infants, less than 1 year of age, who underwent LDLT from 2009 to 2014 at the Department of Liver Surgery, Ren Ji Hospital. Thirty one patients with weight-for-age z-scores less than –2SD constituted the abnormal growth group. Using a multivariate case-matched method, the patients in the abnormal growth group were randomly matched (1:1) to a group of patients with normal growth status. Demographic characteristics, liver function, postoperative complications, survival outcomes, and effects of catch-up growth were compared between the 2 groups.

Results: There were 29 boys and 33 girls with a median age of 8 months (range, 5–11). Baseline characteristics including age, sex, Pediatric End-Stage Liver Disease score, blood group, and history of Kasai procedure were exactly matched between the 2 groups except for nutritional status. Patients from the abnormal growth group had significantly less body weight (6.0 vs. 7.5 kg; $p < 0.01$), height (65 vs. 63 cm; $p < 0.01$), and BMI (17.0 vs. 14.8 kg/m^2; $p < 0.01$) before LDLT.

Complications and graft survival: Acute cellular rejection, pulmonary infections, and cytomegalovirus infections were the 3 most common complications observed in the whole group, and occurred in 13 (21.0%), 11 (17.7%), and 10 (16.1%) patients, respectively. There was no significant difference in any specific early complications or patient and graft survival rates (5-year: 90.2 vs. 96.8%; $p = 0.313$). However, LDLT was followed by notable catch-up growth in both groups, especially for children with more serious growth retardation before LDLT.

Catch up growth: Body weight z scores of the 2 groups became similar 6 months after LT, differences in height z scores between the 2 groups gradually diminished and lost significance 18 months after LT.

Conclusions: In this group of young infants, growth status before LDLT did not affect the rate of early complications or patients/graft outcome at 5 years. Furthermore, following LDLT the abnormal growth group showed weight catch up by 6 months after surgery and height catch up by 18 months following LDLT.

Comments	The liver is an essential organ, playing a pivotal role in energy and nutrient metabolism. Protein energy malnutrition, leading to growth failure, is an inevitable consequence of chronic liver disease in childhood. Severe liver disease leads to disturbances in nutrient digestion, absorption, distribution, storage, and use. Malnutrition in children with CLD has a complicated pathophysiology, it is under diagnosed, and has important prognostic implications. Within the pediatric population, infants and small children are most vulnerable to malnutrition, due to markedly elevated energy and growth requirements as well as limited reserves. Malnutrition is very common among children with CLD, mainly in the cholestatic subgroup, studies from North America and Europe estimated the prevalence of this condition to be around 50–80% [34].

Accurate nutritional assessment is critical to the management of children with CLD. Standard weight and height measurements may be inaccurate in children with CLD, as these can be misinterpreted due to fluid overload, ascites, and organomegaly. Body weight alone may underestimate the incidence of malnutrition in adults and children with CLD by up to 50%. Linear growth is a more sensitive parameter, but stunting and growth decline occur late during follow-up. Thus, other measurements, such as triceps or subscapular skinfolds, mid arm circumference, and arm muscle measurements (mid arm muscle area), should be used.

Arm circumference can be used as an index of energy and protein stores, while skinfold is an indicator of subcutaneous fat (energy) stores, and both measurements can reveal poor nutritional status and early loss in fat stores before height and weight are affected [35].

Using dual X-ray absorptiometry (DXA) for the assessment of body composition (BC), Hurtado-Lopez et al. (page 108), showed that FM had a positive and significant correlation with all the anthropometric indicators except subscapular skinfold and body mass index (BMI). Free-fat mass (FFM) had a significant correlation and could be predicted by arm circumference, arm total area, and arm muscle area. Bone mineral content (BMC) showed significant correlation with arm circumference, arm areas, length, and head circumference. These findings corroborate with the recommendations that nutritional status in children with CLD cannot be limited to usual anthropometric indicators, but should include the set of all measurements and when possible, BC evaluation using either DXA or bioelectrical impedance assessment [36].

Malnutrition has been reported as a significant risk factor for both morbidity and mortality related to surgery in general and liver transplantation in particular [37, 38].

Although the cholangitis rate after Kasai portoenterostomy was higher in patients with HRM, the short-term complication rate and recipients and graft survival after LDLT was similar in infants with poor weight gain who also showed weight and height catch up within 6 and 18 months after transplantation, respectively. These findings confirm the importance of good nutritional status for improved outcome

Human Immunodeficiency Virus Infection

Dietary inadequacies in HIV-infected and uninfected school-aged children in Johannesburg, South Africa

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Background: Dietary inadequacies are of particular concern in children with HIV, as malnutrition can further contribute to immune dysfunction and potentially haste disease progression. The aim of the present study was to assess the dietary intake in a group of school-aged perinatally HIV-infected children with well-controlled disease on antiretroviral treatment (ART).

Methods: This cross-sectional study reported dietary intake data collected from all children at the baseline visit of the CHANGES Bone Study, an observational cohort study of HIV-infected and uninfected children aged 5–9 years, conducted in Johannesburg, South Africa. The analysis includes 220 perinatally HIV-infected children who started ART in infancy and a control group of 220 healthy HIV-uninfected children, comprised of sibling/household members of the HIV-infected subjects and otherwise healthy children of a similar age from the same communities.

The study data included demographic information, anthropometry and dietary intake, evaluated by a single 24-h recall diet questionnaire and a quantitative Food Frequency questionnaire.

Results: There were 228 boys (51.8%), mean ± SD age 6.7 ± 1.4 years. The HIV-infected group was younger (6.4 vs. 7.0 years, $p < 0.0001$). The mean weight-for-age z-score and height-for-age z-score (HAZ) of both the HIV-infected group (–0.83 ± 0.9 and –1.4 ± 0.9, respectively) and HIV-uninfected group (–0.29 ± 1.1 and –0.82 ± 0.9, respectively) fell below the reference, and both indices were significantly lower in the HIV-infected compared with the HIV-uninfected group ($p < 0.0001$). The HIV-infected children had been on ART for a mean of 5.7 ± 1.1 years, 93.6% had viral suppression (HIV RNA quantity <400 copies/mL) and a mean CD4 percentage of 37.3 ± 7.1%, which is

normal for children of this age. There were no significant differences in household characteristics between the groups.

Among the HIV-uninfected children, 85.2% fell below the recommended intake for healthy children aged 6–9 years. Among the HIV-infected children, 82.5% fell below the recommended intake of 1,815 kcal/day (10% higher) for HIV-infected. The diet of HIV-infected children consisted of a higher mean percentage of energy intake from carbohydrates (53.0 ± 9.2 vs. 50.6 ± 10.7%, $p = 0.012$) and slightly lower mean percentage of energy intake from fat (29.8 ± 9.6 vs. 31.8 ± 11.4%, $p = 0.043$) and protein (12.9 ± 4.3 vs. 13.5 ± 4.0%, $p = 0.13$). In addition, HIV-infected children had a higher mean percentage of fat intakes from saturated fat (33.0 ± 7.9 vs. 30.8 ± 6.6%, $p = 0.002$) compared with HIV-uninfected children, and higher mean percentage of fat intake from trans-fat (2.7 ± 2.4 vs. 2.3 ± 1.9%, $p = 0.048$). HIV-infected children had a higher mean percentage carbohydrates coming from added sugars compared with the HIV-uninfected children ($p = 0.017$). Analysis of the 10 leading sources of total energy showed that half of the items were either refined grains or fats/oils and sweets. The food items that contributed with the highest percentage to the total energy intake were sunflower oil (7.3%), savory snacks (6.2%), and bread (4.5%).

Folate, vitamin A, vitamin D, calcium, iodine, and selenium were all micronutrients of concern as >50% of the group failed to meet the estimated average requirement (EAR) in both HIV-infected and HIV-uninfected groups. In addition, vitamin C was a micronutrient of concern for the HIV-uninfected group, with 56% of the group failing to meet the EAR.

Conclusions: The findings from this study reported on the typical diet of HIV-infected and uninfected children in Johannesburg, South Africa. The reported energy intake of HIV-infected children exceeded that of the HIV-uninfected children by approximately 10%. However, neither group met the recommended daily energy intake and the majority (>80%) of children (with and without HIV) failed to achieve the energy recommendations. Both HIV-infected and HIV-uninfected children consumed lower than recommended amounts of protein and excess of added sugars. Furthermore, in a substantial number of children in both groups, micronutrients' intake failed to meet the EAR. The observed shortcomings in the energy intake in this cohort indicate a potential threat to long-term growth and development and suggest that opportunities for interventions to improve dietary intake for both groups should not be wasted.

Comments on this manuscript are incorporated in the comments of the following one (Augustemak de Lima et al., page 115).

Nutrition and Growth in Chronic Disease

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Dyslipidemia, chronic inflammation, and subclinical atherosclerosis in children and adolescents infected with HIV: the positHIVe health study

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Background: HIV-infected children and adolescents may be at increased risk for cardiovascular disease (CVD) due to the presence of chronic HIV infection, related complications, and adverse reactions of chronic antiretroviral treatment (ART). The aim of this study was: (1) to compare cardiovascular risk factors, chronic inflammation, and carotid intima-media thickness (IMTc) between the HIV and a control group; (2) determine the association of HIV and ART regimens with cardiovascular risk factors, chronic inflammation, and IMTc; and (3) identify variables associated with elevated IMTc.

Study design: The PositHIVe Health Study is a cross-sectional study with a focus on lifestyle, physical fitness, and cardiovascular risk factors in HIV-infected children and adolescents (HIV group) and healthy controls (control group). The study was conducted in Florianopolis, Brazil from November 2015 to September 2016.

Participants: The HIV group participants were 8–15 years old and were HIV-infected perinatally. The control group comprised of a 1:1 ratio children and adolescents, gender- and age-matched to the HIV group. The study collected demographic and socioeconomic data, anthropometry and sexual maturation, systolic (SBP) and diastolic blood pressure (DBP) measurements, and information about ART and CD4 T-cell count.

Cardiovascular risk factors, biomarkers of inflammation, and IMTc: Serum lipid profiles, glucose and insulin, HbA1C, C-reactive protein (CRP), and cytokines (interleukin [IL]-6 and TNF-α) were evaluated in blood samples obtained after 10 hours fast. Body composition was assessed using DXA, and fat mass index was calculated by the ratio of body fat (kg) to the square of the height (m). IMTc was determined in the right common carotid artery, using ultrasound, the mean and maximum values of IMTc (mm) were considered for analysis.

Results: The study included 130 children and adolescents (HIV group = 65; control group = 65) aged 8.0–15.2 years.
HIV group had lower height-for-age z-score but higher BMI compared to control group. Eleven participants (16.9%) were not on ART and 44/65 HIV-infected participants (67.7%) had undetectable viral load (<40 copies/mL). HIV-infected children and adolescents were similar to controls with respect to total body fat, trunk body fat, fat mass index, SBP, DBP, insulin, HOMA-IR, and total cholesterol; however, the HIV group had higher values of glucose, triglycerides, LDL-C, total cholesterol (TC)/HDL-C, LDL-C/HDL-C, CRP, IL-6, and TNF-α when compared to the control group. HDL-C and HbA1c were lower in the HIV group. The mean and maximum IMTc were significantly increased in the HIV group compared to the control group, mean (SD)/median (IQR); mean IMTc (mm) 0.526 (0.100) vs. 0.490 (0.044), $p = 0.009$; and IMTc max (mm) 0.615 (0.112) vs. 0.581 (0.057), $p = 0.030$.
Of the 65 HIV-infected participants: 39/65 (60%) were on PI-ART, 11/65 were not treated, and 15/65 were on non-PI-ART.
PI-ART patients had high values of TC/HDL-C, total cholesterol, and triglycerides, increase in TC (18.4 mg/dL), LDL-C (22.6 mg·dL^{-1}), triglycerides (0.67 natural log), HOMA-IR (0.35), IL-6

(0.57 square root), CRP (0.65 natural log), and IMTc (0.05 natural log), compared to control group.

HIV infection in non-PI-ART patients was associated with a lower HDL-C (–10.6 mg/dL) and a higher IL-6 (0.96 of the square root) and IMTc (0.09 of the natural logarithm). They also had an increase in fat mass index (1.25 kg/m^2), IL-6 (0.67 square root), a reduction in SBP (8.6 mm Hg) and HDL-C (24.7 mg/dL) compared to control group.

No statistical differences were found in inflammatory mediators analyzed based on viral load.

In HIV-infected children and adolescents, higher IMTc was associated with increased SBP and decreased TNF-α, independent of IL-6, glucose, and the PI-ART regimen. The final model explained 16% of the variability of the IMTc ($p = 0.0080$; F = 3.48).

In HIV-infected children and adolescents on PI-ART, male gender, lower of trunk body fat, increased glucose, and IL-6 were associated with increased IMTc independent of age and SBP. The final model explained 28% of the IMTc variability ($p = 0.0100$; F = 3.42).

Conclusions: HIV-infected children and adolescents had health profiles potentially associated with premature atherosclerosis due to inflammation, elevated IMTc, higher atherogenic lipid levels, and higher blood glucose levels, regardless of the use of ART. High IMTc was associated with SBP and TNF-α in HIV-infected children and adolescents. In patients using PI-ART, male gender, trunk body fat, glucose, and IL-6 were predictors of increased IMTc.

Comments	Introduction of ART for HIV infection treatment has dramatically reduced the mortality and increased the lifespan of HIV-infected subjects. Lately, atherosclerosis and CVD have become the major cause of morbidity and mortality of HIV-infected subjects [39]. The pathogenesis of atherosclerosis in HIV -infected patients is multifactorial as both chronic HIV exposure and its treatment (ART) are associated with elevated risk of atherosclerosis [40]. Early generations of antiretroviral regimens, especially those that included protease inhibitors (PI), were associated with dyslipidemia (high levels of LDL-C and triglycerides and low HDL-C) and may have had other pro-atherogenic effects too. HIV-infected subjects treated with PI-ART were shown to have a higher prevalence of carotid lesions compared with PI-naive patients or uninfected controls. Newer ART regimens, however, are less likely to cause elevation of LDL and TG, presumably diminishing the pro-atherogenic effects of these treatments. Nevertheless, HIV-associated dyslipidemia is not eliminated, as low levels of HDL persist in both treated and untreated patients. HIV infection itself, rather than antiretroviral regimens, has also been implicated as a cause of dyslipidemia. Indeed, in vitro and in vivo studies revealed the inhibitory effect of HIV protein Nef on cellular cholesterol transporter ABCA1 and ABCA1-dependent reverse cholesterol transport, the key step in HDL formation [41].

Several studies reported an increased risk of atherosclerosis in adult HIV patients [39]. This study of Augustemak de Lima et al. showed that the atheratogenic risk factors are present in the HIV-infected children and adolescents, including higher atherogenic lipid levels, higher blood glucose levels, inflammatory markers, and also elevated IMTc. HIV-infected children/adolescents had a classic atheratogenic lipid profile (low HDL-C) and high IL-6 proinflammatory cytokine irrespective of ART use. Compared to the healthy controls, they also had elevated IMTc.

The increase in the IMTc reflects the cumulative damage in the endothelium structure. IMTc is considered a marker of preclinical atherosclerosis in children with familiar hypercholesterolemia and has been used as a surrogate marker of atherosclerosis [42]. IMTc has been shown to be related to the presence and severity of cardiovascular risk factors [43]. Perinatally, HIV-infected children and adolescents have increased risk of atherosclerotic disease due to exposure to chronic inflammation from the earliest stages of the disease and use of ART from young age.

The correlations between IMTc and SBP and TNF-α in the HIV-infected group suggest that not dyslipidemia but rather high SBP and inflammation affected IMTc. In the PI-ART group, IMTc correlated with male gender, trunk body fat, glucose, and IL-6, suggesting that in these patients other risk factors affected IMTc measure. The combination of inflammatory cytokines, abnormal metabolic profiles, and male gender, shown in this study to be correlated with IMTc, reminds of the classic CVD risk scores, Framingham or the newest 2013 American College of Cardiology and American Heart Association, used to calculate the 10 years CVD risk in adults [44].

The deviant dietary intake of HIV-children reported in the study of Shiau et al. (page 112), with high energy intake from carbohydrates (added sugar) as well as higher mean percentage of fat intake from saturated fat (33.0 ± 7.9 vs. $30.8 \pm 6.6\%$, $p = 0.002$) and from trans-fat (2.7 ± 2.4 vs. $2.3 \pm 1.9\%$, $p = 0.048$) adds further dimensions to atherosclerosis risk factors present in HIV-infected children.

The long-term health monitoring of HIV-infected pediatric patients, keeping the perspective of prevention of atherosclerotic disease in mind, is even more urgent at present due to the increase in the survival of the HIV-infected population. Furthermore, there is a high need to formulate interventions, with lifestyle changes and drug therapies, with the potential to improve the patients' lipid profile, inflammatory status, and reduce the cardiovascular risk in HIV-infected children and adolescents.

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Early Nutrition and Its Effect on Growth, Body Composition and Later Obesity

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Introduction

Early nutrition and early growth are convincingly associated with growth, body composition, development, and health later in life. We have chosen 11 publications from July 1, 2017 to June 30, 2018 which we find are of special interest. We have divided them into 3 topics: Breastfeeding, growth, and obesity (4 papers), Early life protein intake and growth (3 papers), and Early growth, growth patterns, and obesity (4 papers).

Recently, there have been an increasing number of publications on early nutrition and growth from studies in low- and middle-income countries (LMIC). These papers focus on the associations between early nutrition and growth and later undernutrition as well as later overweight and obesity. Many LMICs have a "double burden" of diseases linked to under- and overnutrition. We have therefore included several relevant and interesting papers from LMICs. Five of the selected papers include growth trajectory analyses. These analyses have become a valuable tool to assess how early nutrition is associated with specific growth patterns and how early growth patterns may predict later growth and body composition outcomes.

The growth of breastfed infants, including changes in body composition, is different from formula-fed infants. However, the increasing number of studies within this field shows diverse patterns. There are differences between populations and some of the differences between breastfed and formula-fed infants are also likely to be smaller now, as the composition of infant formula is modified to resemble breast milk more, for example, protein content is reduced. Furthermore, to what degree breastfeeding protects against later overweight and obesity is still discussed. We have chosen 4 recent papers with the common theme breastfeeding, growth, and later obesity.

Early life protein intake is important for ensuring optimal growth during early life. Both protein amount and especially quality are important for optimal growth during early life, and low-quality protein is a major contributor to stunting and wasting in low-income countries. On the contrary, too high protein intake in early life might be linked to later risk of obesity and avoiding high protein intake in early life has been suggested as a preventive strategy for obesity [1]. However, this field is still under considerable research and a few new studies have provided important insights worth highlighting. In the last section "Early growth, growth patterns, and obesity" we have included 3 studies from South Africa, Ethiopia, and China and one study with data from 4 cohorts from different European countries. These 4 papers underline that there are differences between populations when examining the association between early nutrition and growth and long-term health, and that the problem of double burden of disease is important. These issues have to be taken into consideration when exploring this research area, especially the differences between low-, middle-, and high-income countries.

Key articles reviewed for this chapter

Breastfeeding, Growth, and Obesity

Breast-feeding duration for the prevention of excess body weight of mother-child pairs concurrently: a 2-year cohort study
Mastroeni MF, Mastroeni SSBS, Czarnobay SA, Ekwaru JP, Loehr SA, Veugelers PJ
Public Health Nutr 2017;20:2537–2548

Associations of infant feeding with trajectories of body composition and growth
Bell KA, Wagner CL, Feldman HA, Shypailo RJ, Belfort MB
Am J Clin Nutr 2017;106:491–498

The role of early life growth development, the FTO gene and exclusive breastfeeding on child BMI trajectories
Wu YY, Lye S, Briollais L
Int J Epidemiol 2017;46:1512–1522

Excessive weight gain in exclusively breast-fed Infants
Saure C, Armeno M, Barcala C, Giudici V, Mazza CS
J Pediatr Endocrinol Metab 2017;30:719–724

Early Life Protein Intake and Growth

A meat- or dairy-based complementary diet leads to distinct growth patterns in formula-fed infants: a randomized controlled trial

Tang M, Hendricks AE, Krebs NF

Am J Clin Nutr 2018;107:734–742

Evaluation of the efficacy, safety and acceptability of a fish protein isolate in the nutrition of children under 36 months of age

Ochoa TJ, Baiocchi N, Valdiviezo G, Bullon V, Campos M, Llanos-Cuentas A

Public Health Nutr 2017;15:2819–2826

Complementary feeding with cowpea reduces growth faltering in rural Malawian infants: a blind, randomized controlled clinical trial

Stephenson KB, Agapova SE, Divala O, Kaimila Y, Maleta KM, Thakwalakwa C, Ordiz MI, Trehan I, Manary MJ

Am J Clin Nutr 2017;106:1500–1507

Early Growth, Growth Patterns, and Obesity

The associations between adult body composition and abdominal adiposity outcomes, and relative weight gain and linear growth from birth to age 22 in the birth to twenty plus cohort

Prioreschi A, Munthali RJ, Kagura J, Said-Mohamed R, De Lucia Rolfe E, Micklesfield LK, Norris SA

PLoS One 2018;13:e0190483

Accretion of fat-free mass rather than fat mass in infancy is positively associated with linear growth in childhood

Admassu B, Ritz C, Wells JCK, Girma T, Andersen GS, Belachew T, Owino V, Michaelsen KF, Abera M, Wibaek R, Friis H, Kæstel P

J Nutr 2018;148:607–615

Infant BMI peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort

Sun J, Nwaru BI, Hua J, Li X, Wu Z

BMJ Open 2017;7:e015122

The effect of early feeding practices on growth indices and obesity at preschool children from 4 European countries and UK schoolchildren and adolescents

Moschonis G, de Lauzon-Guillain B, Jones L, Oliveira A, Lambrinou CP, Damianidi L, Lioret S, Moreira P, Lopes C, Emmett P, Charles MA, Manios Y

Eur J Pediatr 2017;176:1181–1192

Breast-feeding duration for the prevention of excess body weight of mother-child pairs concurrently: a 2-year cohort study

Mastroeni MF[1, 2], Mastroeni SSBS[1, 3], Czarnobay SA[2], Ekwaru JP[1], Loehr SA[1], Veugelers PJ[1]

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Objective: The aim of the study was to examine the association between breastfeeding duration and the risk of excess body weight (defined as weight-for-age >85th percentile for the children and BMI ≥25.0 kg/m^2 for mothers) concurrently in mother-child pairs 2 years after delivery.

Methods and design: The study was a prospective cohort study in Joinville, Brazil including 305 mothers and their single born term healthy children recruited from the public maternity hospital. Birth length and weight were collected from hospital records. At 2 years, anthropometry was measured on mother-child pairs and information regarding breastfeeding and socioeconomic status was obtained by questionnaires. Breastfeeding was categorized as exclusive breastfeeding according to WHO definition, otherwise as non-exclusive breastfeeding. Multivariable logistic regression was used to examine the relationship between breastfeeding duration and risk of excess body weight in crude and adjusted models.

Results: At 2-year follow-up, in 23.6% of mother-child pairs, both the mother and the infant had excess body weight. Children breastfed for <2 months were more likely to have excess body weight than children breastfed for ≥6 months (OR 2.4; 95% CI 1.1–5.1) in a model adjusted for various potential confounders. Also mothers breastfeeding for <2 months were more likely to be overweight compared with those who breastfed for ≥6 months (OR 2.9; 95% CI 1.1–8.1). As the duration of breastfeeding decreased the likelihood of mother-child pairs having excess body weight progressively increased. In addition to breastfeeding duration, other independent determinants of excess body weight were pre-pregnancy BMI, gestational weight gain and number of pregnancies in mothers, and birth weight in children, all being associated with increased risk of excess body weight.

Conclusions: The risk of both maternal and child excess body weight 2 years after birth seems to be reduced by extending the duration of the breastfeeding period. Since members of the same family could be influenced by the same risk factors, continued promotion and support of breastfeeding may help to attenuate the rising prevalence of overweight in mother-child pairs.

Comments The impact of breastfeeding on later health outcomes has been studied extensively, especially if breastfeeding compared to formula feeding has long-term protecting effect on the risk of obesity. It has been concluded that there is suggestive evidence of a protective effect [2], but other studies could not find an effect [3]. During infancy, formula-fed infants exhibit a different growth pattern showing overall more rapid growth compared to breastfed infants but body composition is also affected by the feeding mode. According to a meta-analysis formula, feeding increases the fat mass in late infancy which may increases the risk of overweight in later life [4].

This study by Mastroeni et al. is interesting because it explores the impact of breastfeeding on overweight in both the mother and the infant 2 years after birth. An in-

verse relationship between duration of breastfeeding and excess body weight was suggested as longer duration of breastfeeding decreased the risk of excess body weight for both children and mothers individually and as mother-child pairs. The weight reducing effect of breastfeeding on mothers is usually explained by the high demands for energy for producing breast milk, and it is suggested that the fat depots build up during pregnancy is a buffer which will provide part of the energy needed for milk synthesis. Hormone levels may also be involved. During late pregnancy and at birth, maternal leptin levels are high to promote high energy stores required for fetal growth and lactation as described above and leptin decreases throughout the lactation period. Mothers not breastfeeding may therefore have a longer period with high leptin level and hence weight retention [5]. Leptin levels were not available in this study but future studies may include this to elucidate the role of leptin levels in mothers during the lactation period adjusted for relevant covariates.

Limitations to this study is that it is a small cohort and the follow-up at 2 years is a relatively short period for investigating the effects later in life.

In a recent study by Rzehak et al. [6], data from contemporary cohorts were combined investigating the effect of breastfeeding on growth at 6 years ($n = 6,708$) and body composition at 20 years (only one cohort). Overall this large study also supported the protective role of breastfeeding on later obesity in childhood and young adulthood. Below we have included a paper by Bell et al. (see the following manuscript) investigating the immediate/short-term protective effects of breastfeeding on body composition in infancy but also a paper by Saure et al. (page 126) describing the rare cases where breastfed infants actually gain excess weight while being exclusively breastfed, reflecting the complexity of this topic. Genetic studies are emerging to further elucidate the role of genetic factors for the possible protective effect of breastfeeding on later obesity, as shown in the paper by Wu et al. (page 125).

Associations of infant feeding with trajectories of body composition and growth

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This manuscript is also discussed in chapter 2 page 22.

Background: Whether breastfeeding is protective against later-life obesity is controversial. To further investigate this, there is a need to know more about differences in infant body composition between breastfed and formula-fed infants, as it may reflect future obesity risk.

Objective: This study aimed to assess the associations of infant feeding with trajectories of growth and body composition from birth to 7 months in healthy infants.

Design: A total of 276 participants from a previous study of maternal vitamin D supplementation during lactation were studied. Mothers used monthly feeding diaries to report the extent of breastfeeding. Infants' anthropometrics and dual-energy X-ray absorptiometry (DXA) were used to as-

sess the body composition at 1, 4, and 7 months. The study compared changes in infant size (z scores for weight-for-age, length-for-age, and body mass index for age) and body composition (fat and lean mass, body fat percentage) between predominantly breastfed and formula-fed infants. Linear regression adjusting for sex, gestational age, race/ethnicity, maternal BMI, study site, and socioeconomic status was used.

Results: In this study, 214 infants (78%) were predominantly breastfed (median duration: 7 months) and 62 were exclusively formula fed. Formula-fed infants had lower birth-weight z scores than breastfed infants (−0.22 ± 0.86 and 0.16 ± 0.88, respectively; $p < 0.01$) but gained more in weight and BMI through 7 months of age (weight z score difference: 0.37; 95% CI 0.04–0.71; BMI z-score difference: 0.35; 95% CI 0–0.69). There was no difference in linear growth (z score difference: 0.05; 95% CI −0.24 to 0.34). Formula-fed infants gained more lean mass (difference: 303 g; 95% CI 137–469 g) than breastfed infants, but not fat mass (difference: −42 g; 95% CI −299 to 215 g).

Conclusions: Formula-fed infants gained weight more rapidly and out of proportion to linear growth than did predominantly breastfed infants. These differences were attributable to greater accretion of lean mass, rather than fat mass. Any later obesity risk associated with infant feeding does not appear to be explained by differential adiposity gains in infancy.

Comments	A strength of this study is the large number of infants and that the body composition was measured with DXA scans, a precise and accurate body composition method, at ages 1, 4, and 7 months. Using DXA scans in this age group can be a challenge because the infants should not move during the scan which takes several minutes. There were no reports of unsuccessful DXA scans.
	The weight growth trajectory of breastfed and formula-fed infants are as seen in other studies. The breastfed infants had a growth pattern close to the WHO growth standards, while the weight of the formula-fed infants from age 2 months was steadily increasing. However, the deposition of fat and lean mass was different from the pattern seen in the highly quoted meta-analysis by Gale et al. [4], which included 15 studies. This meta-analysis found that breastfed infants deposit more fat during the first 6 months, whereas the study by Bell et al. (page 123) reported that there were no difference in fat mass and body fat percentage between the 2 groups at 4 and 7 months. The difference in weight seemed to be caused by a higher lean mass in formula-fed infants at 4 months, which increased further until 7 months. The authors speculate that it could be the higher protein content in infant formula, which could be on the causal pathway leading to obesity.
	More studies using accurate measurement of body composition during infancy is needed. Beyond DXA scan, other accurate methods which can be used during infancy are deuterium dilution or air displacement plethysmography. In the study by Admassu et al. included in this chapter (page 132), body composition was measured monthly by air displacement plethysmography up to the age of 6 months. In another publication from the cohort, it was shown that in the group of infants with a delayed fat deposition trajectory there were a higher percentage of children not breastfed at 3 months compared to those with an accelerated fat deposition trajectory [7]. Thus, the study supports that breastfeeding is associated with early fat deposition.

The role of early life growth development, the FTO gene and exclusive breastfeeding on child BMI trajectories

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Background: A longer duration of exclusive breastfeeding (EXBF) has been shown to reduce the body mass index (BMI) and the risk of being overweight and obese in the general population. Recent studies have implicated the FTO gene in child and adult obesity, and also among FTO gene carriers, EXBF has been linked to reduced BMI. However, it remains unclear whether the preventive effect of EXBF could be explained by its impact on early life growth development, for example, ages at adiposity peak (AP) and adiposity rebound (AR) and BMI velocities in the first years of life, which are major determinants of overweight and obesity later in life.
Methods: This study included 5,590 children from the British Avon Longitudinal Study of Parents and Children (ALSPAC) cohort and modelled their longitudinal BMI profiles with mixed effects models from birth to 16 years of age. From this they also modelled their ages at AP, AR, and BMI velocities in relation to the FTO gene variant and EXBF to examine whether there were gene-environment interactions and to determine whether ages at AP, AR and BMI velocities mediate the effect of EXBF on overweight and obesity.
Results: A longer duration of EXBF (i.e., at least 5 months) has substantial impact on BMI growth trajectories among children carrying the FTO adverse variant by modulating the age at AP, age at AR and BMI velocities. EXBF acts antagonistically to the FTO rs9939609 risk allele and by the age of 15, the predicted reduction in BMI after 5 months of EXBF is $0.56 \, \text{kg/m}^2$ (95% CI 0.11–1.01; $p = 0.003$) and $1.14 \, \text{kg/m}^2$ (95% CI 0.67–1.62; $p < 0.0001$) in boys and girls, respectively.
Conclusions: EXBF influences early life growth development and thus plays a critical role in preventing the risks of overweight and obesity even when those are exacerbated by genetic factors. This is probably mediated in part by having a later AP and AR as well as a slower growth velocity in early life.

Comments In the recent 2 decades, research into the effect of genotypic responses to diet has been increasingly investigated; however, such studies are still limited in infants. The present study takes up a very interesting gene-environment interaction between breastfeeding and the obesity gene FTO. In agreement with other studies [8], the current study shows that a longer duration of breastfeeding protects against obesity in children carrying the FTO obesity risk allele. The present study also takes the analyses a bit further, by showing that the protective effects of breastfeeding for carriers of the risk allele of the rs9939609 SNP (which can be very common among certain populations, for example, 45% in West/Central Europeans) in the FTO gene is mediated in part by having a later AP and AR. The shift in AP and AR seen when carrying the FTO risk allele are offset in infants being exclusively breastfed for 5 months and are thus mediating the effect on later life BMI. The findings in this study are interesting in showing that breastfeeding might be particularly important in a group of children with high genetic predisposition for obesity. Furthermore, the study highlights that the mechanisms linking breastfeeding and obesity might be through shifting AP and AR, as well as the early growth velocity (from birth to AP and from AP to AR). Moreover, the study could in part explain why there are differences between study findings when it comes to breastfeeding and obesity as the genetic background of the included infants might be important for the effect of breastfeeding.

Excessive weight gain in exclusively breast-fed infants

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Background: Breastfeeding is recommended as the best source of nutrition in the first months of life. Based on observational studies exclusive breastfeeding has been associated with decreased weight gain and a protective effect against obesity in childhood. In this study, the objective was to describe the characteristics of a cohort of exclusively breastfed obese infants with the purpose to determine factors that may cause this unusual weight gain.

Methods: Infants who were exclusively breastfed and showed excessive weight gain in the first year of life were followed with a focus on features of the mother, the child, feeding patterns, and the presence of concomitant factors that influence nutritional status. Infants were seen during the period from 2003 to 2015. In a subset of the sample, macronutrients content of breast milk was analyzed.

Results: Out of 73 infants, 63% were girls. At 3 months of life, 64% had a weight-for-height SD score (SDS) >2. At both 6 and 12 months, 100% of the patients had a weight-for-height >2 SDS and the average weight-for-height SDS increased from 6 to 12 months. The mean age at semisolid-food introduction was 7 months. The mean age at weaning was 15.8 months. The babies were fed on demand and no hunger-satiety pattern was observed. In the breast milk samples analyzed, a significantly lower fat content was found.

Conclusions: The results of our study lead to the assumption that inter-individual variations in mother's milk composition may affect the growth patterns of children.

Comments This cohort from Argentina is the largest cohort of exclusively breastfed infants with excessive weight gain published. As a high weight gain during infancy is associated with an increased risk of later overweight and obesity and as there is some evidence that breastfeeding reduces the risk, it is of interest to examine the causes and consequences of an excessive weight gain during exclusive breastfeeding. There was a lower fat content in the breast milk from a subgroup of infants, and protein content was not different from reference values. The milk samples were taken quite late, at an average age of 8.6 months. The authors speculate that because of the low-fat content the infants might have had a higher milk intake as they might adjust their intake according to energy density, and the higher milk intake could have resulted in a high protein intake. The infants were recruited quite late, some after the age of 6 months, which is a potential limitation, as also mentioned by the authors.

The growth pattern of the infants in this cohort showed a continued increase in weight-for-age SD score from 6 to 12 months (4.60–5.97). This is quite different from the pattern in 2 case reports [9, 10] and a small cohort of infants with excessive weight gain during exclusive breastfeeding [11]. Those infants had a marked catch-down during the last half of infancy, when other foods were introduced. The authors mention that aspects of milk composition other than macronutrients might cause the excessive weight gain and mention IGF-1, adiponectin, and leptin. In our cohort, we found that milk leptin values were low and serum leptin values high in those with excessive weight gain, suggesting that leptin could play a role in the excessive weight gain [11].

A meat- or dairy-based complementary diet leads to distinct growth patterns in formula-fed infants: a randomized controlled trial

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Background: Different sources of protein might affect growth differently, and especially a diet with high content of animal protein has been linked to rapid growth. Protein intake from cow milk-based infant formula has been associated with rapid weight gain and increased adiposity, but the effect of protein from complementary foods has not been prospectively evaluated, and the effect of protein from sources other than formula during complementary feeding is not clear.

Objective: The study investigated the effect of protein from 2 common complementary food sources, meat and dairy, on infant growth and weight trajectories.

Design: The study recruited healthy term, formula-fed infants from the metro Denver area. These were matched by sex and race/ethnicity and randomly assigned to a meat or a dairy complementary food group, and these foods were provided from 5 to 12 months of age. The aim of the intervention was to get the total protein intake during this 7 months intervention to ~3 g·kg^{-1}·d^{-1} for both groups. Ad libitum intakes of infant formula (provided), cereal, fruit, and vegetables were allowed and caregivers completed 3-day diet records for the infants at 5, 10, and 12 months of age. Anthropometric measures were assessed during monthly home visits, and blood samples were collected at 5 and 12 months of age.

Results: A total of 71 infants were randomized to the 2 groups and 64 infants completed the intervention (meat: $n = 32$; dairy: $n = 32$, with equal dropout). The average total protein intake (mean ± SD) increased from 2.01 ± 0.06 g·kg^{-1}·d^{-1} at 5 months to 3.35 ± 0.12 g·kg^{-1}·d^{-1} at 12 months and did not differ between groups. During the intervention period weight and weight-for-age z-score increased on average by 0.48 ± 0.07 with no differences between the groups. However, there was a significant group-by-time interaction for both length-for-age z-score (LAZ) and weight-for-length z-score (WLZ). Post-hoc analysis showed that LAZ increased in the meat group (+0.33 ± 0.09; $p = 0.001$ over time) and decreased in the dairy group (−0.30 ± 0.10; $p = 0.0002$ over time); WLZ significantly increased in the dairy group (0.76 ± 0.21; $p = 0.000002$ over time) compared with the meat group (0.30 ± 0.17; $p = 0.55$ over time). Insulin-like growth factor I and insulin-like growth factor-binding protein 3 both increased over time without group differences.

Conclusions: In this study, meat- and dairy-based complementary foods led to distinct growth patterns, especially for length, in formula-fed infants during late infancy. The meat group had higher LAZ, while the WLZ gain was higher in the dairy group, although to a lesser extent.

Comments In this study, a comparison between 2 different complementary food protein sources found a considerably higher growth velocity in the infants receiving meat compared to dairy. The study found rather large effects of 0.74 SD higher LAZ and 0.44 SD lower

WLZ scores and the results highlight that the sources of protein might matter as much as the amount of protein ingested in terms of infant growth. These results suggest that meat intake compared to dairy might promote linear growth without increasing WLZ (and in turn obesity risk). However, the results are in contradiction with an earlier review [12] and a meta-analysis [13], which both concluded that cow's milk stimulates linear growth [12, 13]. In addition, a smaller review reported that meat stimulates cognition but not growth in low-income countries [14]. The reviews mainly included studies in older children and not infants. A limitation of the reported study was that there was no assessment of body composition which could have elaborated the results even further.

The study also tried to examine potential mechanisms for the difference in growth. One of the potential mechanisms is the difference in amino acids content between milk and meat. Differences in amino acid patterns might affect hormones and growth factors, such as insulin-like growth factor 1 (IGF-1) [1]. However, in the present study they found no differences in IGF-1 or IGFBP3 concentrations. In contrast, an earlier study found that higher milk intake, but not meat intake, was associated with higher IGF-1 levels in 2.5 years old children [15]. This could indicate that other mechanisms might be involved during infancy. In this study they found that the intake of isoleucine, lysine, methionine, and histidine were higher in the meat group compared to the dairy group and this might in part explain the differences seen in the 2 groups. However, the exact mechanisms are unclear but could involve epigenetic mechanisms [1].

Studies, such as the present one, are important for establishing evidence-based complementary feeding guidelines which could be a valuable tool for yielding long-term benefits on obesity prevention. However, longer term follow-up of such studies is highly warranted to uncover potential long-term consequences of such interventions.

Evaluation of the efficacy, safety and acceptability of a fish protein isolate in the nutrition of children under 36 months of age

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Background: Malnutrition is a public health challenge in many developing countries. Protein of sufficient quality and quantity is important for growth. Fish protein isolate is a potential low-cost protein of high quality.
Objectives: The aim of the study was to determine the effect of a fish protein isolate (FPi) on the growth of young Peruvian children. Furthermore, the study aimed at assessing the safety and acceptability of daily consumption of FPi.
Method: The study was conducted as a cluster-randomized community-based controlled trial in 6–36 months old children in day care and community nutritional centers in northern Lima. For 6 months, the children received either FPi replacing 50% of animal protein in their lunch or the

same menu prepared with standard animal protein from beef, chicken, pork, liver or egg. FPi contained a mixture of mono-, di-, and tripeptides. Height-for-age (HAZ) and weight-for-height (WHZ) z-scores at the end of the study were used to assess the effect of FPi on growth. Acceptability was determined as daily consumption, measured by weighing the servings before and after intake.

Results: Four and five centers were randomized to the interventions with FPi and the standard control diet, respectively. More than 36,900 meals were prepared and administered in a supervised manner to 441 children. Both groups received the same amount of energy and protein daily (protein constituted approximately 12–15% of total energy). Growth of children who received the FPi diet was similar to that of children with the standard diet. Consumption of the offered lunch meals was similar in the FPi and control group (70 vs. 80%, respectively). However, when assessing acceptability over time, the proportion of children consuming ≥70% of the daily offering was higher with the standard diet. The FPi was safe and well tolerated. No adverse events were reported. The cost of the intervention with FPi was 20–40% lower compared to the standard diet.

Conclusions: The FPi was well accepted and there was no difference in growth between the groups. FPi is a potential source of animal protein at lower cost.

Comments on this manuscript are incorporated in those of the next manuscript (Stephenson et al, page 130).

Complementary feeding with cowpea reduces growth faltering in rural Malawian infants: a blind, randomized controlled clinical trial

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Background: Inadequate dietary intake and environmental enteric dysfunction (EED) are associated with growth faltering in African children.

Objective: This study assessed the effect of complementary feeding with cowpea or common beans vs. a corn-soy blend on growth faltering and EED in rural Malawian infants.

Methods: The study was conducted as a randomized, double-blind, controlled clinical trial in 6 months old infants. Daily complementary feeding of cowpea, common bean or corn-soy blend (CSB) was provided for a period of 6 months. The amount increased from 200 kcal/day at 6–9 months of age to 300 kcal/day from 9 to 12 months of age. The energy supplied constituted approximately 40% of the recommended intake. The primary outcomes were changes in length-for-age z score (LAZ) and improvements in EED, measured as percentage of lactulose excretion in urine (%L). %L <0.2% was considered normal. Student t test was used to compare anthropometric measurements and %L between each legume group and the control group.

Results: The study enrolled 355 infants, of which 291 completed the trial and 288 were breastfed throughout the study duration. Most of the non-completers (42 out of 64) developed acute malnutrition and were therefore excluded from the study. The cowpea and common bean comple-

mentary food provided 4.6–5.2 g protein/day and 4–5 g indigestible carbohydrate/day. LAZ and weight-for-length z scores declined in all 3 groups throughout the trial. The mean (95% CI) changes in LAZ for cowpea, common bean, and CSB from 6 to 9 months were –0.14 (–0.24 to –0.04), –0.27 (–0.38 to –0.16), and –0.27 (–0.35 to –0.19), respectively. LAZ reduced less in infants receiving cowpea than in those receiving control food from 6 to 9 months (p = 0.048). The absolute value of %L as well as the change in %L did not differ between the groups at 9 months of age. The mean (±SD) absolute %L for cowpea, common bean, and CSB was 0.30 ± 0.43, 0.23 ± 0.21, and 0.26 ± 0.31.

Conclusion: Adding cowpea to the normal complementary feeding resulted in less linear growth faltering in Malawian infants.

Comments   Children in low-income countries often consume protein of lower quality. Animal protein contains all essential amino acids, often comes with important micronutrients, has a high bioavailability and can thus support growth in children. However, the cost can be prohibitively high in resource-limited settings. Fish protein isolate (FPi) could potentially become an alternative source of affordable, high-quality protein if it is safe, palatable and if growth stimulation is similar to other animal protein sources. Ochoa et al. (page 128) found FPi to be safe and the intake was almost the same with a consumption of 70% of the meals offered in the FPi group versus 80% consumed in the animal protein group. Over time, the acceptability of the standard diet increased compared to the FPi diet, indicating some palatability differences. Height-for-age and weight-for-height at the end of the study was similar in groups receiving FPi vs. standard animal proteins. In line with this finding, other studies have reported unchanged/normal growth when evaluating fish protein against a control group [16–18]. A recent study in children with severe acute malnutrition tested a new locally produced fish-based ready-to-use food (RUTF) vs. a standard milk-based RUTF and also found similar growth in the intervention groups [19]. The cost of the FPi intervention was 20–40% lower compared to animal protein and supports further research on the use of FPi. A potential drawback of FPi compared to whole (fatty) fish is that essential fatty acids, n-3 and n-6 will be lacking in a purified protein ingredient. Essential fatty acids are known to be important for eye and brain development and may have an effect on growth. This has been shown in a recently published cross-sectional study on serum metabolites from Malawian children that found low n-3 and n-6 to be associated with stunting [20].

The effects of nutritional interventions on treatment and prevention of malnutrition are lower than expected. One possible explanation is that the gut barrier is compromised impairing uptake and utilization of nutrients supplied. A number of studies are currently investigating the link between child growth and different biomarkers associated with environmental enteric dysfunction (EED). The lactulose-mannitol test is a frequently used biomarker of EED. This study by Stephenson et al. found that a daily dose of cowpea but not common bean or corn-soy blend reduced growth faltering slightly in children from 6 to 12 months of age. There was no effect of the interventions on percentage of lactulose secreted in urine. A parallel study by the same research group in older children (12–23 months of age) supplying the same interventions for 48 weeks found no effects on stunting [21]. In contrast, they found reduced percentage of lactulose in children receiving common beans but not cowpea or corn-soy blend, indicating improved gut permeability in this group. This shows the complexity of testing both growth and biomarkers related to EED. Better biomarkers may be needed to understand if and how growth and gut health are interacting.

It is still important to continue searching for more affordable sources of high-quality protein for resource-limited setting/low-income countries to treat and prevent malnutrition. This could be through combinations of different plant proteins resulting in an amino acid content with a higher quality measured by PDCAAS or DIAAS or mixtures of plant and animal (including fish) protein. However, this might not be the only intervention needed as correcting EED might be needed before an effect of such supplements can be seen.

Early Growth, Growth Patterns, and Obesity

The associations between adult body composition and abdominal adiposity outcomes, and relative weight gain and linear growth from birth to age 22 in the birth to twenty plus cohort

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Background: The prevalence of overweight and obesity in low- or middle-income countries is increasing at rapid rates and this calls for studies examining early life predictors and potential modifiable risk factors of adiposity.

Objectives: The aim of this study was to examine the growth trajectories from birth, and associations with adult body composition in the Birth to Twenty Plus Cohort, Soweto, South Africa.

Methods: Conditional weight and height indices were generated, indicative of relative rate of growth between years 0–2, 2–5, 5–8, 8–18, and 18–22. Whole body composition was measured at 22 years (range 21–25) using dual energy X-ray absorptiometry (DXA). Total fat-free soft tissue mass (FFSTM), fat mass and abdominal visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were recorded. Associations were analyzed using multiple linear regression models adjusted for sex, gestational age, ethnicity, socioeconomic status, and maternal height.

Results: Data were available for 1,088 participants (536 males and 537 females) at year 22 and regression analyses included 266 participants with complete DXA data at year 22 and complete growth data at each time point. Birth weight was positively associated with FFSTM and fat mass at year 22 ($\beta = 0.11$, $p < 0.01$ and $\beta = 0.10$, $p < 0.01$ respectively). Relative weight gain for each of the time periods from birth to year 22 was positively associated with FFSTM, fat mass, VAT, and SAT at year 22. Relative linear growth from birth to year 22 was positively associated with FFSTM at year 22. Relative linear growth from birth to year 2 was positively associated with VAT at year 22. Overweight at 2 years of age was positively associated with FFSTM, fat mass, VAT, and SAT at year 22 while, being born small for gestational age and being stunted at age 2 years were negatively associated with FFSTM at year 22.

Conclusion: The importance of optimal birth weight and growth tempos during early life for later life body composition, and the detrimental effects of pre- and postnatal growth restriction are clear; yet contemporary weight-gain most strongly predicted adult body composition. Thus, interventions should target body composition trajectories during childhood and prevent excessive weight gain in early adulthood.

Comments	Earlier studies have shown that increased childhood weight gain is associated with a higher risk of obesity later in life in high as well as low- and middle-income countries [22, 23]. This study found relative weight gain during all time periods from birth to 22 years to be associated with FFSTM, fat mass, abdominal VAT, and SAT at 22 years. The associations were strongest for fat tissue and increased with age confirming that excessive weight gain during childhood increases the risk of adult adiposity. Another publication from the same South African birth cohort reported that relative weight gain before 5 years of age was associated with early onset of specific BMI trajectories related to obesity or excess weight [24].
	Stunting during early life is debated as a risk factor for later obesity. Two smaller studies from Brazil indicated a higher risk of obesity in stunted compared to matched non-stunted children and adolescents [25, 26]. In contrast, a large birth cohort study in Brazilian boys found stunting at 2 and 4 years of age to be associated with reduced fat mass index but not fat-free mass index at 18 years [27]. A Sub-Saharan study found no association between early life stunting and later obesity [28]. In this paper, Prioreshi et al. reported that stunting at 2 years was associated with less FFSTM but not associated with FM at 22 years, and another study from the same cohort reported that stunting at 2 years was not associated with overweight through young adulthood [29]. Children born SGA also had less FFSTM at 22 years.
	High quality data on body composition from larger birth cohorts are important to understand and prevent the double-burden of malnutrition and obesity in low- and middle-income countries.

Accretion of fat-free mass rather than fat mass in infancy is positively associated with linear growth in childhood

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Background: The relation between changes in body composition during early infancy and linear growth during childhood require further description and study.
Objective: The aim of this study was to assess the associations of early infancy fat mass (FM) and fat-free mass (FFM) accretion with linear growth from 1 to 5 years of age in Ethiopian children.

Methods: A follow-up study based on the infant Anthropometry and Body Composition cohort was conducted in Jimma, Ethiopia. Children were followed from birth to 5 years of age. FM and FFM were measured 6 times or less from birth to 6 months by using air-displacement plethysmography. Linear mixed-effects models were used to identify associations between standardized FM and FFM accretion rates during early infancy and linear growth from 1 to 5 years of age. Standardized accretion rates were generated by dividing FM and FFM accretion by their respective SD.

Results: FM and FFM accretion rates were estimated for 535 children. Of these, 454 had length and height data from 1 to 5 years and 354 with complete data were included in the analysis. The majority (73.1%) were exclusively or predominantly breastfed at 2.5 months of age. Sex, birth order, and maternal and paternal education were associated with different FFM accretion rates from 0 to 6 months, whereas FM accretion from 0 to 4 months varied with birth order only. FFM accretion from 0 to 6 months of age was positively associated with length at 1 year ($\beta = 0.64$; 95% CI 0.19–1.09; $p = 0.005$) and linear growth from 1 to 5 years ($\beta = 0.63$; 95% CI 0.19–1.07; $p = 0.005$). The strongest association with FFM accretion was observed at 1 year. The association with linear growth from 1 to 5 years was mainly explained by the 1-year association. FM accretion from 0 to 4 months was positively associated with linear growth from 1 to 5 years ($\beta = 0.45$; 95% CI 0.02–0.88; $p = 0.038$) in the fully adjusted model.

Conclusions: In Ethiopian children, FFM accretion was associated with linear growth at 1 year and no clear additional longitudinal effect from 1 to 5 years was observed. FM accretion showed a weak association with linear growth from 1 to 5 years.

Comments   There are few studies investigating body composition in infancy and very few from low-income countries. As expected, Ethiopian boys had higher FFM accretion than girls, and improved maternal and paternal education were both associated with higher FFM accretion. Birth order affected both FFM and FM accretion with a tendency to higher accretion rates in first-born infants. The authors previously published a cross-sectional study showing that FFM but not FM at birth was associated with height in Ethiopian children at 2 years [30]. The current study additionally found accretion of FFM from 0 to 6 months to be associated with linear growth from 1 to 5 years, with most of the effect generated in the first year. However, the study also found a weak association between FM accretion at 0–4 months and linear growth at 1–5 years. It is new that postnatal FM accretion may contribute to linear growth. But the fat mass might act as an energy buffer during early infancy leading to linear growth later. Long-term cohort studies are needed to investigate the role of FM and FFM accretion on later body composition and cardiometabolic risk.

Infant BMI peak as a predictor of overweight and obesity at age 2 years in a Chinese community-based cohort

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Background: Infant body mass index (BMI) peak has proven to be a useful indicator for predicting childhood obesity risk in American and European populations. However, it is currently unclear whether this is also the case in other populations such as China.

Objectives: In this study, authors characterized infant BMI trajectories in a Chinese longitudinal cohort and evaluated whether BMI peak could predict overweight and obesity at age 2 years.

Methods: The study used serial measurements ($n = 6–12$) of weight and length from healthy term infants ($n = 2,073$) in a birth cohort established in urban Shanghai. Measurements were used to estimate BMI growth curves from birth to 13.5 months using a polynomial regression model. BMI peak characteristics, including age (in months) and magnitude (BMI, in kg/m^2) at peak and pre-peak velocities (in $kg/m^2/month$), were estimated. The relationship between infant BMI peak and childhood BMI at age 2 years was examined using binary logistic analysis.

Results: The mean age at peak BMI was 7.61 months, and the magnitude was $18.33 kg/m^2$. Boys ($n = 1,022$) had a higher average peak BMI (18.60 vs. $18.07 kg/m^2$, $p < 0.001$) and earlier average achievement of peak value (7.54 vs. 7.67 months, $p < 0.05$) than girls ($n = 1,051$). With every $1 kg/m^2$ increase in peak BMI and 1 month increase in peak time, the risk of overweight at age 2 years increased 2.11 times (OR 3.11; 95% CI 2.64–3.66) and 35% (OR 1.35; 95% CI 1.21–1.50), respectively. Similarly, a higher BMI magnitude (OR 2.69; 95% CI 2.00–3.61) and later timing of infant BMI peak (OR 1.35; 95% CI 1.08–1.68) were associated with an increased risk of childhood obesity at age 2 years.

Conclusions: The study showed that infant BMI peak is valuable in predicting early childhood overweight and obesity in a Chinese population in urban Shanghai. Because this is the first Chinese community-based cohort study of this nature, future research is required to examine infant populations in other areas of China and to examine if there are differences between the populations.

Comments Compared to the interest there has been in how adiposity rebound (BMI nadir at about 5–6 years of age) is related to later adiposity, there has only been a few papers describing factors associated with the infant BMI peak, which happens around 7–9 months of age, and how it is related to later adiposity. In the paper by Wu, which is included earlier in this chapter, they showed how breastfeeding duration was associated with the age of the infant BMI peak. The present study which analyzed a large cohort of infants from China found convincingly that a higher BMI magnitude and a later age at the peak was associated with a higher risk of obesity at 2 years. The cohort had data on duration of breastfeeding, and duration of breastfeeding was associated with a borderline significant lower risk of obesity at 2 years. In the discussion it is mentioned that breast-

feeding might have an effect on the age of BMI peak, but it was not mentioned if duration of breastfeeding was associated with the age of infant BMI peak in this cohort. In a Danish cohort, we found that longer duration of exclusive breastfeeding was associated with an earlier BMI peak [31]. There is convincing data that a high growth velocity during infancy is associated with a higher risk of later overweight and obesity across population groups [22, 23]. However, growth and BMI trajectories during infancy are complex. Therefore, it is likely to improve our understanding of early development of overweight and obesity if we obtain a better understanding of factors associated with the BMI infant peak and how it is related to later risk of obesity. This could, for example, be genetic susceptibility, as shown in the paper by Wu et al. (page 125).

The effect of early feeding practices on growth indices and obesity at preschool children from 4 European countries and UK schoolchildren and adolescents

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This manuscript is also discussed in chapter 2 page 29.

Background: Healthy growth and childhood obesity are influenced by early life.

Objectives: The current analysis aimed to examine the association of feeding practices during infancy with growth and adiposity indices in preschool children from 4 European countries and in UK schoolchildren and adolescents.

Methods: Existing data from 4 European birth cohorts (ALSPAC-UK n = 6,124–7,540, depending on age at follow-up; EDEN-France, n = 1,070; EuroPrevall-Greece, n = 309; and Generation XXI-Portugal, n = 3,387) were used. Anthropometrics and body composition indices (including BMI, bioelectrical impedance, and dual energy X-ray absorptiometry) were collected. Parallel multivariate regression analyses were performed to examine the research hypothesis.

Results: Overall, the analyses showed that breastfeeding and timing of complementary feeding were not consistently associated with height z-score, overweight/obesity, and body fat mass in children or adolescents. However, breastfeeding duration for less than 6 months was associated with lower height z-scores in 5-year-old children from the French EDEN cohort ($p < 0.001$) but with higher height z-scores in 4-year-old children from the ALSPAC cohort ($p = 0.006$). Furthermore, introduction of complementary foods earlier than 4 months of age was positively associated with fat mass in 5-year-old children from the French EDEN cohort ($p = 0.026$).

Conclusion: Duration of any breastfeeding and age of introduction of complementary foods, do not appear to be consistently associated with height z-score, overweight/obesity, and body fat mass in preschool children from 4 European countries and in UK schoolchildren and adolescents. Thus, no clear influence can be observed.

Comments	This is an important study analyzing the modifiable potential risk factors for later overweight and obesity, duration of breastfeeding, and age at introduction of complementary foods in 4 different European populations. The only significant results related to adiposity was that in one of the 4 cohorts, the French EDEN cohort, introduction of complementary feeding before the age of 4 months was positively associated with fat mass, and in the ALSPAC cohort those breastfed less than 1 months had more body fat at the age of 13 year. However, there were no significant relations between duration of breastfeeding and age at introduction of complementary feeding and overweight and obesity in any of the cohorts.
	Breastfed infants are on average shorter at the age of 12 months than formula-fed infants and a few studies have suggested that they have a catch-up later and are not shorter during childhood [32, 33]. It is thus interesting that children who were breastfed for a short duration (<6 months) compared with those breastfed longer, were shorter in the French population (5 years old) and taller in the UK population (4 years old). The authors have no suggestions for this difference.
	It is disappointing from a public health perspective that the 2 modifiable factors, duration of breastfeeding and age at introduction of complementary feeding, had no overall effect on later overweight and obesity in these 4 cohorts. However, the authors mention that limitations of this study include differences in methodological procedures and purpose of the 4 cohorts.

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Malnutrition and Catch-Up Growth during Childhood and Puberty

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"Good nutrition allows children to survive, grow, develop, learn, play, participate and contribute – while malnutrition robs children of their futures and leaves young lives hanging in the balance." In May 2018, UNICEF, WHO, and the World Bank Group released the latest edition of the joint child malnutrition estimates for 1990–2017 (UNICEF-WHO-WB. Joint Child Malnutrition Estimates, 2018) [1]. The report shows that malnutrition, a major cause of stunting and wasting, is still a major global burden. Worldwide, in 2017, among the under-5-year age group, stunting affected approximately 151 million children (22.2%) and wasting, nearly 51 million (7.5%). Stunting and wasting are associated with weakened immunity, increased risk of morbidity and mortality, and developmental delays. Wasted and stunted children begin their lives at a marked disadvantage: they face learning difficulties, lower earnings as adults, and barriers to participation in their communities. Improving children's nutrition requires effective and sustained multi-sectoral programming over the long term. Many countries are moving in the right direction, but there is a long way to go. Based on indicators of stunting and wasting, the joint report estimated that progress so far was insufficient to reach the World Health Assembly targets set for 2025 and the Sustainable Development Goals set for 2030 for children under 5 years old.

This chapter reviews the most recent data on childhood malnutrition and catch-up growth, published between July 1, 2017 and June 30, 2018, by predefined topics.

Etiology and assessment of malnutrition: Four publications were selected. Three are reviews illustrating the intricate links between nutrition, inflammation, and growth restriction [2]; summarizing the current knowledge on metabolic phenotyping of early life malnutrition [3]; and expanding on the under-studied topic of nutrition and stunting in adolescence [4]. The fourth paper is a large longitudinal study on the most influential risk factors for early life stunting in 7 locations worldwide [5].

Treatment of malnutrition: This year saw several new publications covering different strategies for the treatment of malnutrition. Seven papers were selected for this chapter. Two are systematic reviews of the role of micronutrient supplementation [6] and the impact of nutrition-specific and nutrition-sensitive interventions [7], and one is a review of the effect of protein or selected amino acids supplementation on malnutrition [8]. Three are randomized controlled trials evaluating the effects of high-dose vitamin D3 [9], the effects of three important factors of food supplementation: matrix, soy quality, and percentage of protein from milk [10], and the effect of supplementation with ready-to-use therapeutic foods compared to a liquid oral nutritional supplement [11]. The seventh paper describes a large cross-sectional study of the association between stunting and two indicators of dietary quality, namely, dietary diversity and animal-source food consumption, based on existing data from 39 demographic and health surveys [12].

Strategic planning: Two manuscripts were selected. One is a review and analysis of the new nutrition-related additions to the well-established Lives Saved Tool model and their implications for nutrition-intervention strategy planning [13]. The second is a report on an additional optimization tool for resource allocation in nutrition intervention, including a case study demonstrating its use [14].

Key articles reviewed for this chapter

Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children

Millward DJ

Nutr Res Rev 2017; 30: 50–72

Metabolic phenotyping of malnutrition during the first 1000 days of life

Mayneris-Perxachs J, Swann JR

Eur J Nutr 2018, Epub ahead of print. https://doi.org/10.1007/s00394-018-1679-0

Adolescent undernutrition: global burden, physiology, and nutritional risks

Christian P, Smith ER

Ann Nutr Metab 2018;72:316–328

Childhood stunting in relation to the pre- and postnatal environment during the first 2 years of life: The MAL-ED longitudinal birth cohort study

MAL-ED Network Investigators

PLoS Med 2017;14:e1002048

Nutrition (micronutrients) in child growth and development: a systematic review of current evidence, recommendations and opportunities for further research

Yakoob MY, Lo CW

J Dev Behav Pediatr 2017;38:665–679

Evidence-based approaches to childhood stunting in low and middle income countries: a systematic review

Hossain M, Choudhury N, Adib Binte Abdullah K, Mondal P, Jackson AA, Walson J, Ahmed T

Arch Dis Child 2017;102:903–909

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

Arsenault JE, Brown KH

Nutr Rev 2017;75:699–717

High-dose vitamin D3 in the treatment of severe acute malnutrition: a multicenter double-blind randomized controlled trial

Saleem J, Zakar R, Zakar MZ, Belay M, Rowe M, Timms PM, Scragg R, Martineau AR

Am J Clin Nutr 2018;107:725–733

Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: a randomised 2 × 2 × 3 factorial trial in Burkina Faso

Fabiansen C, Yaméogo CW, Iuel-Brockdorf AS, Cichon B, Rytter MJH, Kurpad A, Wells JC, Ritz C, Ashorn P, Filteau S, Briend A, Shepherd S, Christensen VB, Michaelsen KF, Friis H

PLoS Med 2017;14:e1002387

Impact of therapeutic foods 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 2018;37:858–863

Diet quality and risk of stunting among infants and young children in low- and middle-income countries

Krasevec J, An X, Kumapley R, Bégin F, Frongillo EA

Matern Child Nutr 2017;13(suppl 2):e12430

Nutrition interventions in the Lives Saved Tool (LiST)

Clermont A, Walker N

J Nutr 2017;147:2132S–2140S

Optima nutrition: an allocative efficiency tool to reduce childhood stunting by better targeting of nutrition-related interventions

Pearson R, Killedar M, Petravic J, Kakietek JJ, Scott N, Grantham KL, Stuart RM, Kedziora DJ, Kerr CC, Skordis-Worrall J, Shekar M, Wilson DP

BMC Public Health 2018;18:384

Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children

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This systematic review was designed to assess the specific role of various nutrition- and inflammation-related factors in the regulation of linear growth at the growth plate to better understand the mechanisms leading to stunting. The complex molecular signaling pathways that regulate linear growth are modulated by specific nutrients. Animal models have shown that the synthesis of growth-plate protein and proteoglycans and cell cycle progression, which are essential for linear growth, are particularly sensitive to dietary protein and zinc intake. These processes are mediated by insulin, insulin-like growth factor-1 and its binding proteins, triiodothyronine, amino acids and Zn^{2+}, and inhibited by corticosteroids and inflammatory cytokines. Observational studies in humans noted that the prevalence of stunting was increased among poorly nourished children whose diets are mainly plant-based, and interventional studies reported that this rate might be reduced, albeit to a limited extent, by correcting deficiencies of energy, protein, zinc, and iodine and multiple micronutrient deficiencies. Milk is the only animal-based food that has consistently shown to exert an important impact on linear growth in children, whether undernourished or well-nourished. Inflammation, by contrast, restricts endochondral ossification through various mediators, including pro-inflammatory cytokines, the activin A-follistatin system, glucocorticoids, and fibroblast growth factor 21, thereby contributing to stunting. Inflammation accompanies infections and environmental enteric dysfunction, conditions which are common in the absence of clean water, sufficient sanitation, and hygiene (WASH). Its presence may explain why nutritional interventions in stunted children are often unsuccessful. Optimal interventions to decrease stunting should aim at improving WASH as well as nutrition.

Comments Focusing on the growth plate, this review provides an in-depth perspective on the complex relationships among nutrition, inflammation, and growth that lead to stunting in poor-resource countries.

Metabolic phenotyping of malnutrition during the first 1,000 days of life

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Background: Suboptimal nutrition occurring in the first 1,000 days of life is known to impair children's growth and cognitive development and to increase their risk of non-communicable diseases as adults. Metabolic phenotyping is a novel technique whereby a diverse range of low-molecular-weight metabolites (<1 kDa) may be sampled simultaneously for comprehensive assessment of an

individual's biochemical status. In the last decade, several studies have applied this approach to identify and highlight the metabolic disruptions caused by different forms of early-life malnutrition of the first 1,000 days.

Methods: Relevant manuscripts were divided by the developmental period evaluated: prenatal, early postnatal (0–6 months), and late postnatal (6–24 months). The last group was further divided into 2 subgroups: caloric malnutrition (acute, chronic, or enteric dysfunction) and specific micronutrient deficiency (iron, zinc, vitamin B12, vitamin D, and vitamin E).

Results: According to the metabolic modifications observed, pathways involved in energy, amino acid and bile acid metabolism, as well as interactions between host and gut microbiota appear to be affected by early malnutrition.

Conclusions: The information drawn from systems biology studies can help shed light on the mechanisms associating malnutrition with impaired development and highlight potential biomarkers to identify individuals at risk. This information can also assist clinicians in developing individualized interventional strategies.

Comments	It makes perfect sense to apply systems biology to the field of childhood malnutrition. This is a complex multifactorial condition that affects a multitude of processes in the human body and the microbiome and has different consequences depending on the time of occurrence during the early period of life. This comprehensive review provides a synopsis of the evidence gathered so far on the metabolic effects of undernutrition on human development during childhood, providing an excellent basis for future research.

Adolescent undernutrition: global burden, physiology, and nutritional risks

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Summary: An estimated 90% of the 1.8 billion young people (age 10–24 years) in the world live in low- and middle-income countries (LMICs). Although the leading causes of death in adolescents are related to infectious diseases, violence, and injuries, malnutrition is nonetheless a major determinant of health in this age group that needs to be addressed. During puberty, growth velocity increases and reaches its peak. The adolescent growth process is subject to endocrine control and is particularly sensitive to undernutrition. Dietary requirements for energy, protein, iron, and calcium increase, and insufficient dietary intake can lead to anemia and micronutrient deficiencies. Catch-up growth is possible during this period if the deficiencies are treated.

In girls, approximately 15–25% of adult height is achieved during adolescence. However, cultural and social norms that support early marriage and pregnancy place adolescent girls at risk of poor nutritional status, impaired linear growth, and poor general well-being. These factors, in turn, adversely affect the growth of their offspring. Therefore, there is an important need for research into adolescent nutrition to identify underlying factors and develop interventions, particularly in LMICs and in females. Adolescence provides a second window of opportunity (after infancy) for improving dietary deficiencies, and by taking advantage of it; we might put an end to the intergenerational cycle of growth failure.

Comments	Adolescents are a unique population group with many specific requirements. Although public health authorities recognize the relevance of adolescent health, policy decisions often fall short because of the lack of evidence regarding nutrition in this age group [15]. Adolescents are characterized by a rapid spurt in growth, which increases their nutritional requirements. This also places them at risk of nutritional deficiencies in settings in which food insecurity prevails. At the same time, studies have shown that puberty provides a second window of opportunity (after infancy) for nutritional and educational intervention [16] and subsequent catch-up growth. The factors that make catch-up growth possible in this age group are not clear and require further research. The available data on adolescent stunting are limited because most studies used body mass index estimates as an outcome measure rather than height-for-age z-score. Stunting is a particularly important consideration in adolescent girls in the context of early pregnancies, which are unfortunately very common in LMICs worldwide. Approximately 16 million girls aged 15–19 years enter motherhood each year [15]. This review found a prevalence of stunting of over 25% in a WHO/CDC reference population of more than 240,000 new adolescent mothers. Pre-pregnancy stunting may affect both the growth potential of the adolescent mother and place her offspring at risk of preterm birth and small-for-gestational age. There is also concern regarding the quality of breast milk and lactation success in undernourished adolescent mothers, but there is very little information on this topic. These large knowledge gaps need to be filled to optimize intervention strategies for this age group.

Childhood stunting in relation to the pre- and postnatal environment during the first 2 years of life: The MAL-ED longitudinal birth cohort study

MAL-ED Network Investigators

PLoS Med 2017;14:e1002048

Aims: This longitudinal study sought to identify the preselected biological and social factors that have the strongest influence on stunting in resource-poor settings.

Methods: The study cohort included 1,868 newborns from resource-poor locations in Bangladesh, Brazil, India, Nepal, Peru, South Africa, and Tanzania who were followed from shortly after birth to age 24 months, between November 2009 and February 2014. Data were collected on the following parameters: longitudinal anthropometry, sociodemographic characteristics, maternal-reported illnesses, and antibiotic use; child feeding practices; dietary intake beginning at 9 months; and analyses of longitudinal blood, urine, and stool samples including non-diarrheal enteropathogens, micronutrients, markers of gut inflammation and permeability, and systemic inflammation. Length-for-age z-scores were divided into 3 groups (not stunted, <–1; at risk, –1 to –2; and stunted, >–2), and multivariable ordinal logistic regression was used to determine the cumulative odds of being in a lower length-for-age category (at risk or stunted).

Results: Complete longitudinal data were available for 1,197 children. The risk of having a length-for-age z-score below –1 increased from 43% (range 37–47% across sites) in the first few days of life (0–17 days post-delivery) to 74% (range 16–96%) at 24 months. The prevalence of stunting was 3 times higher at age 2 years than at birth. Risk factors for being at a lower length-for-age at 24 months category included lower initial weight-for-age (interquartile cumulative OR 1.82, 95% CI 1.49–2.23), shorter maternal height (OR 2.38, 95% CI 1.89–3.01), higher load of enteropathogens in non-diarrheal stools (OR 1.36, 95% CI 1.07–1.73), lower socioeconomic status (OR 1.75, 95% CI 1.20–2.55), and lower percent of energy from protein in diet (OR 1.39,

95% CI 1.13–1.72). Similar associations were found across the different sites participating in the study.

Conclusions: Neonatal and maternal factors were major contributors to lower length-for-age throughout the first 24 months of life. However, the rate of stunting increased with age and the contribution of other parameters assessed, namely, enteropathogens in non-diarrheal stools, socio-economic status, and dietary intake, increased by 24 months relative to the prenatal and neonatal factors.

Comments	This study is part of a collaborative international project, Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development, or MAL-ED. The central hypothesis of the project is that enteric infections and undernutrition, and the resulting impairment in gut function are the main factors underlying growth failure in childhood in low- and middle-income countries. The study was conducted in multiple sites using synchronized protocols, yielding an abundance of data, including gut enteropathogens in the absence of symptoms and markers of gut inflammation and permeability.
	The strength of this study is the quality of the data collected. Several results are in line with previous studies suggesting that factors leading to stunting are established early in childhood and that neonatal and maternal factors play a significant role in defining length-for-age [17, 18]; the rate of stunting increases from birth to 24 months [19]; and low protein intake is associated with stunting. The main contribution of this study to the earlier body of evidence is the finding that the enteropathogen burden, which was asymptomatic (not associated with diarrheal illness), was significantly associated with suboptimal growth whereas overt infections were not. Although this finding was not supported by an increase in markers of permeability or gut inflammation, it is still surprising and interesting and raises new questions regarding the interactions between enteric infections and growth.

Nutrition (micronutrients) in child growth and development: a systematic review of current evidence, recommendations and opportunities for further research

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Background: Pediatric malnutrition, especially micronutrient deficiencies, is common in resource-poor countries but can also occur in resource-rich countries. It is important to treat macronutrient deficiencies as early as possible (during pregnancy or early childhood) to support optimal childhood development, which has important implications later in life.

Aims: The aim of this systematic review was to highlight the current evidence on the role of micronutrient supplementation in child growth and development and suggest further research trajectories, with considerations for planning policies/programs and methods of their large-scale implementation.

Methods: A literature search was conducted using PubMed and Cochrane Library Summaries until December 31, 2016. Systematic reviews, meta-analyses, and randomized controlled trials of micronutrient supplementation in children were selected for analysis.

Results: The recent literature on the effects of micronutrients including iron, iodine, folic acid, zinc, vitamin A, and vitamin D on growth and development in early childhood was summarized. Since individuals may have a deficiency of more than single nutrient, we also reviewed the role of multiple micronutrients. Calcium, magnesium, selenium, and vitamin B complex were covered in brief as well. The effects of integrated nutrition and psychosocial interventions on child growth and cognitive development were discussed.

Conclusions: Micronutrient supplementation plays an important role in child growth and development during pregnancy as well as early childhood. It also provides benefits in terms of reduction of infection and mortality (for example, zinc and vitamin A). All these should be recognized by authorities when making policy recommendations or guidelines. Combined nutritional and psychosocial interventions such as parental psychosocial stimulation, parenting programs, and caregiver responsiveness, can have an additive or even synergistic effect on child development and should be part of large-scale programs to achieve optimal benefits.

Comments	This review has important implications for the promotion of child growth and development, especially in resource-poor countries. It underscores the role of micronutrient supplementation and other nutrition interventions like breastfeeding, complementary feeding, and combined nutritional and psychosocial interventions.
	The evidence of the benefit of supplementation is strongest in 3 areas: folate and iron during pregnancy to prevent neural tube defects and anemia; iodine for all children in iodine-deficient areas to prevent developmental delay; and vitamin A and zinc to reduce rates of infection and mortality. However, the effect of these micronutrients in preventing stunting at an early age is less clear, as randomized clinical trials are unethical in young children.
	The authors also discuss several controversies concerning current policies. For example, it remains unclear if iron and folate supplementation during pregnancy should be replaced by multiple micronutrients. More evidence of the benefit of micronutrient supplementation is needed before a new recommendation for universal use can be made.

Evidence-based approaches to childhood stunting in low and middle income countries: a systematic review

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Background: The 2025 WHO targets for nutrition are to reduce and maintain the prevalence of childhood wasting to less than 5% and to reduce the number of stunted children by 40% [20, 21]. If current trends continue, projections indicate that 127 million children under 5 years of age will be stunted in 2025. Therefore, further investment and new nutritional interventions are necessary to reduce the number to 100 million.

Nutrition-specific interventions address the immediate causes of undernutrition, such as inadequate dietary intake, and some of the underlying causes, such as feeding practices and access to food. Nutrition-sensitive interventions may address some of the underlying and basic causes of

malnutrition by incorporating nutrition goals and actions from a wide range of sectors, for example, agriculture and food security, social safety nets, and water sanitation and hygiene [1, 22]. A combination of nutrition-specific and nutrition-sensitive interventions may be an effective strategy to optimize reductions in stunting.

Aims: This systematic review sought to evaluate the effect of nutrition-specific and nutrition-sensitive interventions, alone or in combination, to reduce stunting in children from low- and middle-income countries (LMICs). The purpose of the review was to provide a comprehensive synthesis of the available evidence that could assist policymakers and donors.

Methods: Electronic databases were used to identify review studies published between 1980 and 2015 in which nutrition-specific and nutrition-sensitive interventions were implemented for children under 5 years old in LMICs. The primary outcome was a change in stunting prevalence, estimated as the average annual rate of reduction (AARR). A program was considered efficient in terms of reduced stunting if the AARR was ≥3%.

Results: The final review included 18 papers which described a total of 14 programs in 19 LMICs where nutrition-specific approaches to reduce stunting had been implemented, either alone or in combination with nutrition-sensitive interventions. The AARR of the programs ranged from 0.6 to 8.4%. The most common interventions were nutrition education and counseling, growth monitoring and promotion, immunization, water sanitation and hygiene, and social safety nets. Combined interventional packages resulted in the greatest reductions in stunting (AARR 4.3–8.4%). Successful interventions (AARR ≥3%) were characterized by political commitment, multi-sectoral collaboration, community engagement, community-based service delivery platform, and wider program coverage and compliance.

Conclusions: For all settings, programs that combine nutrition-specific and nutrition-sensitive interventions, mainly those with strong health access and safety net components, appear to be the most effective in reducing stunting in LMICs.

This review supports the multi-sectoral approach to malnutrition proposed by UNICEF to accelerate the reduction in the prevalence of stunting [23].

Comments	Nutritional intervention is essential to reduce stunting. However, nutrition per se should not be the sole focus of interventions if they are to be successful. According to the UNICEF brief, interventions need to be not only nutrition-specific but also nutrition-sensitive for optimal effect, and this can be achieved only by the collaborative effort of multiple sectors, including agriculture, education, and social welfare. Nutrition-sensitive programs can help to improve the impact of nutrition-specific interventions and create a stimulating environment in which young children can grow and develop to their full potential [23].
	This review supports the UNICEF approach, showing that in most settings, a combination of nutrition-specific and nutrition-sensitive intervention resulted in the greatest reductions in stunting (AARR 4.3–8.4%). However, there was no single fixed combination of interventions that consistently demonstrated the greatest benefit in all contexts. In Bangladesh, Peru, and 9 sub-Saharan African countries, stunting was effectively reduced with nutrition education, vitamin supplementation, immunization, sanitation and hygiene practices, and social safety net programs. However, the same combination of interventions was not similarly effective in other countries, such as Ethiopia, Haiti, India, Malawi, and Mexico. The authors offered several possible explanations for the difference in outcomes, including the need for more secure targeting of younger children from rural households and the effects of other programs in the same or a neighboring community. Thus, program managers and policymakers need to identify the unique characteristics and needs of different settings and implement tailored, context-specific intervention packages to each.

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

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Background: Observational studies of dietary protein adequacy in low-income countries indicate that most young children consume adequate amounts of protein with reference to recommendations [24–26]. However, these studies did not consider important potential effect modifiers, such as the true availability of amino acids (protein digestibility), protein quality, usual dietary intake, and effects of infection on dietary protein utilization. Given the uncertainties in the interpretation of studies of dietary protein adequacy, the role of protein in growth restriction might be better evaluated by examining the impact of protein supplementation on children's growth.
Aims: The aim of the review was to provide an updated synopsis of the effect of protein or selected amino acid supplementation on growth in young children.
Methods: A PubMed search was conducted for interventional studies published until February 2015 using the following search terms: children or infants, protein or amino acids, supplementation or intervention and growth.
Results: Eighteen studies in which supplementary protein or amino acids were provided to children aged 6–35 months were identified for inclusion. Eight studies were conducted in hospitalized children recovering from acute malnutrition. The recommended protein intake levels for healthy children supported normal growth rates, but, higher intake was needed to promote catch-up growth. The 10 community-based studies failed to demonstrate a consistent benefit of protein supplementation on children's growth. Several weaknesses in the designs of these studies are highlighted, such as lack of assessment of protein quantity and quality in the usual diet of the participants or of biomarkers of protein status.
Conclusions: Critical design issues limit conclusions that can be drawn from the available studies on the effect of dietary supplementation on growth in children at risk, and additional appropriately designed trials are needed. Future studies need to meet several important criteria: (1) the target study population should be children at high-risk for malnutrition and stunting who are in the age range of 6–12 months when growth faltering typically starts and complementary foods are introduced. (2) The nutritional intervention should take into account the sufficient quantity of protein required to bring the total available protein intake up to and above the estimated requirements; the increased need for protein during and after infections; and means of ensuring that sufficient energy is provided so the protein supplementation can be utilized for growth. (3) The duration of the intervention should be long enough to assess linear growth. (4) The sample should be large enough to permit examination of potential effect modifiers (such as diet, initial anthropometric status, and morbidity).

Comments	This extensive and elegant review highlights the need for further well-designed interventional studies, specifically randomized controlled trials, to establish the role of protein supplementation in child growth. Issues such as protein quantity, protein quality, and specific amino acids should be considered.
	It is noteworthy that malnutrition is commonly associated with multiple deficiencies in macronutrients (especially high-quality proteins) and micronutrients. Therefore, a reasonable clinical approach should use a mixture of both to support growth [27]. The best combination in terms of components and quantities has still to be elucidated.

High-dose vitamin D3 in the treatment of severe acute malnutrition: a multicenter double-blind randomized controlled trial

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Background: Vitamin D deficiency is common in children with severe acute malnutrition. Studies have shown that it is associated with rickets and severe wasting [28]. In addition, vitamin D requirements may be increased in the presence of a systemic inflammatory response, which is also common in children with severe acute malnutrition [29]. Supplementation with vitamin D has been found to promote weight gain in low-birth-weight infants [30] and to have positive effects on neurodevelopment, the musculoskeletal system, and immune function [31–34].
Ready-to-use therapeutic foods intended for children with severe-acute malnutrition usually contain relatively small amounts of vitamin D and may not be sufficient to correct a vitamin D deficiency.

Aims: The aim of this study was to determine the effects of high-dose vitamin D3 supplementation on weight gain and development in children with severe acute malnutrition.

Methods: A randomized double-blind placebo-controlled trial was conducted in children aged 6–58 months with severe-acute malnutrition in Pakistan. At 2 and 4 weeks after starting ready-to-use therapeutic food, participants were randomized to receive 2 oral doses of 200,000 IU vitamin D3 (5 mg) or placebo. The primary outcome parameter was the proportion of participants gaining more than 15% of baseline weight at 8 weeks after starting the therapeutic food (end of study). Secondary outcomes were mean weight-for-height or -length z-score and the proportion of participants with delayed development (assessed with the Denver Development Screening Tool II), adjusted for baseline values, at 8 weeks after starting ready-to-use therapeutic food.

Results: Of the 194 children who were recruited to the study, 185 completed follow-up (93 in the intervention group and 92 in the control group) and were included in the analysis.
In a subset of 90 participants who underwent biochemical analyses, mean serum 25(OH)D concentrations at the end of the study were significantly higher in those given high-dose vitamin D3 group than in controls (99.4 vs. 46.6 nmol/L, $p < 0.001$).
At the end of the study, there was no significant difference between the intervention and control groups in the proportion of participants with weight gain of >15% from baseline (84/93 vs. 80/92; RR 1.04; 95% CI 0.94–1.15; $p = 0.47$). However, weight-for-height or -length z-score was significantly higher in the intervention group than the control group (adjusted mean difference: 1.07; 95% CI 0.49–1.65; $p < 0.001$). Furthermore, at the end of the study, the intervention group had a lower proportion of participants with delayed global development (adjusted RR [aRR] 0.49; 95% CI 0.31–0.77; $p = 0.002$), delayed gross motor development (aRR 0.29; 95% CI 0.13–0.64; $p = 0.002$), delayed fine motor development (aRR 0.59; 95% CI 0.38–0.91; $p = 0.018$), and delayed language development (aRR 0.57; 95% CI 0.34–0.96; $p = 0.036$). No adverse effects of the intervention were reported during the study.

Conclusions: The results of this multicenter double-blind randomized controlled trial demonstrated that dietary supplementation with high-dose vitamin D3 improved the mean weight-for-height or weight-for-length z score and developmental indices in children aged 6–58 months with severe acute malnutrition receiving standard therapy.

Despite the high dose of vitamin D administered, no adverse effects were reported, and no hyper-calcemia was observed in a subset of 90 participants for whom results of biochemical analyses were available.

Additional studies, with longer follow-up and different malnourished pediatric populations are needed to confirm these pioneering findings.

Comments	This elegant double-blind randomized controlled trial showed for the first time that provision of high-dose vitamin D, in addition to ready-to-use therapeutic food, is a safe and efficient means of promoting weight gain and improving the developmental status of young children with severe acute malnutrition. These findings suggest that the vitamin D content of current ready-to use therapeutic food is not optimal for these purposes in this patient group. Further studies in other pediatric populations and of longer duration are needed. Confirmation of these findings would support the inclusion of high-dose vitamin D in the treatment protocol for pediatric malnutrition. Given that megadoses of vitamin D may have adverse effects, future studies should also conduct dose-response analyses to determine the optimal (maybe lower) vitamin D dose that will promote good outcomes with the lowest risk.
	The mechanism by which high-dose vitamin D improves weight gain and development in children is not yet clear. The authors suggest that it may involve the immune-modulatory actions of vitamin D that were previously reported to protect against acute infections and accelerate the resolution of inflammation [32, 34].

Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: a randomised 2 × 2 × 3 factorial trial in Burkina Faso

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Background: Children with moderate acute malnutrition may be treated by a matrix of corn-soy blend (CSB) or lipid-based nutrients (LNS) [35]. There are considerable differences between the two in terms of composition, cost, and manner of consumption and delivery. However, recommendations on the optimal supplementary food in this population are limited by the sparsity of available data.

Aims: The aim of this randomized controlled trial was to evaluate the effects of matrix (CSB or LNS), soy quality (dehulled soy, which contains higher levels of anti-nutrients which impair mineral absorption or the more expensive soy isolate), and percentage of total protein from dry skimmed

milk (0, 20, and 50%) in increasing fat-free tissue accretion in toddlers with moderate acute malnutrition.

Methods: A total of 1,609 children aged 6–23 months with moderate acute malnutrition were recruited. The trial was double-blinded with respect to soy quality and milk content, but not matrix. All supplements were given for 12 weeks and contained 500 kcal per daily serving.

LNS was provided in sachets, each containing a daily serving, ready for consumption. CSB was provided in bags of 1.7 kg containing a fortnightly ration (120 g/child/day divided into 3 meals, 40 g/meal) to be cooked with water and consumed as a porridge. The LNS had a fat content of 31.4 ± 32.1 g per daily serving, and the CBS, 11.4 ± 11.7 g per daily serving. The corresponding protein content was 12.5 ± 13.5 and 15.9 ± 16.8 g.

Fat-free mass (FFM) was assessed by the deuterium dilution technique, and the FFM index (FFMI) was calculated by dividing FFM by length squared. The primary outcome parameter of the study was the change in FFMI from baseline to 12 weeks of intervention. Secondary outcomes were recovery rate and additional anthropometric measures.

Results: During the intervention, 4 children died and 61 (3.8%) were lost to follow-up, leaving 1,548 children (96.2%) for intention-to-treat analyses. Of these, 119 discontinued the intervention before 12 weeks. Thus, the per-protocol analyses included 1,429 (88.8%) children.

At baseline, 95% of the children were breastfed. The mean weight was 6.91 ± 0.93 kg, mean FFM 83.5 ± 5.5%, mean weight-for-height z score (WHZ) –2.22 ± 0.51, and mean height-for-age z-score (HAZ) –1.70 ± 1.1. After 12 weeks of intervention, analysis of the whole study cohort yielded a mean weight increase of 0.90 kg (95% CI 0.88–0.93); 93.5% of the weight gain (95% CI 89.6–97.4) comprised FFM. WHZ increased by 0.68 (95% CI 0.65–0.72) and HAZ decreased by 0.17 (95% CI 0.15–0.19).

Supplementation with LNS increased FFMI accretion by 0.083 kg/m^2 compared to CSB ($p = 0.042$). However, there was no significant difference in the increase in FFMI by soy type, irrespective of matrix. The presence of 20% milk protein was associated with a non-significant trend of greater FFMI accretion compared to 0% milk protein (0.097 kg/m^2, $p = 0.055$), and there was no effect of 50% milk protein (0.049 kg/m^2; $p = 0.32$).

There was no effect modification by season, admission criteria, baseline FFMI, stunting, inflammation, or breastfeeding ($p > 0.05$).

An interaction between matrix and soy quality was found for weight gain ($p = 0.017$), with LNS resulting in a 128 g greater weight gain than CBS ($p < 0.01$) if both contained soy isolate, but there was no difference between LNS and CSB if both contained dehulled soy (mean difference 22 g; $p = 0.49$). Similarly, LNS with soy isolate increased the weight by 89 g compared to LNS with dehulled soy ($p = 0.005$). This greater effect of soy isolate was not observed for CSB.

LNS was associated with a 7% higher recovery rate for moderate acute malnutrition than CBS (69 vs. 62%, $p = 0.002$) and a 6% lower non-response rate (24 vs. 30%, $p = 0.007$). No such differences were observed for soy quality (soy isolate or dehulled soy) or for the percentage of total protein from dry skimmed milk (0, 20, and 50%).

Conclusions: The findings suggest that in toddlers with moderate acute malnutrition, nutritional supplements that provide the full range of macronutrients and micronutrients result in a gain of mainly FFM. The results of this randomized factorial trial suggest that LNS products yield more FFM and higher recovery rates than CSB products. In addition, LNS products containing dehulled soy may be improved by shifting to soy isolate. Further research is needed to determine the role of milk protein content relative to soy protein content in breastfed toddlers with moderate acute malnutrition.

Comments This randomized controlled trial evaluated the effects on body composition of three important factors of food supplementation, aimed at treating moderate acute malnutrition in toddlers: matrix, soy quality, and percentage of protein from dry skimmed

milk. The novelty and strength of this study lie in the factorial design which made it possible to simultaneously assess all three generic factors as well as their possible interactions. An additional strength is the assessment of body composition and not only weight gain using the deuterium dilution technique. The main limitation of this study (and many other food supplementation studies) is that no data were collected on nutritional intake of the participants or on the individual adherence to the supplements. Thus, the effects of the supplements on the intake of the regular diet could not be assessed and a dose-response analysis could not be performed.

This study found that the percentage of dry skimmed milk in the supplement (0, 20, and 50%) had no significant effect on body composition. The authors suggest that this finding may be related to the fact that 95% of the children were breastfed during the study. It disagrees with earlier reports, such as that of Stobaugh et al. [36], wherein malnourished toddlers ($n = 2,230$, aged 6–59 months) receiving a milk protein (whey)-based ready-to-use supplementary food (RUSF) showed better nutritional recovery than toddlers receiving a soy-based RUSF, even though the whey RUSF contained 33% less total protein and provided about 8% less energy. There is still a lack of evidence to set policy on the composition of supplementary foods for children with moderate acute malnutrition, and more studies are needed in this important field.

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

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Background: Ready-to-use therapeutic foods (RUTFs) are produced as energy-dense pastes and were developed to treat severe acute malnutrition in children aged 5 years and under in low- and middle-income countries (LMICs). The main advantage of RUTFs is their stability: they can be stored at room temperature for several months and eaten without the addition of water or milk, thus reducing the risk of contamination. Liquid oral nutritional supplements (ONSs) are widely used for the treatment of disease-associated malnutrition and poor appetite in more affluent societies. However, there are few data on the long-term efficacy of both supplementation types (RUTF and ONS) in the treatment of children with moderate malnutrition.

Aims: The aim of this study was to compare the effect of supplementation with a RUTF or ONS on weight, height, and body composition changes in children at risk of malnutrition.

Methods: A randomized controlled design was used. A total of 68 moderately underweight (–2< weight z-score: <–1) Pakistani children aged 5–10 years were randomized to receive RUTF or ONS in addition to their regular diet for 4 weeks. The 2 types of supplements were similar for energy, macronutrients and micronutrients content (500 kcal/day, about 13 g proteins). The RUTF was supplied as a thick paste tasting like peanut butter, packaged in a sachet. The ONS (Fortini, Strawberry, Nutricia) was strawberry flavored and was supplied in ready-to-drink 200 mL bottles. As the RUTF and ONS have a different outwardly appearance, it was impossible to blind the participants to the group allocation. The outcome measures of the study were changes in weight, height, and skinfold thickness from before to after treatment.

Results: At baseline, there were no significant differences between the RUTF and ONS groups in weight z-score, height z-score, BMI z-score, or triceps and subscapular thickness z-scores. After 4 weeks of intervention, significant increases were observed in weight, height, BMI, skinfold thickness, and all z-scores in both the RUTF and ONS groups. There were no between-group differences in the change in any of the outcome parameters at the end of the study. The weight gain (0.6 kg) in both groups was lower than expected (2 kg).

Conclusions: This study shows that RUTF and ONS are similarly effective in improving nutritional outcomes in children aged 5–10 years at risk of malnutrition. The weight gain, which was similar in the 2 groups, was lower than expected.

Comments	The increase in globalization and worldwide economic growth in recent years has led to a tendency to apply practices used in affluent countries to less developed ones. As a result, RUTF has been largely replaced by ONS in the treatment of malnutrition in children from low- and middle-income countries. In the present community-based randomized control trial, we compared the effectiveness of these two supplements (500 kcal/day) in the 5–10-year age group. The results showed no difference between them in any of the nutritional outcomes assessed.
	After 4 weeks of intervention, the average weight gain of the whole cohort was 0.6 kg, which was considerably lower than the expected gain of approximately 2 kg. The authors suggest that the most probable explanation for this discrepancy is energy compensation. That is, the children compensated for most of the extra energy provided by intake of the supplements by eating less in the following meal. However, the study (like most other studies on the effects of nutritional supplementations on malnutrition) failed to assess habitual dietary intake during the intervention, which makes it impossible to confirm this assumption.
	More studies are needed to establish the best strategies for supplementation in the treatment of malnourished children.

Diet quality and risk of stunting among infants and young children in low- and middle-income countries

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Background: In low- and middle-income countries, age-appropriate complementary feeding practices are usually not optimal in terms of food diversity, meal frequency, and acceptance of diet. Although there is strong evidence of a favorable impact of improved complementary feeding on mortality in young children, the association between feeding practices and linear growth remains unclear.

Aims: The aim of this study was to systematically examine the association between two indicators of dietary quality, namely dietary diversity and animal source food (ASF) consumption, and stunting based on existing survey data.

Methods: This cross-sectional study was based on 39 datasets from demographic and health surveys from 39 countries conducted between 2010 and 2014. Only surveys that met the following

criteria were included: (1) dataset was available on the Demographic and Health Surveys website and allowed for generation of the 7 food groups used in the dietary diversity measure [37]; (2) length was measured as part of the survey; (3) all controlling variables were available; and (4) a minimum of one (most recent) national-level survey per country was available. The analyses were based on data of 74,548 children aged 6–23 months.

Dietary diversity was defined as follows: (1) number of food groups the child consumed (range 0–5 or more) out of the 7 defined by the WHO for diet diversity [37]: flesh food (meat, poultry, fish, and organ meat); dairy products; eggs; grains or tubers; pulses or legumes or nuts; vitamin A-rich fruits and vegetables; and other fruits and vegetables; and (2) the number of animal-sourced foods (ASF) the child consumed (range 0–3): dairy products, eggs, and meat from any animal, including organ meat, poultry, fish, and shellfish.

Multiple logistic regression models adjusted for child, maternal, and household characteristics were used to assess the association between dietary quality and stunting. Stratified models by child age and by World Bank country income classifications [38] were applied as well.

Results: The number of food groups consumed and the number of ASF on the previous day were significantly associated with stunting, in a dose response manner, even after adjusted by child, maternal, and household covariates.

Compared to children who consumed 5 or more foods, the odds of being stunted were 1.345 times higher in children consuming zero food groups on the previous day (95% CI 1.233–1.468), 1.365 times higher in children who consumed one food group (95% CI 0.267–1.471); and 1.095 times higher in children who consumed 4 food groups (95% CI 1.021–1.174).

Compared to children who consumed all 3 types of ASF (dairy, egg, meat), the odds of being stunted were 1.436 time higher in children who consumed zero ASF (95% CI 1.317–1.565), 1.282 times higher in children who consumed one type of ASF (95% CI 1.179–1.392), and 1.156 times higher in children who consumed 2 types of ASF (95% CI 1.063–1.257).

An estimated 12.6% of all cases of stunting would have been prevented had all children consumed 5 or more food groups. Outcomes by country/income groupings showed a stronger association of diet diversity with ASF consumption for upper- and lower-middle-income countries than for low-income countries.

Conclusions: This large cross-sectional study based on data from demographic and health surveys from 39 countries showed that better dietary quality, expressed by larger diet diversity and multiple ASF consumption was inversely associated with stunting. The associations differed by country/income group. Further research is needed to understand the effects of dietary diversity and ASF on stunting in different settings.

Comments	This large cross-sectional study demonstrated that a diverse diet that includes various food groups as well as various animal protein sources is important in the prevention of stunting. This is the first study to show that consumption of multiple types of ASF (dairy, egg, meat) might be protective compared to fewer types of ASF. The authors suggest that more types of ASF may be a marker of diet quality, as different types of ASF have different essential nutrients that can support linear growth via various mechanisms.
	A main limitation of this study is its cross-sectional design which precludes conclusions related to causality. The authors suggest 3 possible scenarios: (1) stunting leads to poor dietary quality; that is, stunted children are fed less because they demand less food; (2) poor dietary quality causes stunting, that is, nutrients from a variety of food are needed to support growth; and (3) a still unknown factor is responsible for stunting and poor dietary quality. Support from the literature is strongest for the second scenario, with previous observational and interventional studies showing that a variety of nutrients are needed to support optimal growth [27].

Nutrition interventions in the Lives Saved Tool (LiST)

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Summary: The Lives Saved Tool (LiST) is a software modeling instrument that was originally developed in 2003 to evaluate the influence of improved coverage of effective interventions on mortality in children under 5 years old. As nutrition plays an essential role in maternal and child morbidity and mortality, the model has been extended to include nutrition and nutrition-related outcomes (e.g., stunting and wasting) and interventions (antenatal and postnatal, breastfeeding optimization, child supplemental feeding, and acute malnutrition treatment). This review provides an update on the nutrition-related model structure and on estimations and outcomes that are currently available through LiST, focusing on new nutrition-related additions to the model. It describes the model itself, as well as the relevant associations found by the model with respect to 5 of the 6 World Health Assembly Nutrition Targets for 2025: childhood stunting, maternal anemia, low birth weight, exclusive breastfeeding, and childhood wasting [1].

Optima nutrition: an allocative efficiency tool to reduce childhood stunting by better targeting of nutrition-related interventions

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Background: Childhood stunting resulting from chronic malnutrition afflicts millions of lives in low- and middle-income countries. However, large-scale effective interventions require substantial investments. Optimal allocation of the available resources can be accomplished by developing quantitative tools, specifically targeted at planning nutritional interventions.
Methods: Optima is an established framework for the analysis of resource allocation optimization. We applied this approach to develop a new tool, Optima Nutrition, for purposes of allocative efficiency analyses related to childhood stunting. At the center of the Optima approach is an epidemiological model for estimating the burden of disease, adapted from the Lives Saved Tool (LiST). Six nutritional interventions were included in the tool: antenatal micronutrient supplementation, balanced energy-protein supplementation, exclusive breastfeeding encouragement, promotion of improved infant and young child feeding (IYCF) practices, public provision of complementary foods, and vitamin A supplementation. In this study, we used the Optima Nutrition to analyze the allocation of nutritional resources in 7 districts in Bangladesh using both publicly accessible data and data derived from a complementary costing study.
Results: In the Bangladesh case study, despite limited resources, better allocation of investments in nutrition interventions could prevent the stunting of an additional 1.3 million children (an extra

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5%) by 2,030 compared to the current program. Results of the Optima Nutrition analyses showed that the strategies that should be prioritized in this case are the promotion of improved IYCF practices and vitamin A supplementation. Once these interventions are fully funded, the next priority for resource allocation is public provision of complementary foods. The program should focus on the regions of Dhaka and Chittagong which have the largest number of stunted children.

Conclusions: A resource optimization tool can provide valuable input and direct nutrition investments to achieve better results.

Comments Childhood malnutrition is a complex, multifactorial condition which requires a multidisciplinary approach. While nutrition intervention coverage clearly needs to be expanded, data on the most cost-effective way to do so are sparse.

The LiST is an important tool not only for analyzing the efficacy of nutritional interventions, but also to help countries design their own maternal and child care programs. In 2015, the Children's Investment Fund Foundation initiated and funded a project to update LiST and promote its use as part of nutrition planning in low- and middle-income countries via regional training workshops, online support, and webinars. The article by Clermont and Walker provides a thorough and updated review and analysis of this important instrument and the robust database at its core. It was published in November 2017 as a part of an AJN supplement dedicated to the LiST, along with additional important updates and analyses on the accomplishments of this project.

The article by Pearson et al. [14] describes another optimization model adapted from the original LiST, which may potentially save the lives of millions of children, by making the best of limited resources. Future studies are needed for evaluating the implementation and outcome of these models.

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Pregnancy: Impact of Maternal Nutrition on Intrauterine Fetal Growth

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Introduction

This chapter of the Yearbook on Nutrition and Growth reviews major manuscripts, studies published between July 2017 and June 2018 addressing the issue of the influence of maternal nutrition during pregnancy on intrauterine fetal growth. We carefully selected human studies, mainly of randomized-controlled or prospective design, along with several animal studies dealing with the effect of several nutrient supplementations on fetal growth and metabolic programming. This year, we focused on studies addressing the issue of maternal diet counseling during pregnancy and nutrition during pregnancy. We hope that this chapter will aid clinicians and other healthcare providers to update their knowledge on the effect of various intervention options and their effect on fetal growth and development.

Key articles reviewed for the chapter

Intensive prenatal nutrition counseling in a community health setting: a randomized controlled trial

Peccei A, Blake-Lamb T, Rahilly D, Hatoum I, Bryant A

Obstet Gynecol 2017;130:423–432

Effect of maternal supplement beverage with and without probiotics during pregnancy and lactation on maternal and infant health: a randomized controlled trial in the Philippines

Mantaring J, Benyacoub J, Destura R, Pecquet S, Vidal K, Volger S, Guinto V

BMC Pregnancy Childbirth 2018;18:193

Is a vegetarian diet safe to follow during pregnancy? A systematic review and meta-analysis of observational studies

Tan C, Zhao Y, Wang S

Crit Rev Food Sci Nutr 2018, Epub ahead of print

Maternal intake of milk and milk proteins is positively associated with birth weight: a prospective observational cohort study

Mukhopadhyay A, Dwarkanath P, Bhanji S, Devi S, Thomas A, Kurpad AV, Thomas T

Clin Nutr ESPEN 2018;25:103–109

Effect of individualised dietary education at medical check-ups on maternal and fetal outcomes in pregnant Japanese women

Tajirika-Shirai R, Takimoto H, Yokoyama T, Kaneko H, Kubota T, Miyasaka N

Asia Pac J Clin Nutr 2018;27:607–616

The Mediterranean diet adherence by pregnant women delivering prematurely: association with size at birth and complications of prematurity

Parlapani E, Agakidis C, Karagiozoglou-Lampoudi T, Sarafidis K, Agakidou E, Athanasiadis A, Diamanti E

Matern Fetal Neonatal Med 2017, Epub ahead of print

Quantification of fetal organ volume and fat deposition following in utero exposure to maternal Western diet using MRI

Sinclair KJ, Friesen-Waldner LJ, McCurdy CM, Wiens CN, Wade TP, de Vrijer B, Regnault TRH, McKenzie CA

PLoS One 2018;13:e0192900

Maternal undernutrition during the pre- and post-conception periods in twin-bearing hairsheep ewes: effects on fetal and placental development at mid-gestation

Macías-Cruz U, Vicente-Pérez R, Mellado M, Correa-Calderón A, Meza-Herrera CA, Avendaño-Reyes L

Trop Anim Health Prod 2017;49:1393–1400

Antenatal pomegranate juice rescues hypoxia-induced fetal growth restriction in pregnant mice while reducing placental cell stress and apoptosis

Chen B, Longtine MS, Riley JK, Nelson DM

Placenta 2018;66:1–7

Human Studies

Intensive prenatal nutrition counseling in a community health setting: a randomized controlled trial

Peccei A, Blake-Lamb T, Rahilly D, Hatoum I, Bryant A

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Background: Previous data support the use of various interventions, including maternal nutritional consultation for the reduction of gestational weight gain (GWG) in at-risk women. However, the composite effect did not demonstrate an effect on pregnancy conditions, besides a trend towards a decrease in the rate of fetal macrosomia.
Aims: The objective of the current study was to assess the effect of a nutritional intervention delivered to overweight and obese women in a community health setting on GWG and postpartum weight retention.
Methods: This was a randomized controlled trial of an intensive nutrition counseling intervention for overweight and obese women by a registered dietitian throughout pregnancy and 6 months postpartum. The primary outcome was the rate of GWG within the Institute of Medicine (IOM) guidelines. Secondary outcomes included neonatal birth weight and risk for adverse maternal and neonatal outcomes.
Results: Of 300 women who were randomized, 200 were allocated to the intervention group (115 obese and 85 overweight) and 100 served as controls. In intent-to-treat analysis, assignment to the intervention group did not have a significant effect on the maintenance of GWG within IOM guidelines (34.2% compared with 27.5%, OR 1.4, 95% CI 0.8–2.4). However, among obese women, assignment to the intervention group was associated with a decreased risk for large gestational age (LGA) neonates (7% compared with 17%; OR 0.3, 95% CI 0.1–0.99) as compared to the control with neither primary nor secondary outcomes being significantly different among overweight women in the intervention group. Yet, in as-treated analysis, women in the intervention group had lower neonatal birth weight and a decreased rate of LGA (6% compared with 14%; OR 0.4, 95% CI 0.2–0.96). Among overweight women, participation in the intervention was associated with lower GWG (26.1 pounds compared with 31.4 pounds; difference –5.3 pounds, 95% CI –10.0 to –0.6), lower neonatal birth weights (3,237 g compared with 3,467 g; difference -230, 95% CI –452.8 to –7.8), and lower percent of initial body mass index at 6 months postpartum.
Conclusions: Intensive nutrition counseling was not associated with a significant improvement in the proportion of obese and overweight women who had GWG within IOM guidelines. Neverthe-

less, intensive prenatal nutrition counseling may decrease LGA births among a group of overweight and obese women from culturally diverse backgrounds at risk for perinatal complications.

Comments The prevalence of overweight and obese women is rising, especially in those from low income families and certain cultures. One of the strength of the current study is that nutritional counseling was giving by registered dietitian, who took into account the cultural diversity of the study population and adjusted dietary recommendations accordingly. The current study has shown that intensive nutrition counseling by itself did not result in significant improvement in adherence to IOM GWG guidelines. Nevertheless, when data were analyzed according to actual treatment, intervention was found to improve the maternal and neonatal outcomes. Low carbohydrate was found to reduce the risk for LGA in obese women even though it was not associated with improving maternal GWG. Therefore, women should be encouraged during counseling that even if one does not succeed in improving GWG, preventing excess fetal growth can still be achieved. The pregnancy period represents a window of opportunity for improving women's health. Thus, as a next step, collaboration with primary care providers and community outreach workers should be made to help women prioritize their health in the early postnatal period and later in life.

Effect of maternal supplement beverage with and without probiotics during pregnancy and lactation on maternal and infant health: a randomized controlled trial in the Philippines

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Background: During pregnancy, there is an increase in maternal demand of several nutrients and energy. To meet this increase, adequate nutrition is essential.
Aims: The aim of the current study was to explore the effect of a maternal nutritional supplement enriched with probiotics during pregnancy and early lactation on the incidence of infant diarrhea.
Methods: Healthy, pregnant women were randomized between 24 and 28 weeks of gestation in a ratio of 1:1:1 to receive either no supplement or two servings per day of an oral supplement (140 kcal/serving) providing 7.9 g protein, multivitamin/minerals, and enriched or not with the probiotics *Lactobacillus rhamnosus* and *Bifidobacterium lactis*. Intervention was initiated at the third trimester of pregnancy until at least 2 months post-delivery. Incidence of infant diarrhea until 12 months post-delivery was analyzed by Poisson regression. Other outcomes, including the effect on maternal health and fetal growth, were also evaluated and analyzed by ANOVA.
Results: Of 223 women who were randomized, 208 mother/infant pairs were included in the final analysis. No significant difference in the incidence of infant diarrhea was observed between all three groups. The mean maternal weight gains at delivery were similar among groups, despite an increase in caloric intake in the supplemented groups. There were no statistically significant differences between the study groups regarding the rate of pregnancy-related or fetal adverse outcomes.

Mean weight-, length-, BMI- and head circumference-for-age z-scores were below the WHO median value for all groups. The effect of the combined supplementation versus the no supplementation have shown that at 12 months, the combined supplemented group had gained statistically significant weight (8.97 vs. 8.61 kg, $p = 0.001$) and height (74.2 vs. 73.4 cm, $p = 0.031$), and had a higher weight-for-age z-score (–0.62 vs. –0.88, $p = 0.045$) as compared to the no supplement group. **Conclusions:** According to the current study, nutritional supplement with or without probiotics administered during the third trimester and at the early postpartum period was safe with no increased risk for neonatal diarrhea. Despite the fact that no difference in the rate of infant diarrhea was observed between the three groups, the analysis of the combined supplemented groups showed beneficial effects of maternal supplementation on infant weight and length gains at 12 months.

Comments	The current study is one of a few randomized control trials, which examines the safety and potential beneficial effect of oral nutritional supplements, with and without probiotics, during the third trimester of pregnancy on maternal and child health. The primary outcome (the risk of infant diarrhea) is not the scope of the current chapter, yet, to consider a new therapy or nutritional supplement product it is prudent to establish its safety. Regarding efficacy, in the current study, fetal weight was not found to be affected by nutritional supplements, with and without probiotics. Since the study groups were relatively small and this outcome (birth weight) was not defined as primary outcome, it is difficult to conclude regarding the use of specific intervention for this purpose. However, the use of nutritional supplements was found to be associated with higher infant weight gain at one year of age. Therefore, future studies must be planned. In those studies, larger cohorts are needed and the selection of the study cohort should focus on high-risk populations, such as those at risk for fetal growth restriction (FGR) or those with a sonographic diagnosis of small for gestational age fetus. In addition, the results of the current study showed that the weight differences between the infants of the study group were found significant only at one year of age but not at birth. It may suggest that beginning nutritional supplements only late during gestation cannot sufficiently affect the neonatal growth. Thus, beginning intervention earlier is gestation maybe more appropriate to explore the potential effect on fetal/neonatal weight.

Is a vegetarian diet safe to follow during pregnancy? A systematic review and meta-analysis of observational studies

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Background: Nowadays, strictly vegetarian diet is gaining popularity among individuals from various ages, cultures, and ethnicities. However, the effect of vegetarian diet on adverse pregnancy outcome was not extensively explored.
Aims: The aim of the current research was to determine the association between vegetarian diet during pregnancy and various maternal-fetal outcomes using a meta-analysis of published data.

Methods: In the current study, several online databases were searched (i.e., PubMed-Medline, EM-BASE, and Cochrane Library) for relevant articles that were published by August, 2017. Quantitative data were analyzed by a random-effects model with pooled ORs or weighted mean difference (WMD) and 95% CI as aggregate estimations.

Results: Overall, 841 potential references were evaluated, of them, 19 observational studies were identified for each of the meta-analysis and narrative review (total of 38 studies). The overall estimated relation between vegetarian pregnancy and low birth weight (LBW) was not statistically significant (1.27 [0.98–1.65], $p = 0.07$, $I^2 = 0\%$). Vegetarian Asian (India/Nepal) women had an increased risk for LBW neonate (1.33 (1.01–1.76), $p = 0.04$, $I^2 = 0\%$). However, the WMD of neonatal birth weight in five studies suggested no difference between vegetarians and omnivores. A potential association between maternal vegetarian diet and other adverse outcome, including the risks of hypospadias, intrauterine growth retardation, maternal anemia, and gestational diabetes mellitus was not found mainly because of the high heterogeneity of the included studies, lack of high-quality evidence, and limited studies included.

Conclusions: Maternal vegetarian diet in women from Asian origin was associated with an increased risk for LBW infants as compared with omnivores.

Comments	Large populations across the world consume strictly vegetarian diet. Although in some cases maternal decision to avoid meat products is made due to personal beliefs, in many others it is the result of low socioeconomic background or lack of availability of meat products. Surprisingly, data are scarce regarding the potential effect of vegetarian diet and various pregnancy complications. Since previous studies had relatively low sample size, conclusions could not be drawn from each of them separately in a reliable manner. This is the reason why the current meta-analysis is of most importance. The results of this study is reassuring as it was shown that vegetarian diet has little to no impact on the risk for LBW. Yet, these results should be considered with caution since all of the included studies were observational and the authors were unable to adjust potential confounders, which may lead to bias (e.g., genetic background, maternal body mass index or gestational weight gain). In addition, all the studies about birth weight were hospital-based, and selection bias may have occurred. Therefore, large-scale prospective studies focusing on pre- and/or early gestational nutrition will help clarify the correlation between vegetarian diet and various adverse outcomes during pregnancy.

Maternal intake of milk and milk proteins is positively associated with birth weight: a prospective observational cohort study

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Background: There is a high prevalence of low birth weight (LBW) infants born in India each year. Although prior studies have shown a positive relation between maternal milk intake and neonatal

birth weight, the relations between protein and vitamin B12 from milk have not been systematically explored.

Aims: The aim of the current study was to examine the association between maternal intake of milk, protein from milk and vitamin B12 from milk and neonatal birth weight.

Methods: This was a prospective, observational cohort study in a single urban South Indian hospital. The dietary intakes of milk and milk products were assessed using validated food frequency questionnaire, and birth outcomes were recorded. Pregnant women (17–40 years) attending antenatal screening at the Department of Obstetrics and Gynecology were invited to participate in the study. Socio-demographic details, including maternal age and obstetric history to classify the parity and education as a surrogate of socioeconomic status, were collected at baseline visit (first trimester). Information regarding maternal anthropometry, dietary intake, clinical status, and blood biochemistry as per the routine antenatal care was collected at the second and third trimesters.

Results: Overall, 2,036 births were included in the final analysis. The median consumption of milk products in the first trimester was 310 g/day and average birth weight was 2,876 g (at mean gestational age of 38.6 ± 1.5 weeks). Birth weight was positively associated with maternal intake of milk products and of % protein from milk products (%milk protein) in the first trimester (β = 86.8, 95% CI 29.1–144.6; β = 63.1, 95% CI 10.8–115.5; $p < 0.001$ for both). Intake of milk products and of %milk protein in the third trimester was positively associated with gestational weight gain (GWG) between the second and third trimesters (one-way ANOVA, $p < 0.001$ and $p = 0.001$, respectively). However, no association was observed between %vitamin B12 from milk products and neonatal birth or maternal GWG.

Conclusions: According to the findings of the current study, intake of milk products in the first trimester and especially, protein from milk products is positively associated with birth weight in this specific population.

Comments	During pregnancy, adequate protein intake is essential for the maintenance of fetal tissue accretion and for placental tissue support. There are several issues that should be discussed regarding the results of this prospective large study. First, in the current study, the median intake of milk products was 310 (198–465), 417 (295–575) and 425 (296–592) g/day and protein intake was 53.0 (44.0–63.6), 62.9 (52.5–74.0), and 63.8 (53.2–76.1) g/day. Although these values are comparable with the estimated average requirement proposed by the US dietary reference intakes, they represent lower average intake than recommended by Indian Council of Medical Research. Thus, it is unclear whether a similar effect can be expected in a population with higher mean intake of milk products and protein. Second, in the study cohort, 28.3% of neonates were small for gestational age (SGA), 16.9% were LBW, and 9.7% were delivered prematurely. Caution should be used while applying the results of the current study in other populations with lower rate of these variables. However, these data must be used as a warning sign and necessitate special attention and resources to explore other ways to reduce the rate of adverse neonatal outcome, which often accompany SGA, LBW or premature infants. Finally, the associations of intakes of milk product and %milk protein with birth weight were strongest in the first trimester. As milk is an especially rich source of branched chain amino acids, especially in a predominantly vegetarian population like the one included in the current study, it is plausible that higher milk consumption during the periconceptional period was associated with increased neonatal birth weight due to improved nutritional quality of the uterine glandular secretions and more effective placental formation. In addition, it reflects the importance of diet counseling early in gestation and preferably prior to conception.

Effect of individualised dietary education at medical check-ups on maternal and fetal outcomes in pregnant Japanese women

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Background: In Japanese women, a potential cause for low birth weight (LBW) infants may be relatively high prevalence of low maternal weight and insufficient pregnancy weight gain.

Aims: The current study aimed to explore the effects of individualized dietary education at medical routine check-ups during pregnancy on maternal and fetal outcomes in Japan.

Methods: The study included 406 underweight and normal weight pregnant women, who attended routine antenatal check-ups at an obstetric facility until ≥30 weeks of gestation and delivered singleton fetuses at 36–41 weeks gestation. On each visit, maternal weight gain was assessed based on the official "Dietary Guidelines for Pregnant and Lactating Women." For those with insufficient or excess weight gain status around 28 weeks gestation, an individualized dietary advice was provided by dieticians. The risk for various maternal and neonatal outcome was compared with a control group comprised of uncomplicated singleton deliveries (36–41 weeks gestation) at the same facility from 2008 to 2010 (n = 792) to examine the effect of dietary education on perinatal outcomes.

Results: There was no significant difference in the prevalence of women with pre-pregnancy body mass index (BMI) in the underweight category (24–25% in both groups). Adequate weight gain occurred in 74.9% of the intervention group as compared to only 65.7% in the controls ($p < 0.01$). There were no significant differences in mean birth weight or the proportion of LBW infants. However, the proportion of extremely small for gestational age (SGA) infants (defined as birth weight <3rd centile) was lower in the intervention group compared to the controls (0 vs. 1.5%, $p = 0.011$). No significant differences were observed in the frequency of caesarean delivery, pregnancy-induced hypertension, or Apgar scores <7 in 1 min.

Conclusions: Dietary education during antenatal check-ups promotes adequate maternal weight gain and helps prevent extreme fetal growth resistance.

Comments	Low birth weight and SGA are considered risk factors for short- as well as long-term neonatal outcome including future heart disease and metabolic syndrome. Despite the worldwide trends of increasing rates of maternal obesity, in Japan, current national data shows that BMI >25 kg/m^2 is relatively rare among women of reproductive age. However, the prevalence of pre-pregnancy underweight and low gestational weight gain is high, which are associated with poor fetal growth. The current study shows that simple intervention such as dietary advice can not only improve the maternal weight gain status, but also improve the neonatal outcome. Of note, the primary limitation in this study is the lack of prospective control group, but rather using an historic one. Nevertheless, despite choosing low-risk women for the control group, the intervention group still had superior maternal and neonatal outcome. It would be interesting to explore the effect of dietary intervention starting earlier during gestation as in this particular study it was offered only at the third trimester.

The Mediterranean diet adherence by pregnant women delivering prematurely: association with size at birth and complications of prematurity

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Background: The Mediterranean diet pattern is characterized by increased consumption of unprocessed and plant foods, olive oil, and fish, with minimal consumption of animal fats, meat, sugars, and salt. This diet is associated with lower risk of metabolic syndrome and gestational diabetes.

Aims: In the current study, the authors aimed to explore whether adherence to Mediterranean diet during pregnancy by mothers delivering prematurely affects intrauterine growth as expressed by neonates' anthropometry at birth and complications of prematurity.

Methods: This was a single-center, prospective, observational cohort study of 82 women who delivered preterm singletons. Pregnant women were recruited during their hospitalization in the obstetric department for imminent preterm delivery or immediately after delivering prematurely. Maternal and neonatal demographic and clinical data were recorded ad analyzed. A food frequency questionnaire was filled by the mothers, and the Mediterranean diet adherence (MDA) score was calculated. Based on 50th centile of MD score, participants were classified into high-MDA and low-MDA groups according to their MDA score.

Results: Of 82 women included is the study cohort, 37 women were allocated to the low-MDA group and 45 to the high-MDA group. The low-MDA mothers had significantly higher pre-gestational body mass index and higher rates of overweight/obesity and hypertensive disorders of pregnancy (i.e., gestational hypertension or preeclampsia). Neonates in the high-MDA group had significantly lower risk for fetal growth restriction (FGR) and higher z-scores of birth weight and body mass index. Regarding prematurity-related comorbidities, the high-MDA group was less likely to develop necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity, while they were at an increased risk for respiratory distress syndrome, although the differences were not statistically significant. However, adjustment for confounders revealed MDA as a significant independent predictor of hypertension/preeclampsia, FGR, birth weight z-score, NEC, and BPD.

Conclusions: Women with high adherence to Mediterranean diet and delivering prematurely are at lower risk for hypertensive disorders of pregnancy, FGR, and several adverse neonatal outcomes associated with prematurity.

Comments	In the current study, high adherence to Mediterranean diet was shown to be beneficial in cases of preterm birth to both mother and child. There are several mechanisms that are involved in the pathophysiology of preterm birth. One of these is intrauterine inflammation and oxidative stress. Moreover, after birth, neonates born prematurely may experience difficulty balancing between oxidant and antioxidant factors, which further augments their exposure to oxidative stress and in turn may be prone to complications. Available data suggest that anti-inflammatory and antioxidant treatment during pregnancy could prevent the related neonatal morbidity in low birth weight

infants. In addition, an in vitro model of preeclampsia-oxidative stress indicated that antioxidant therapy with vitamin E and C and N-acetylcysteine supplementation could counteract the adverse effects related to reactive oxygen species on placenta. Therefore, maternal adherence to the Mediterranean diet may have the potential to reduce several of maternal and neonatal adverse outcomes as shown in this study. However, due to the small sample size of the study cohort and the lack of information regarding the dietary habits during pregnancy conclusion cannot be drawn. Nevertheless, the current study should prompt other prospective studies with detailed information regarding maternal diet composition to define adherence to Mediterranean diet in a more accurate and reproducible manner.

Animal Studies

Quantification of fetal organ volume and fat deposition following in utero exposure to maternal Western diet using MRI

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Background: It is well established that the in-utero environment affects future health and that an insult or mal-programming during the fetal period may be associated with an increased risk for metabolic disease later in life.
Aims: In the current study, investigators aimed to examine the feasibility of using magnetic resonance imaging (MRI) for the identification of differences in fetal liver size and fat deposition using guinea pigs exposed to an in utero environment influenced by maternal consumption of a Western diet (WD).
Methods: Female guinea pigs were weaned from birth onto either an energy-dense WD or a control diet and were maintained on this diet throughout their lives. They were mated at 6 months of age and maintained on a WD or CD throughout pregnancy. Feed intake was recorded daily throughout the life of the sow. Maternal weights were collected at mating and at MR scanning. Magnetic resonance imaging was used to evaluate maternal adipose tissue, fetal liver, fetal brain, fetal adipose tissue, and total fetal volumes and for the measurement of maternal and fetal hepatic fat fractions.
Results: Sows which were given a WD had lower pre-pregnancy weight as compared to the control group ($p = 0.04$), however their weight gain over pregnancy did not differ from the controls. Magnetic resonance imaging showed less total adipose tissue in the WD group ($p = 0.04$) and higher hepatic fat content ($p = 0.04$). When controlling for litter size, fetuses of the WD had larger livers ($p = 0.02$), smaller brains ($p = 0.01$), and higher total adipose tissue volume ($p = 0.01$) when normalized by fetal volume. An increase in fetal hepatic fat fractions was also observed in the WD compared to CD group ($p < 0.001$).

Conclusions: Maternal WD consumption prior to and during gestation induces differences in maternal and fetal content volume and fat deposition in guinea pigs, as measured using MRI.

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Several prior studies have shown that maternal WD was associated with an increased risk for long-term metabolic health risk for the offspring. Yet, the in-utero manifestations that may facilitate future metabolic morbidity are still not fully understood. The investigators of the current study provide insight into the fetal adaptations to maternal WD consumption as they examined the differences in fetal brain and liver volumes, as well as fetal fat deposition in guinea pigs born to sows on either a life-long energy-dense WD or a CD. In this study, there was an observed decrease in brain to fetal volume ratio in the WD group compared to the CD group. Magnetic resonance imaging is considered safe during pregnancy to both mother and fetus. Nowadays, this modality is mainly used during pregnancy for the evaluation of suspected fetal or placental anomalies and for maternal indications. It would be interesting to use MRI for other purposes, such as surveillance on maternal compliance with a proposed diet or even fetal effects in cases of maternal diabetes (e.g., focusing on changes in the size or volume of the fetal pancreas). In addition, MRI can be used for dynamic testing. The results of this study show the value of MRI in the study of adverse in utero environments that are associated with later life metabolic syndrome, however, this modality has an enormous potential for research on the in-utero environment.

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Maternal undernutrition during the pre- and post-conception periods in twin-bearing hairsheep ewes: effects on fetal and placental development at mid-gestation

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Background: It is well established that deprived nutrition during the periconceptional period alters fetal programming, which may in turn adversely affect the fetal development and growth throughout pregnancy in sheep. Yet, the effect may be different between singleton and twin gestations.
Aims: The aim of the current study was to evaluate the consequences of long-term undernutrition (UN) in the pre- and post-conception periods on fetal and placental development at mid-gestation of hair breed ewes with twin pregnancy.
Methods: Effects of pre- and post-conception UN on fetal and placental development at mid-gestation were assessed using 28 Katahdin × Pelibuey multiparous ewes. The ewes were blocked by weight and assigned to the following four dietary treatments (7 ewes in each group): ewes fed 100% (control) or 60% of their nutritional requirements 30 days before mating (UNPre), 50 days after mating (UNPost) or during both periods (UNB). Four twin-bearing ewes were selected per treatment at day 50 post-conception and then slaughtered at day 75 of gestation to analyze their fetuses.

Results: Fetuses in the control group were heavier (*p* < 0.05) than UNPost and UNB fetuses in 14.6 and 9.4%, respectively. Organ weights as percentage of the fetal weight (except for liver) and morphometric measurements (except for abdominal girth) were not statistically different between fetuses of the control and UN (UNPre, UNPost, and UNB) groups. Placental mass was heavier in the control group as compared to the UNB group, but not as compared to other groups. The number of placentomes per ewe and placental efficiency were unaffected by UN treatments. Type A (+13.8%) and B (–12.6%) placentomes varied between the UNB groups and the controls.

Conclusions: The results of the current study indicate that fetal and placental development of ewes carrying twins is mainly altered when maternal undernutrition occurs simultaneously before conception and during the first third of pregnancy.

Comments	The current study suggests a model of induced nutritional restriction to promote loss of body reserves to evaluate the effects of peri-conceptional UN on fetal and placental development at mid-gestation. The results of this study suggest that fetal weight is adversely affected from maternal UN. However, to promote significant alterations in placenta development, maternal UN should occur both before and after conception. This indicates that fetal development at mid-gestation in ewes carrying twins is regulated by different ways, which are differently affected by the period of maternal undernutrition. Another interesting finding is the evidence that the placentas of the ewes from the UNPost group had reduced type A and B placentomes development when compared to those of the controls. This in turn may have led to a decreased fetal weight at mid-gestation in UNPost ewes despite the fact that the mass of placentomes and placenta weight were not significantly different between the groups. This observation highlights the different effects (i.e. maternal, fetal, placental) of various periods of undernutrition and emphasizes the importance of maternal diet consultation prior to conception and in the first trimester.

Antenatal pomegranate juice rescues hypoxia-induced fetal growth restriction in pregnant mice while reducing placental cell stress and apoptosis

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Background: Placental insufficiency and related hypoxia is one of the main etiologies for fetal growth restriction (FGR). Pomegranate juice is replete with phytochemicals having biological effects at non-pharmacological concentrations.

Aims: The aim of the current study was to assess whether exposure of pregnant mice to hypoxia late in gestation induces cellular stress in the placenta, which can be ameliorated by antecedent maternal consumption of pomegranate juice.

Methods: Pregnant mice were exposed to 12% (HPX) or 21% oxygen (NOX), with food ad libitum or food restricted (FR), and with consumption of pomegranate juice or glucose between 12.5 and 18.5 days post-conception (DPC). The 13% glucose control reflected the sugar content of the equivalent pomegranate juice administered. The food intake was recorded daily in the HPX groups and the average amount of food that the HPX mice consumed were provided to the NOX-FR group

between 15.5 and 18.5 DPC. The outcomes of the 9 groups ($n = 10$) at 18.5 DPC were compared, quantifying fetal and placental weights and placental labyrinthine and junctional zone depths and areas. Cellular stress was assayed by the expression of Hsp90, which serves as a molecular chaperone that is upregulated in response to cell stressors and that protects an array of proteins that mediate key downstream signaling. Apoptosis was assayed by TUNEL staining and expression of cleaved caspase 3.

Results: Maternal exposure to 12% oxygen or food restriction in 21% oxygen, induced FGR, compared to control. Placentas of the hypoxic ad libitum group had lower labyrinth to junctional zone ratio as compared to those of the normoxic food-restricted. Antenatal pomegranate juice prior to and during hypoxic exposure significantly improved fetal growth, reduced Hsp90 expression, and limited apoptosis in the labyrinth, while enhancing junctional zone apoptosis.

Conclusions: FGR, cell stress, and placental apoptosis are induced by exposure of pregnant mice to hypoxia. The sensitivity of placental labyrinth and junctional zone differ among exposure to different levels of oxygen and to pomegranate juice. Pomegranate juice offers benefits in the prophylaxis of FGR in mice, but its effect on the junctional zone requires further study.

Comments	The results of this important study indicate that FGR in mice can be induced by either exposure to low fraction of inspired oxygen (FiO2) or food restriction. Of note, each (low FiO2 or food restriction) has a different effect on placental sub-components indicating that FGR represents a final common pathway rather than a single pathology. Antenatal pomegranate juice administration was shown to rescue the growth-restricted phenotype in hypoxic mice by reducing cell stress and apoptosis. Previous studies have hypothesized that maternal supplementation with vitamin C and E may have a prophylactic effect on the development of FGR in at-risk pregnancies, yet with disappointing results. Here, a beneficial effect of pomegranate juice is described at a non-pharmacological level with multiple effects on the placental responses to normoxia, hypoxia, and food restriction during pregnancy. The strengths of the current study are that multiple control groups were included and multiple parameters of the placental phenotypes were assessed and measured. Although the results cannot indicate specifically which phytochemical is most beneficial for reduced cellular stress, they show that calorie supplementation is a key factor in the rescue of sub-optimal fetal growth as glucose supplementation also positively ameliorates the risk for FGR. Further studies are required to determine whether pomegranate juice can be used in prophylaxis of women at risk for sub-optimal fetal growth.

Overall Commentary

Prevention remains the most effective management in medicine. It reduces pain and complications and is cost-effective. It is important to note that prevention of maternal diseases and comorbidities has a dual effect. Not only does it improve maternal health and quality of life, but it also prevents fetal complications and reduces the risk for future comorbidities including the metabolic syndrome, obesity and more. This is the reason why the pregnancy period is considered as the window of opportunity – not merely to the mother but also to her children and for many generations ahead. However, health and balanced diet is only a single component in the determinants of fetal/offspring growth and development. Therefore, maternal nutrition, like any other intervention, should be personalized to achieve its maximal benefit.

Disclosure Statement

The authors report no conflict of interest.

Stunting in Developing Countries

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Introduction

In the 2018 Nutrition and Growth Yearbook, this chapter surveyed the numerous trials of lipid-based nutrient supplements (LNS) that had been published in the previous year with stunting as their primary endpoints. The results were disappointing with no trials showing significantly meaningful reductions in stunting. This laid out a significant challenge to nutritionists for which a thematic response was that nutrition-specific interventions cannot succeed on their own and must be accompanied by so-called nutrition-sensitive interventions. Primary among these are improvements in water, sanitation, and hygiene (WASH) conditions that must be radically improved before nutritional interventions will be effective. In the 2018 Yearbook we summarized the theoretical constructs under-pinning these assumptions, especially the theory that persistent gut damage – termed environmental enteric disease – results in a constellation of features including malabsorption and chronic inflammation that both wastes energy and nutrients as well as limits children's responses to somatotropic hormones. At the time of writing last year's chapter, results from the large WASH benefits and SHINE trials, funded by the Bill and Melinda Gates Foundation, were eagerly awaited. The WASH benefits results from Bangladesh and Kenya have now been published and are summarized below. The full publication of the SHINE trial results is still awaited, but the data were presented at the American Society for Tropical Medicine and Hygiene (ASTMH) and will be summarized below.

Key articles reviewed for the chapter

Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial

Luby SP, Rahman M, Arnold BF, Unicomb L, Ashraf S, Winch PJ, Stewart CP, Begum F, Hussain F, Benjamin-Chung J, Leontsini E, Naser AM , Parvez SM, Hubbard AE, Lin A, Nizame FA, Jannat K, Ercumen A, Ram PK, Das KK, Abedin J, Clasen TF, Dewey KG, Fernald LC, Null C, Ahmed T, Colford JM Jr

Lancet Global Health 2018;6:e302–e315

Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Kenya: a cluster-randomised controlled trial

Null C, Stewart CP, Pickering AJ, Dentz HN, Arnold BF, Arnold CD, Benjamin-Chung J, Clasen T, Dewey KG, Fernald LCH, Hubbard AE, Kariger P, Lin A, Luby SP, Mertens A, Njenga SM, Nyambane G, Ram PK, Colford JM Jr

Lancet Global Health 2018;6:e316–e329

Impact of fortified versus unfortified lipid-based supplements on morbidity and nutritional status: a randomised double-blind placebo-controlled trial in ill Gambian children

Unger SA, Drammeh S, Hasan J, Ceesay K, Sinjanka E, Beyai S, Sonko B, Dondeh BL, Fulford AJ, Moore SE, Prentice AM

PLoS Med 2017;14:e1002377

Early life interventions for childhood growth and development in Tanzania (ELICIT): a protocol for a randomised factorial, double-blind, placebo-controlled trial of azithromycin, nitazoxanide and nicotinamide

DeBoer MD, Platts-Mills JA, Scharf RJ, McDermid JM, Wanjuhi AW, Gratz J, Svensen E, Swann JR, Donowitz JR, Jatosh S, Houpt ER, Mduma E

BMJ Open 2018;8:e021817

Identifying the etiology and pathophysiology underlying stunting and environmental enteropathy: study protocol of the AFRIBIOTA project

Vonaesch P, Randremanana R, Gody JC, Collard JM, Giles-Vernick T, Doria M, Vigan-Womas I, Rubbo PA, Etienne A, Andriatahirintsoa EJ, Kapel N, Brown E, Huus KE, Duffy D, Finlay BB, Hasan M, Hunald FA, Robinson A, Manirakiza A, Wegener-Parfrey L, Vray M, Sansonetti PJ; AFRIBIOTA Investigators

BMC Pediatrics 2018;18:236

The consumption of dairy and its association with nutritional status in the South East Asian Nutrition Surveys (SEANUTS)

Nguyen Bao KL, Sandjaja S, Poh BK, Rojroongwasinkul N, Huu CN, Sumedi E, Aini JN, Senaprom S, Deurenberg P, Bragt M, Khouw I; SEANUTS Study Group

Nutrients 2018;10:759

Micronutrient adequacy is poor, but not associated with stunting between 12–24 months of age: a cohort study findings from a slum area of Bangladesh

Sanin KI, Islam MM, Mahfuz M, Ahmed AMS, Mondal D, Haque R, Ahmed T

PLoS One 2018;13:e0195072

Effect of zinc supplementation on growth outcomes in children under 5 years of age

Liu E, Pimpin L, Shulkin M, Kranz S, Duggan CP, Mozaffarian D, Fawzi WW

Nutrients 2018;10:E377

Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial

Luby SP[1], Rahman M[2], Arnold BF[3], Unicomb L[2], Ashraf S[2], Winch PJ[4], Stewart CP[5], Begum F[2], Hussain F[2], Benjamin-Chung J[3], Leontsini E[4], Naser AM[2], Parvez SM[2], Hubbard AE[3], Lin A[3], Nizame FA[2], Jannat K[2], Ercumen A[3], Ram PK[6], Das KK[2], Abedin J[2], Clasen TF[7], Dewey KG[5], Fernald LC[3], Null C[7], Ahmed T[2], Colford JM Jr[3]

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Background: Malnutrition and diarrheal disease in children have been known for decades to impair child health and growth. However, there is little evidence on interventions that are successful in improving growth and reducing diarrhea. The aim of the study was to assess whether water quality, sanitation, and handwashing interventions alone or combined with nutrition interventions can reduce diarrhea or growth faltering.
Methods: The WASH Benefits Bangladesh study was a cluster-randomized trial conducted in rural villages in Gazipur, Kishoreganj, Mymensingh, and Tangail districts of Bangladesh. This study enrolled pregnant women who lived near enough to each other in a cluster to allow delivery of interventions by a single community promoter and evaluated outcomes at 1- and 2-years' follow-up.
Pregnant women in geographically adjacent clusters were block-randomized to one of seven clusters: chlorinated drinking water (water); upgraded sanitation (sanitation); promotion of

handwashing with soap (handwashing); combined water, sanitation, and handwashing; counselling on appropriate child nutrition plus lipid-based nutrient supplements (nutrition); combined water, sanitation, handwashing, and nutrition; and control (data collection only). Primary outcomes were caregiver-reported diarrhea among all children who were in utero or younger than 3 years at enrolment in the past 7 days and length-for-age z score at year 2 in index children.

Results: Between May 31, 2012 and July 7, 2013, pregnant women (*n* = 5,551) in 720 clusters were randomly allocated to one of the 7 groups. Three hundred thirty-one (6%) women were lost to follow-up.

Data on diarrhea at year 1 or 2 (combined) were available for 14,425 children and data on length-for-age z score in year 2 were available for 4,584 children.

A high adherence rate was documented with all interventions. Compared with a prevalence of 5.7% (200 of 3,517 child weeks) in the control group, 7-day diarrhea prevalence was lower among index children and children under 3 years at enrolment who received sanitation (prevalence ratio 0.61, 95% CI 0.46–0.81), handwashing (0.60, 95% CI 0.45–0.80), combined water, sanitation, and handwashing (0.69, 95% CI 0.53–0.90), nutrition (0.64, 95% CI 0.49–0.85), and combined water, sanitation, handwashing, and nutrition (0.62, 95% CI 0.47–0.81); diarrhea prevalence was not significantly lower in children receiving water treatment (0.89, 95% CI 0.70–1.13). Compared with control (mean length-for-age z score –1.79), children were taller by year 2 in the nutrition group (mean difference 0.25 [95% CI 0.15–0.36]) and in the combined water, sanitation, handwashing, and nutrition group (0.13 [95% CI 0.02–0.24]).

No effect on linear growth was observed in the individual water, sanitation, and handwashing group, and combined water, sanitation, and handwashing group.

Conclusions: The trial had high intervention adherence, low attrition, and ample statistical power to detect small effects. Children receiving interventions with nutritional components had small growth benefits compared with those in the control cluster. Water quality, sanitation, and handwashing interventions did not improve child growth, neither when delivered alone nor when combined with nutritional interventions. Children receiving sanitation, handwashing, nutrition, and combined interventions had less reported diarrhea. Combined interventions showed no additional reduction in diarrhea beyond single interventions.

Comments on this manuscript are incorporated in those of the following one (Null et al., page 176).

Null C[1–3], Stewart CP[4], Pickering AJ[5, 7], Dentz HN[1, 4], Arnold BF[8], Arnold CD[4], Benjamin-Chung J[8], Clasen T[3], Dewey KG[4], Fernald LCH[9], Hubbard AE[10], Kariger P[9], Lin A[8], Luby SP[6], Mertens A[8], Njenga SM[11], Nyambane G[1], Ram PK[12], Colford JM Jr[8]

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Background: Malnutrition and enteric infection are thought to act together to impair child health and survival, yet there is limited evidence of low-cost interventions effective at breaking this cycle. The aim of this study was to assess whether combining water, sanitation, handwashing, or nutrition interventions could result in added benefits for health and growth.

Methods: The Kenya WASH Benefits study was a cluster-randomized trial conducted in rural villages in Bungoma, Kakamega, and Vihiga counties in Kenya's western region with the use of a cluster design to facilitate the logistics of the behavior change component of the interventions and to minimize contamination between intervention and comparison households. This study enrolled pregnant women from villages in rural Kenya and evaluated outcomes at 1 and 2 years of follow-up. Geographically adjacent clusters were block-randomized to active control (household visits to measure mid-upper-arm circumference), passive control (data collection only), or compound-level interventions including: household visits to promote target behaviors: drinking chlorinated water (water); safe sanitation with disposing feces in an improved latrine (sanitation); handwashing with soap (handwashing); combined water, sanitation, and handwashing; counselling on appropriate maternal, infant, and young child feeding plus small-quantity lipid-based nutrient supplements from 6 to 24 months (nutrition); and combined water, sanitation, handwashing, and nutrition. Primary outcomes were caregiver-reported diarrhea in the past 7 days (based on all data from year 1 to 2) and length-for-age z score at year 2 in index children.

Results: Between November 27, 2012 and May 21, 2014, women ($n = 8,246$) in 702 clusters were enrolled and randomly assigned an intervention or control group.

Data on diarrhea at year 1 or 2 were available for 6,494 children and data on length-for-age z score in year 2 were available for 6,583 children (86% of living children were measured at year 2). Adherence indicators for sanitation, handwashing, and nutrition were more than 70% at year 1, handwashing fell to <25% at year 2, and for water it was <45% at year 1 and <25% at year 2; combined groups were comparable to single groups.

No effect was found of any interventions (improved water quality, safe sanitation, handwashing, nutrition, or combinations of interventions) on caregiver-reported diarrhea prevalence during the first 2 years of life. Compared with active control (length-for-age z score –1.54) children in nutri-

tion and combined water, sanitation, handwashing, and nutrition were taller by year 2 (mean difference 0.13 [95% CI 0.01–0.25] in the nutrition group; 0.16 [95% CI 0.05–0.27] in the combined water, sanitation, handwashing, and nutrition group). The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.

Conclusions: This study demonstrates that none of the interventions reduced diarrhea, and only the interventions that included nutrition counselling and nutrient supplementation improved growth. However, there was no advantage in integrating water, sanitation, and handwashing with nutrition.

Comments These large, expensive and well-executed trials unfortunately provide yet further grounds for pessimism in the search for simple, low-cost panaceas against childhood stunting in low-income settings. They have, however, the great merit of giving clear and robust answers that mean that the experiments do not need to be repeated. This is particularly so because the results of the analogous SHINE Trial in Zimbabwe (presented at the American Society for Tropical Medicine and Hygiene meeting in November 2017 and soon to be published in Lancet Global Health) show extremely similar results. In all three trials, the IYCF intervention produced an improvement in length-for-age z-scores but, in common with the meta-analyzed results from prior complementary feeding interventions, the effect sizes are very modest. The maximum benefit was 0.25 z-score in the nutrition alone arm in the Bangladesh trial which equates to less than one sixth of the deficit shown by these children compared to the WHO Growth Standards. Why were the trials so inefficacious? The reason cannot be ascribed to poor execution of the studies; they were efficiently executed and sufficiently powered. Adherence in Bangladesh was very good. In Kenya there was a notable decline in adherence but, as the authors point out, the adherence rates were as good as in most prior trials and would likely be even lower in a real-life non-trial scenario. The results are also at odds with global time-series data from DHS surveys that show that stunting rapidly disappears as countries pass through the economic transition and become wealthier. A likely interpretation is not that the interventions have been inappropriate in their target of reducing environmental contamination and the resultant diarrhea and gut damage, but rather that the interventions need to be much more ambitious. Soon to be published data from our own studies suggest that there is a very high threshold of environmental conditions that needs to be exceeded before child growth will respond and that this will require what we have termed "WASH++" and others have termed "Transformative Wash." There are data to suggest that piping clean water *into the home* (as occurs in most households in wealthy nations) may be a critical component. A role for nutritionists in this debate is not to become pessimistic about the power of good nutrition but to point to the need for concerted efforts across a wider front than nutrition alone.

Impact of fortified versus unfortified lipid-based supplements on morbidity and nutritional status: a randomised double-blind placebo-controlled trial in ill Gambian children

Unger SA[1–3], Drammeh S[1], Hasan J[1], Ceesay K[1], Sinjanka E[1], Beyai S[1], Sonko B[1], Dondeh BL[1], Fulford AJ[1, 2], Moore SE[1, 2, 4], Prentice AM[1, 2]

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Background: Children in deprived populations tend to suffer from a combination of nutrient deficiencies. Therefore, recent intervention programs have favored the use of multiple micronutrients (MMN) that are also widely prescribed in primary healthcare clinics, despite the absence of a supporting evidence base. Due to tight interplay between nutrition and infection, targeting ill children who would have a greater need of nutrient replenishment, clinic-based distribution of small-quantity lipid-based nutrient supplements (LNS) might be more efficient, and easily implementable.

This trial evaluated the effectiveness of MMN in improving morbidity and growth in sick children presenting to a rural primary healthcare clinic in Gambia.

Methods: In this double-blind randomized controlled clinical trial, the administration of small-quantity LNS (SQ-LNS) fortified with 23 micronutrients was evaluated in children aged 6 months to 5 years presenting with an illness. Participants were randomly assigned to receive 1 of 3 interventions: (1) supplementation with micronutrient-fortified SQ-LNS for 12 weeks (MMN-12), (2) supplementation with micronutrient-fortified SQ-LNS for 6 weeks followed by unfortified SQ-LNS for 6 weeks (MMN-6), or (3) supplementation with unfortified SQ-LNS for 12 weeks (MMN-0) to be consumed in daily portions.

Primary outcomes, assessed in 1,085 children, were repeat clinical presentations and linear growth over 24 weeks.

Results: MMN supplementation was associated with a small increase in height-for-age z-scores 24 weeks after recruitment (effect size for MMN groups combined: 0.084 SD/24 weeks, 95% CI 0.005–0.168; $p = 0.037$; equivalent to 2–5 mm depending on age).

The trial showed no effect of small-quantity lipid-based MMN supplementation compared to unfortified supplement on subsequent all-cause morbidity as assessed by clinic visits over 6 months. In post-hoc analysis, clinic visits significantly increased by 43% over the first 3 weeks of fortified versus unfortified SQ-LNS (adjusted IRR 1.43; 95% CI 1.07–1.92; $p = 0.016$), with respiratory presentations increasing by 52% with fortified SQ-LNS (adjusted IRR 1.52; 95% CI 1.01–2.30; $p = 0.046$).

Despite a significant increase in children's reported appetite, there was only a small benefit on linear growth.

Conclusions: Prescribing micronutrient-fortified SQ-LNS to acutely ill non-malnourished and mild-to-moderately malnourished children presenting at a primary care clinic in rural Gambia had only a minimal effect on growth compared to unfortified SQ-LNS. Micronutrient supplementation also did not reduce morbidity. Evidence for an early increase in repeat visits indicates that caution is warranted when prescribing MMN in a primary care setting with a need for the establishment of evidence-based guidelines.

It is highly likely that a combination of recurrent infection, persistent gastrointestinal enteropathy, and chronic inflammation are major factors in limiting the response to nutritional intervention.

Comments The objective of this study was to test whether a more targeted approach to LNS supplementation, by offering it to sick children who were presented at the clinic by their mothers, might be more efficacious than a community-wide approach. Once again, and in common with most prior LNS trials, the benefit to linear growth was small. There was no detectable benefit on repeat clinic visits and, if anything, the *post-hoc* analysis indicated that the MMNs increased the number of infections (possibly due to the iron in the supplements). The authors again conclude that the much-needed additional nutrients were blocked from being effective by the constellation of factors surrounding environmental enteric diseases.

This next abstract summarizes the protocol for an on-going trial in Tanzania. It is included here to illustrate novel approaches to breaking the deadlock of rather inefficacious nutritional interventions to combat stunting that have been summarized in the previous editions of this Yearbook.

Early life interventions for childhood growth and development in Tanzania (ELICIT): a protocol for a randomised factorial, double-blind, placebo-controlled trial of azithromycin, nitazoxanide and nicotinamide

DeBoer MD[1], Platts-Mills JA[2], Scharf RJ[1, 2], McDermid JM[2], Wanjuhi AW[1], Gratz J[2], Svensen E[3], Swann JR[4], Donowitz JR[5], Jatosh S[6], Houpt ER[2], Mduma E[6]

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Introduction: Childhood growth and thriving remain suboptimal in low-resource settings worldwide, underscoring the need to better understand underlying etiologies and to identify interventions towards improving outcomes. In many developing areas in the world, high carriage of enteropathogens in early childhood, even in the absence of diarrhea, were associated with growth deficits. The role of antimicrobials for linear growth in this population remains unclear. Another potential means of improving growth is by targeting the tryptophan-kynurenine-niacin pathway that has been linked to enteric inflammatory responses to intestinal infections. However, it is not known in these settings whether scheduled antimicrobial intervention to reduce subclinical enteric pathogen carriage or repletion of the tryptophan-kynurenine-niacin pathway improves linear growth and development. The primary objectives of this trial are to determine if interventions with antimicrobials and nicotinamide are associated with increased length-for-age z-score (LAZ, relative to placebo-treated children) by age 18 months.

Methods: As per protocol, this randomized factorial, double-blind, placebo-controlled trial will be conducted in the rural setting of Haydom, Tanzania. The study will recruit children ($n = 1,188$) within the first 14 days of life, who will be randomized in a 2×2 factorial design to administration of antimicrobials (azithromycin and nitazoxanide, randomized together) and nicotinamide as a daily oral dose. For breastfed children aged 0–6 months, nicotinamide will be given to the mother, and for children aged 6–18 months it will be given to the child directly. Mother/child pairs will be followed up via monthly in-home visits.

The primary outcome is the child's length-for-age z-score at 18 months. The trial will assess other secondary outcomes to assess additional anthropometry, gut health, cognitive development and blood metabolomics and measurements of tryptophan-kynurenine-niacin pathway.

Enrolment began September 5, 2017 and is planned to continue through September 5, 2018. Children will be followed up until the age of 18 months, resulting in a planned completion in February 2020. The primary analysis will be performed once data collection is complete for the variables involved. Following completion of data accrual, data will be made publicly available in an online database.

Comments	Antibiotics have previously been shown, in some but not all studies, to benefit the survival and growth of children recovering from severe-acute malnutrition, and the survival of children when administered on a mass prophylactic basis. The combined impact of antibiotics with modulation of the tryptophan-kynurenine-niacin pathways has not been previously studied. Results from this study are eagerly awaited and will be summarized in a future Yearbook.

Identifying the etiology and pathophysiology underlying stunting and environmental enteropathy: study protocol of the AFRIBIOTA project

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Background: Stunting (linear growth delay) remains one of the most pressing global health problems, with roughly one out of four (155 million) children under 5 years of age affected. While the prevalence of stunting has slightly decreased globally in the past two decades, it has only marginally decreased in Sub-Saharan Africa, and the actual number of affected children has increased. The current potential causes of stunting include: unbalanced diet and insufficient vitamin/micronutrient intake, poor hygiene, and repeated infections. To date, although evidence about social and

other risk factors that contribute to stunting exists, its pathophysiological mechanisms remain largely elusive. In addition, there is still no proper intervention to cure stunting, and the most effective interventions correct for at best one third of the observed linear growth delay.

The hypothesis is that pediatric environmental enteropathy (PEE), a chronic inflammation of the small intestine, plays a major role in the pathophysiology of stunting, failure of nutritional interventions and diminished response to oral vaccines, potentially via changes in the composition of the pro- and eukaryotic intestinal communities.

The main objective of AFRIBIOTA is to shed light on the pathophysiology underlying stunting and PEE with interactions between dysbiosis and stunting/PEE in children between the age of 2 and 5 years. Secondary objectives include: identification of the broader socioeconomic environment, biological and environmental risk factors for stunting and PEE, and testing of a set of candidate biomarkers for PEE, and assessment of host outcomes including mucosal and systemic immunity and psychomotor development.

Methods: This is a case-control study recruiting children in Bangui, Central African Republic and in Antananarivo, Madagascar. In each country, children aged 2–5 years ($n = 460$) with no overt signs of gastrointestinal disease will be recruited (260 with no growth delay, 100 moderately stunted and 100 severely stunted). The intestinal microbiota composition (gastric and small intestinal aspirates; feces), the mucosal and systemic immune status, and the psychomotor development of children with stunting and/or PEE will be compared to non-stunted controls. Anthropological and epidemiological investigations of the children's broader living conditions will be performed with assessment of risk factors using a standardized questionnaire.

AFRIBIOTA may enable implementation of new biomarkers and design of evidence-based treatment strategies for stunting and PEE.

Comments In the 2018 Yearbook, we summarized a collection of papers discussing the contribution of an altered gut microbiome to the etiology of stunting. The AFRIBIOTA study will use a case-control design to examine these issues in children from CAR and Madagascar and attempt to place them in the wider context of the children's living conditions.

The consumption of dairy and its association with nutritional status in the South East Asian Nutrition Surveys (SEANUTS)

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Background: Although the proportion of under nutrition in the Southeast Asian region decreased from 31% in 1990 to 10% in 2015, 16% of the children under 5 years of age are still moderately to severely underweight.

Dairy products contribute to a healthy diet by providing energy, protein, and micronutrients such as calcium, magnesium, and vitamins B1, B2, and B12. Dairy protein is considered to be of high quality as it provides all the essential amino acids, with high bioavailability, and in many guidelines, dairy is often advised as part of a healthy diet.

A few studies have linked dairy consumption with nutritional status, but many of them were relatively small or conducted in selected groups. The objective of this study was to determine whether children who consumed dairy products as part of their daily diet had a better nutritional status as measured by anthropometric indices and blood status for iron, vitamin A and D compared to children who did not.

Methods: SouthEast Asian Nutrition Survey (SEANUTS) is a nationally representative multi-center survey in Indonesia, Malaysia, Thailand, and Vietnam, conducted between 2010 and 2011, to assess the nutritional status and lifestyle factors in children aged 0.5–12 years old. In this study, the associations between dairy consumption and nutritional status in the SEANUTS were investigated. National representative data of 12,376 children aged 1–12 years were pooled, representing nearly 88 million children in this age category.

Results: The prevalence of stunting and underweight was lower in children who consumed dairy on a daily basis (10.0 and 12.0%, respectively) compared to children who did not use dairy (21.4 and 18.0%, respectively; $p < 0.05$). The prevalence of vitamin A deficiency and vitamin D insufficiency was lower in the group of dairy users (3.9 and 39.4%, respectively) compared to non-dairy consumers (7.5 and 53.8%, respectively; $p < 0.05$).

Conclusions: The present study shows that the incidence of dairy consumption was positively associated with the nutritional status of 1–12-year-old children in the SEANUTS population. Children were less likely to be stunted or underweight and less likely to be vitamin A-deficient or vitamin D insufficient when dairy was part of their daily diet.

Comments	This analysis of a very large dataset found an association between dairy consumption and lower rates of stunting, and deficiencies of vitamins A and D. It should, however, be noted that it is not possible to infer a causative link. Dairy intake is likely to correlate with many other nutrition and lifestyle factors that could ameliorate the risk of stunting.

Micronutrient adequacy is poor, but not associated with stunting between 12–24 months of age: a cohort study findings from a slum area of Bangladesh

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Background: The diets of infants in low- and middle-income countries are predominantly cereal based and a majority of them consume diluted family foods with lower nutrient densities. Such complementary foods usually lack inclusion of animal protein sources and subsequent adequacy and bioavailability of several micronutrients such as vitamin A, zinc, iron, which are critical for growth. As a result, it has been estimated that more than 50% of the preschool children are anemic and approximately 140 million preschool children have subclinical vitamin A deficiency. In Bangladesh, undernutrition is still prevalent and recent national demographic and health survey reports that prevalence of stunting, wasting and underweight in under-5 children in this country are 36, 14, and 33%, respectively. This study aimed to follow a cohort of children, and to evaluate their dietary micronutrient intake and adequacy, and to unveil any causal relationship between micro-

nutrient adequacy and stunting along with other determinants in a slum setting in Dhaka, Bangladesh.

Methods: This study is part of an international, multidisciplinary, multi-country study, the MAL-ED study that focuses on the interaction between enteric infection and malnutrition. Bangladesh is one of the field sites among the included eight countries. Children (*n* = 265) were enrolled and followed since birth until 24 months of age. Anthropometric, morbidity, and dietary intake (based on 24-h multiple-pass recall) data were collected monthly. Micronutrient adequacy of the diet was determined by the mean adequacy ratio (MAR), which was constructed from the average intake of 9 vitamins and 4 minerals considered for the analysis. Generalized estimating equation regression models were used to establish the determinants of stunting between 12 and 24 months of age.

Results: The prevalence of low-birth-weight (LBW) was 28.7% and approximately 50% of the children were stunted by the age of 24 months. The average micronutrient intake was considerably lower than the recommended dietary allowance, and the MAR was only 0.48 at 24 months of age compared to the optimum value of 1. The MAR was not associated with stunting between 12 and 24 months of age. LBW was the significant determinant (AOR = 3.03, 95% CI 1.69–5.44) after adjusting for other factors, such as age and gender.

Conclusions: The prevalence of stunting is high among children less than 2 years old living in an urban slum area in Dhaka, Bangladesh, and the dietary micronutrient adequacy is poor among this population. However, the data did not show any evidence suggesting a plausible causal association between poor micronutrient adequacy and stunting among the studied children between 12 and 24 months of age. Having a history of LBW was attributed as the prominent risk factor for the development of stunting among these children. Therefore, improving the nutritional quality of complementary food in terms of adequacy of micronutrients is imperative for optimum growth but may not be adequate to mitigate undernutrition in this setting.

Comments on this manuscript are incorporated in those of the following one (Liu et al., page 183).

Effect of zinc supplementation on growth outcomes in children under 5 years of age

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Background: Zinc has many critical effects for child growth. Thus, zinc supplementation may be a crucial intervention to improve child growth and reduce underweight and stunting globally. While several randomized trials have examined the effect of zinc supplementation on child growth outcomes, the results of these trials, as well as prior reviews of these trials, have been mixed. To address these uncertainties, a systematic review and meta-analysis of randomized controlled trials in which study participants received preventive zinc supplementation for 3 months

or longer to improve child growth, was performed including separate analyses by different time periods (maternal, infancy/childhood) and varied growth outcomes, including at birth and childhood height, weight, corresponding Z-scores, and risk of underweight, stunting, and wasting.

Methods: PubMed, EMBASE, Cochrane Library, Web of Science, and trial registries were searched for eligible trials up to October 10, 2017. Inclusion selection and data extractions were performed independently and in duplicate. Study quality was evaluated by the Cochrane Risk of Bias tool.

Results: Seventy-eight trials with 34,352 unique participants were identified, including 24 during pregnancy and 54 in infancy/childhood. Maternal zinc supplementation did not significantly increase birth weight (weighted mean difference [WMD] = 0.08 kg, 95% CI –0.05 to 0.22) or decrease the risk of LBW (RR = 0.76, 95% CI 0.52–1.11).

Zinc supplementation after birth increased height (WMD = 0.23 cm, 95% CI 0.09–0.38), weight (WMD = 0.14 kg, 95% CI 0.07–0.21), and weight-for-age *z*-score (WMD = 0.04, 95% CI 0.001–0.087), but not height-for-age z-score (WMD = 0.02, 95%CI –0.01 to 0.06) or weight-for-height z score (WMD = 0.02, 95% CI –0.03 to 0.06).

Child age at zinc supplementation appeared to modify the effects on height (*P*-interaction = 0.002) and HAZ (*P*-interaction = 0.06), with larger effects of supplementation starting at age ≥2 years (WMD for height = 1.37 cm, 95% CI 0.50–2.25; WMD for HAZ = 0.12, 95% CI 0.05–0.19).

No significant effects of supplementation were found on the risk of stunting, underweight or wasting.

Conclusions: Zinc supplementation in infants and children, but not during pregnancy, improved specific growth outcomes. There is also evidence for potentially stronger effects on height and HAZ by child age, with greater effects when supplements were given to children aged ≥2 years, rather than infants. No other evidence was found for significant effects of zinc supplementation on other growth outcomes including risk of stunting, underweight or wasting. These findings suggest recommendation and policy development for zinc supplementation to improve growth among young children.

Comments	Both of the above papers show very marginal associations between micronutrient adequacy of the diet or zinc supplementation and stunting. The second paper with the newly updated meta-analysis of a very large number of studies is particularly discouraging in showing a meta-analyzed benefit of only 2.3 mm averaged over all ages and no impact on height-for-age z-score. Results in children over 2 years of age were slightly more encouraging but still only amounted to 13.7 mm.
	These last papers add to others summarized above and in previous Yearbooks that lead to the inevitable conclusion that there are large elements of the etiology of stunting that are still not understood and that nutrition interventions can only make a limited impact. It is important that this does not lead to the unjustified conclusion that nutritional interventions are not warranted; more likely that stunting represents a very difficult deficit to overcome by nutritional interventions alone.

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