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Contents

VII List of Contributors
IX Preface
  Koletzko, B. (Munich); Shamir, R. (Petach Tikva/Tel Aviv); Turck, D. (Lille);
  Phillip, M. (Petach Tikva/Tel Aviv)

1 The Physiology and Mechanism of Growth
  Grimberg, A. (Philadelphia, PA); Phillip, M. (Petach Tikva/Tel Aviv); Wong, J. (Glasgow);
  Ahmed S.F. (Glasgow)

16 Obesity, Metabolic Syndrome, and Nutrition
  Shalitin, S. (Petach Tikva/Tel Aviv); Battelino, T. (Ljubljana); Moreno, L.A. (Zaragoza)

52 Term and Preterm Infants
  Turck, D. (Lille); van Goudoever, J.B. (Amsterdam)

80 Cognition
  Agostoni, C.; Bettocchi, S. (Milan)

95 Nutrition and Growth in Chronic Disease
  Hartmann, C. (Haifa); Shamir, R. (Petach Tikva/Tel Aviv)

118 Early Nutrition and Its Effects on Growth, Body Composition, and Later Obesity
  Lind, M.V.; Larnkjær, A.; Mølgaard, C.; Michaelsen, K.F. (Copenhagen)

134 Malnutrition and Catch-Up Growth during Childhood and Puberty
  Yackobovitch-Gavan, M. (Petach Tikva/Tel Aviv); Bhutta, Z.A. (Toronto, ON/Karachi)

152 Pregnancy: Impact of Maternal Nutrition on Intrauterine Fetal Growth
  Hiersch, L.; Yoge, Y. (Tel Aviv)

165 Stunting in Developing Countries
  Prentice, A.M. (Banjul/London)

175 Author Index
184 Subject Index
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Preface

Over the years it has become clear that although nutrition is not the only important factor in child growth and may also not be the main factor that determines adult height, adequate nutrition is crucial for normal growth. Millions of children all over the world suffer from stunted growth because of their under- or malnutrition, which may affect not only their future growth, but also their cognitive development as well as limit their ability to develop their skills and become adults well integrated in society. Although the precise mechanism of the interaction between nutrition and growth has not been fully elucidated, a lot has been achieved since we published our previous Nutrition and Growth yearbook last year. Tremendous research efforts are invested all over the world in trying to understand the mechanisms leading to stunted growth, the right diet composition for optimal children growth, and the appropriate rehabilitation diet for children suffering from under- or malnutrition at all age groups during the growth period.

In the present volume, specialists in nutrition and growth selected some of the best studies from peer-reviewed journals published in the last year. The authors have chosen a limited number of manuscripts to share with the readers and added their comments on them. We realize we may have missed some other important studies which are also of value to the readers, even though we tried our best to achieve a comprehensive literature search. We hope that the summary of the published manuscripts and our comments will stimulate the readers to look for more manuscripts in the field, and that our comments will serve as “food for thought” which will lead to more studies. We believe that the interaction between nutrition and growth is a very important issue for growing children, their parents, and the medical teams treating them through the neonatal period, infancy, childhood, and adolescence. We believe that nutritional needs are different for each age group and encourage researchers to explore the field further.

This third yearbook on Nutrition and Growth is based on articles published from July 1, 2015 to June 30, 2016. We hope you will find the book helpful and useful.

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The understanding that hormonal regulation of children’s growth, in particular the GH-IGF-I axis, is not the sole important factor that determines human growth and adult height was supported this year with more manuscripts in the literature. More and more evidence supports the role of multiple genes and signaling pathways in determining the pace and the magnitude of children’s growth. It is clearer now that growth is a delicate and very complicated process, which is indeed determined by complex genetic forces. However, epigenetic and environmental factors such as nutrition have a powerful influence on the growth process. This year we have learned more about the physiology and the mechanism of children’s growth, insight that may lead to new thoughts and ideas related to possible intervention in pathophysiological conditions. We have tried our best to select some of the best manuscripts published between July 2015 and June 2016 on the topic. We are aware of the possibility that we might have missed some other very important manuscripts, but hope that reading the chapter, the summary of the abstracts, and the comments of the authors will encourage the reader to explore the literature for more relevant publications.
Key articles reviewed for this chapter

**Short stature: comparison of WHO and national growth standards/references for height**
Christesen HT, Pedersen BT, Pournara E, Petit IO, Júlíusson PB

**Discovery of a genetic metabolic cause for Mauriac syndrome in type 1 diabetes**
MacDonald MJ, Hasan NM, Ansari IU, Longacre MJ, Kendrick MA, Stoker SW
*Diabetes* 2016;65:2051–2059

**Pubertal development in healthy children is mirrored by DNA methylation patterns in peripheral blood**
Almstrup K, Lindhardt Johansen M, Busch AS, Hagen CP, Nielsen JE, Petersen JH, Juul A
*Sci Rep* 2016;6:28657

**Epigenetic control of skeletal development by the histone methyltransferase Ezh2**
*J Biol Chem* 2015;290:27604–27617

**The association of serum choline with linear growth failure in young children from rural Malawi**

**Associations of sleep duration and quality with disinhibited eating behaviors in adolescent girls at-risk for type 2 diabetes**
Kelly NR, Shomaker LB, Radin RM, Thompson KA, Cassidy OL, Brady S, Mehari R, Courville AB, Chen KY, Galescu OA, Tanofsky-Kraff M, Yanovski JA
*Eat Behav* 2016;22:149–155

**Longitudinal analysis of the intestinal microbiota in persistently stunted young children in South India**
*PLoS One* 2016;11:e0155405

**Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children**
*Science* 2016;351:pii: aad3311
Growth and obesity through the first 7 y of life in association with levels of maternal glycemia during pregnancy: a prospective cohort study
Am J Clin Nutr 2016;103:794–800

Evidence that up-regulation of microRNA-29 contributes to postnatal body growth deceleration
Mol Endocrinol 2015;29:921–932

Early weight gain, linear growth, and mid-childhood blood pressure: a prospective study in Project Viva
Perng W, Rifas-Shiman SL, Kramer MS, Haugaard LK, Oken E, Gillman MW, Belfort MB
Hypertension 2016;67:301–308

Linear growth and fat and lean tissue gain during childhood: associations with cardiometabolic and cognitive outcomes in adolescent Indian children
Krishnaveni GV, Veena SR, Srinivasan K, Osmond C, Fall CH

Short stature: comparison of WHO and national growth standards/references for height
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PLoS One 2016;11:e0157277

Background: In 2006 and 2007 the World Health Organization (WHO) produced multiethnic, multinational growth standards for children below the age of 5 years and 5–19 years of age, respectively. This study sought to compare the use of the WHO growth standard to national growth references for height assessment of short children.

Methods: 5,996 short pediatric patients diagnosed with growth hormone deficiency (GHD), Turner syndrome (TS), or small for gestational age (SGA) enrolled in the noninterventional NordiNet International Outcome Study (IOS) were selected because they came from 9 European countries with available national growth references. The study compared the proportion of subjects whose baseline height standard deviation scores (SDS) were categorized as short by the WHO versus national references, using the cutoffs of −2 SD for GHD, −2 SD for TS, and −2.5 SD for SGA (i.e., calculated the difference in sensitivity).
Results: For those ≥5 and <5 years, significantly fewer subjects with GHD, TS, or SGA were identified by the WHO growth standard than their national references in the Czech Republic, Denmark, Germany, Netherlands, Norway, Sweden, and Switzerland. For both age groups, and for all 3 indications, significantly more French subjects were identified by the WHO standard than their national reference. For the UK, the WHO standard identified significantly more subjects than the national reference for those ≥5 years with SGA, while all younger subjects and those ≥5 years with GHD or TS did not differ between the 2 growth references.

Conclusions: The authors concluded that the most appropriate tools for assessing the growth of European youth are the most recent national or regional growth charts.

Comments: This paper highlights the importance of assessing a child’s growth according to the most appropriate reference. This is true for both healthy children and children with certain syndromes (syndrome-specific growth charts). Growth charts originated with descriptive data about how children grew in certain reference populations. Since growth charts were being used clinically to judge the growth of individual patients, the WHO set out to create growth standards that depict how healthy children should grow. Thus, the WHO examined how children grew in cities from 6 different countries (Pelotas, Brazil; Accra, Ghana; Delhi, India; Oslo, Norway; Muscat, Oman; and Davis, CA, USA) under presumably ‘ideal’ human growing conditions (excluding children from lower socioeconomic status, not at sea level, not born at term, from multiple birth gestations, with perinatal morbidities or childhood health conditions, maternal smoking during pregnancy or lactation, and not exclusively breastfed for at least 4 months). The growth patterns across the 6 regions were remarkably similar (and remarkably different from other growth references based on nonbreastfed infants). Another strength of the WHO standards was that they were created from a total of 18,973 longitudinal measurements of 882 children from birth through age 24 months. In the USA, the Centers for Disease Control and Prevention (CDC) recommends that clinicians use the WHO growth standards for patients through age 24 months; however, it recommends the CDC growth charts for patients age 2 years and older [1, 2]. The reasons for this are that the WHO standards have a natural break at age 2 years, when measurements switch from recumbent lengths to standing heights, and they rely on cross-sectional data beyond 2 years of age. Without the strength of longitudinal data as for the first 2 years, it did not provide an advantage over the local (CDC) growth charts for older children. The current study suggests local growth charts should be used in Europe as well to be more representative of national growth patterns.

Discovery of a genetic metabolic cause for Mauriac syndrome in type 1 diabetes

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Diabetes 2016;65:2051–2059

Background: Mauriac syndrome refers to growth failure and delayed puberty associated with massive hepatomegaly (from glycogen deposition) in children with poorly controlled type 1 diabetes mellitus (IDDM). Although the syndrome has been long known (first reported in 1930), its mechanistic cause remains elusive.
**Methods:** A 13-year-old boy presented with Mauriac syndrome after having IDDM since age 30 months and worsening hyperglycemia over the last 3 years (HbA1c = 10.2%). Genomic DNA was collected from him and his parents for sequencing, and subsequent in vitro studies tested the functional impact of the identified mutation.

**Results:** The proband was found to have a heterozygous mutation in the catalytic subunit of liver glycogen phosphorylase kinase (PhK), an enzyme that regulates glycogenolysis by upregulating the activity of glycogen phosphorylase, the enzyme that catalyzes the first step in glycogen breakdown. The mutant subunit found in the patient was shown to completely inhibit PhK activity in a dominant negative fashion that leads to increased glycogen content of human liver cells in vitro. The patient’s liver, on biopsy, showed hepatocytes swollen with glycogen, but no inflammation and no steatosis. He also had transient neutropenia when in particularly poor glycemic control.

**Conclusions:** Mauriac syndrome results from the combined effects of chronic hyperglycemia and a mutant enzyme of glycogen metabolism. It is hypothesized that mutations of other glycogen metabolism enzymes may be involved similarly in causing Mauriac syndrome in other patients with poorly controlled IDDM.

**Comments**

This paper illustrates 2 salient features of clinical mechanistic detective work. The first is the importance of a prismatic case. Yes, the patient was found to have a dominant negative heterozygous mutation in the catalytic subunit of PhK, and yes the in vitro experiments provided supporting mechanistic evidence. But what made the story so compelling was the specific pedigree. The patient’s mother also had the same dominant negative heterozygous mutation in the catalytic subunit of PhK, but she did not have IDDM. The patient’s father also had poorly controlled IDDM, first diagnosed at age 6 years, but no PhK mutation. Neither parent had hepatomegaly or growth failure. It was only their son, who had both, who developed Mauriac syndrome from the combination of the glycogenolytic defect and chronic hyperglycemia.

The second feature is the importance of seeking modulating factors in chronic disease. The authors began their questioning with the observation that although their patient with Mauriac syndrome had poorly controlled IDDM (HbA1c = 10.2%), many patients with even poorer control do not develop Mauriac syndrome. Therefore, the authors reasoned, there must be another interacting factor that contributed to the development of Mauriac syndrome in their patient. This was reminiscent of Lester Baker’s logic in his seminal work with “brittle diabetics”. “How can no insulin be worse than no insulin?!” he used to say, “there must be something else” that caused the blood glucose and ketone lability in these particular patients with IDDM. Working with Salvador Minuchin and Bernice Rosman, he found that “brittle diabetics” experienced hyperglycemic and ketone excursions from adrenaline surges related to psychodynamics in the family (“psychosomatic families”), and proposed that family therapy was critical to the successful management of these patients’ diabetes [3].
Pubertal development in healthy children is mirrored by DNA methylation patterns in peripheral blood

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Background: Although the age of pubertal onset in healthy boys and girls is 60% heritable, candidate gene approaches failed to explain the 5-year-wide normal ranges. The authors hypothesized that epigenetic mechanisms (changes in DNA methylation patterns) may be involved in pubertal timing.

Methods: Blood was collected both before and after pubertal onset (defined as Tanner breast stage ≥B2 or testicular volume ≥4 ml) from 22 healthy girls and 32 healthy boys enrolled in the longitudinal study, the COPENHAGEN puberty cohort. Each blood sample was assigned a specific pubertal age (i.e., years from pubertal onset). Genome-wide changes in DNA methylation patterns were examined and related to age and changes of puberty.

Results: The authors found 94 core CpGs associated with pubertal age, the most significant region for both genders being chromosome 7 between SLC12A9 and TRIP6 containing the promoter for TRIP6 and potential binding sites for transcription factors. Changes in methylation of this region were also associated significantly with testosterone levels in boys and with FSH and LH levels in both genders. Circulating levels of TRIP6 in 20 boys and 18 girls significantly increased as the subjects progressed from pre- to mid- (around onset) to postpuberty. Immunohistochemistry showed specific TRIP6 expression in adult Leydig cells and prepubertal Sertoli cells (but not in prepubertal Leydig or mature Sertoli cells, and only weak expression in oocytes and granulosa cells). Using elastic net prediction models, methylation patterns predicted pubertal development more accurately than chronological age.

Conclusions: Pubertal timing is related to epigenetic changes, evident as changes in DNA methylation patterns in peripheral blood.

Comments: Pubertal onset and pubertal tempo are the unpredictable variables in the clinical management of growth during adolescence. It would be very exciting to identify markers in peripheral blood that can give us a better handle. Given the changeability of pubertal timing, for example secular trends or related to nutritional status, it is not surprising that epigenetic rather than genetic changes play an important role in its regulation. Perhaps it is surprising that the gene identified in this study of pubertal timing was TRIP6. TRIP6 (thyroid hormone receptor interactor 6) interacts with TRβ only in the presence of thyroid hormone, is involved in actin cytoskeleton rearrangements, modulates transcriptional activity of the glucocorticoid receptor, and is involved in NF-κB and JNK signaling by LPA2 receptor and TRAF6 binding. Thyroid hormone (T3) induces expression of both StAR and LHR in Leydig cells. In immature Sertoli cells, T3 induces expression of the androgen receptor that together with FSH drives Sertoli cell proliferation and induction of spermatogenesis during puberty. Perhaps it shouldn’t be so surprising after all. If we look at the growth plate as a model, the various hormone systems interact to regulate growth. Reproduction is similarly under multiple hormonal influences.

Epigenetic control of skeletal development by the histone methyltransferase Ezh2

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J Biol Chem 2015;290:27604–27617

Summary: In this article the authors investigated the expression profile of a large cohort of more than 300 epigenetic regulators during osteogenic differentiation of human mesenchymal cells derived from the stromal vascular fraction of adipose tissue. They found that the polycomb group protein Ezh2 (enhancer of zeste homolog 2) is downregulated during osteoblastic differentiation. They demonstrated that chemical inhibition and siRNA knockdown studies show that Ezh2, a histone methyltransferase that catalyzes trimethylation of histone 3 lysine 27 (H3K27me3), suppresses osteogenic differentiation. They also showed that blocking Ezh2 activity promotes osteoblast differentiation and suppresses adipogenic differentiation of AMSCs. By using high-throughput RNA sequence analysis, they revealed that Ezh2 inhibition stimulates cell cycle inhibitory proteins and enhance the production of extracellular matrix proteins. Conditional genetic loss of Ezh2 in uncommitted mesenchymal cells results in multiple defects in skeletal patterning and bone formation. These changes are attributed to growth plate abnormalities and premature cranial suture closure because of precocious maturation of osteoblasts. The authors concluded that the epigenetic activity of Ezh2 is required for skeletal patterning and development, and that Ezh2 expression declines during terminal osteoblast differentiation and matrix production.

Comments: The evidence of the role of epigenetic control on skeletal differentiation and growth are accumulating. In their elegant work, the authors documented the role of Ezh2 histone methyltransferase in differentiation of mesenchymal cells and osteoblast function. Previous studies have shown the effect of nutrition on epigenetic regulatory systems including Sirt 1 (histone deacetylase) and miRNA in the epiphyseal growth plate of the long bones. Recently, Pinto et al. [4] investigated the interaction between nutrition and epigenetic regulatory enzymes in the liver and showed that food restriction can lead to a significant increase in the levels of histone deacetylase level in the liver. Therefore, several lines of evidence suggest that epigenetic forces have a major role in skeletal development and in linear growth, and that they might be the link that mediates the interaction between nutrition and growth.
The association of serum choline with linear growth failure in young children from rural Malawi

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**Background:** Choline is an essential nutrient for several important body functions. Choline is important for cell structure, cell signaling, neurotransmission, lipid transport, and bone formation. Choline is irreversibly converted to betaine and trimethylene N-oxide (TMAO). The relation between serum choline and its metabolites with linear growth was never fully elucidated.

**Objective:** In the present study the authors investigated the relationship between serum choline and its closely related metabolites, betaine and TMAO, with linear growth and stunting in young children.

**Design:** In a cross-sectional study, the investigators measured serum choline, betaine, and TMAO concentration using liquid chromatography isotopic dilution tandem mass spectrometry in 325 Malawian children, ages 12–59 months. Sixty-two percent of them were stunted.

**Results and Conclusions:** In this study the authors found that linear growth failure in young children is associated with low serum choline and elevated betaine-to-choline and TMAO-to-choline ratio. The authors call for more studies designed to understand whether low dietary choline intake explains low circulating choline among stunted children living in low-income countries and whether increasing choline intake may modify choline deficiency, thus improving growth and development.

**Comments**

Stunting is prevalent worldwide and is estimated to affect more than one quarter of children below the age of 5 years. Stunting is not just a height and weight issue, but is also associated with impaired cognitive function, increased morbidity and mortality, and a greater chance of living in poverty in adulthood. The authors of the above study delineated nicely the importance of choline and its metabolites in different functions of the body from cell membrane structure and cell growth to coordination of neuronal functions. They also described the importance of choline and its metabolites in bone linear growth. The results of the present study might make one wonder whether choline, in addition to its important role as an essential nutrient, and its metabolites can also serve as markers of a child’s nutritional status and can be used to assess successful nutritional intervention and catch-up growth. The definition of stunting as a height-for-age z score greater than –2 is problematic since not all children in this category will benefit from nutritional intervention. Can the serum levels of choline and its metabolites distinguish between those that will benefit from it and those that will not? Can early change in the levels of choline and its metabolites predict the efficacy of nutritional rehabilitation and who will catch up during such an intervention? Such prospective studies are definitely needed.
Associations of sleep duration and quality with disinhibited eating behaviors in adolescent girls at-risk for type 2 diabetes

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Objectives: The association between sleep duration and daytime sleepiness has been associated with an increased risk for type 2 diabetes in adults. Less attention was given to the characteristics of sleep in adolescents at risk for diabetes or to the possible behavioral mechanisms, such as disinhibited eating, through which sleep may affect metabolic functioning.

Methods: The authors evaluated the association of sleep duration and daytime sleepiness with a multimodel assessment of disinhibited eating in 19 overweight/obese adolescent girls with a family history of type 2 diabetes who also had mild-to-moderate depression symptoms. Participants reported sleep duration and daytime sleepiness with the Sleep Habits Survey and Children’s Sleep Habit Questionnaire. Adolescents’ binge eating was assessed with the Eating Disorder Examination interview. They also conducted a series of test meals to measure total energy intake and eating in the absence of hunger (EAH).

Results: The authors found that reported sleep duration was positively related to test meal total energy intake ($p = 0.04$), but not to EAH. Daytime sleepiness was associated with a greater odds of objective binge eating in the previous month ($p = 0.009$).

Conclusions: The investigators concluded that in overweight/obese adolescent girls with a family history of type 2 diabetes, reported sleep characteristics are associated with disinhibited eating behaviors that have been related to extreme weight gain and adverse metabolic control.

Comments: Overweight and obesity influence children’s growth rates, the timing of the pubertal onset, pubertal tempo, and the final height. There are many lines of evidence linking the length and quality of sleep to eating behavior and body weight. Experimentally, induced sleep loss in adults was associated with different hormonal changes including alternations in appetitive hormones. It is therefore logical to assume that sleep duration in adolescence will also be associated with changes in appetite. Indeed, the authors of the above study confirmed that association. While the genetic and family background is a variant that we cannot change, one might wonder if we can influence the sleep duration of children and especially of adolescence and expect changes in their eating behavior, weight gain, growth rate, and pubertal changes. These kinds of prospective interventional studies will also shed light on the complex mechanisms that control the interaction between the duration and quality of sleep and eating behavior and growth and puberty.
Longitudinal analysis of the intestinal microbiota in persistently stunted young children in South India

Dinh DM1, 2, Ramadass B4, Katulla D4, Sarkar R4, Braunstein P5, Tai A3, Wanke CA1, 2, 4, Hassoun S5, Kane, AV1, Naumova EN2, 4, 6, Kang G2, 3, Ward HD1, 2, 4

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PLoS One 2016;11:e0155405

Summary: Previous clinical studies have demonstrated that moderate-to-severe malnutrition which leads to stunting (height for age z score less than –2.0 SD) is linked to the gut microbiome. There have been no previous longitudinal studies comparing gut microbiota of persistently stunted children and those without stunting from the same community. The investigators conducted a preliminary longitudinal study of gut microbiota of 10 children with persistent stunting and 10 with no stunting in South India, with follow-up until 24 months of age. There was a similar increase in diversity indices of gut microbiota in the cases and controls over the period of follow-up. Gut microbiota of children in the stunted group contained more bacterial species linked with an inflammatory environment whereas microbiota in the controls were enriched with probiotic species of bacteria.

Comments

Childhood undernutrition is the leading cause of stunting worldwide and has been linked to poor health outcomes like persistent stunting, immune dysfunction, recurrent infections, and neurocognitive deficits. There is now evidence to suggest that alterations in postnatal gut microbiota are related to undernutrition and stunting. Research in this area faces numerous challenges, in particular defining normal gut microbiota for a particular age group/population and also determining whether any differences in gut microbiota are due to the underlying condition itself or an effect of the undernutrition and environment the child is placed in. Dinh et al. conducted the first longitudinal prospective evaluation of gut microbiota in a small group of children with and without stunting in South India. The results from their pilot study suggest that the Desulfovibrio strain of bacteria, common in people with inflammatory bowel disease, and Bilophila wadsworthia, reported in children with kwashiorkor and in IL-10-deficient mice with colitis, were more common in children with stunting. On the other hand, microbiota enriched with probiotic species like Bifidobacteria longum and Lactobacillus mucosae were more common in the controls. This pilot study has several strengths mainly due to the fact that a group of controls from the same population was included in this prospective study. The results are still preliminary due to the small sample size and differences in factors which could influence gut microbiota, especially diarrheal illness and use of antibiotics. In addition, the control group had higher birth weights; therefore, it is still unclear if any differences in gut microbiota relate to the postnatal environment. Nevertheless, these results should encourage larger-scale studies to address this important issue worldwide and to design studies of therapies targeting gut microbiota.
Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children


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Science 2016;351 pii: aad3311

Note: This article is discussed also in the chapter by Yackobovitch-Gavan and Bhutta [this vol., pp. 134–151] and in the chapter by Prentice [this vol., pp. 165–174].

Summary: Fecal samples from 6- and 18-month-old children from Malawi with healthy growth patterns and those with undernutrition were transplanted into germ-free mice fed a representative Malawian diet. Transmission of fecal samples from children with malnutrition led to growth impairment, abnormal bone morphology, and metabolic disturbances in the mice. Cohousing mice transplanted with feces of children with malnutrition and mice transplanted with feces of children with healthy growth patterns led to invasion of age- and growth-discriminatory gut microbiome from the latter to the former groups of mice, associated with reversal of growth impairment. Introducing feces of mice that were transplanted with fecal samples of healthy children into mice who were transplanted with fecal samples of children with malnutrition also led to amelioration of growth impairment and metabolic disturbances.

Comments: This elegant translational study showed that gut microbiota immaturity is causally related to undernutrition. This study identified immaturity of the gut microbiome in feces of children with malnutrition. Age and growth discriminatory taxa identified from this study could direct future important translational studies in this area, especially in the area of therapeutic intervention. Importantly, therapies directed at restoration of age-appropriate microbiota could be important future studies and allow for personalization of therapy, given that current studies of complementary feeding have only produced modest improvement of growth in malnutrition.
Growth and obesity through the first 7 y of life in association with levels of maternal glycemia during pregnancy: a prospective cohort study

Zhu Y1, Olsen SF2, Mendola P1, Yeung EH1, Vaag A3, Bowers K1, Liu A1, Bao W1, Li S1, Madsen C3, Grunnet LG3, Granstrom C2, Hansen S2, Martin K1, Chavarro JE5, Hu FB5, Langhoff-Roos J4, Damm P6, Zhang C1

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Am J Clin Nutr 2016;103:794–800

Summary: Maternal hyperglycemia during pregnancy may be associated with excessive fetal growth, obesity, and metabolic disturbances later on in life. Prospective longitudinal studies with long-term follow-up and careful adjustment of possible confounders are limited. Zhu et al. conducted a study investigating the association of fasting plasma glucose at 28 weeks’ gestation in 661 women with gestational diabetes with growth and weight of the offspring over 7 years after adjusting for confounders like maternal prepregnancy weight, socioeconomic status, and smoking. Higher maternal plasma glucose at 28 weeks’ gestation was associated with an increased risk of overweight/obesity even after adjustment for various confounding factors.

Comments

Previous studies on the association between maternal glucose during pregnancy and offspring subsequent growth, weight gain, and metabolic disturbances have produced conflicting results. While there were significant associations with offspring parameters at birth and 7 years, this was not present during infancy. The impact of maternal hyperglycemia on offspring overweight/obesity was shown not to be mediated by excessive fetal growth in this study. Other possible mechanisms explored in previous studies include disruptions in hypothalamic neuropeptidergic neurons, altered nephrogenesis, and β-cell dysfunction in the offspring as a result of exposure to intrauterine hyperglycemia. Studies such as the present one are still unable to conclusively tease out the effect of postnatal lifestyle issues on offspring weight and metabolic consequences. Another limitation of this study which should be addressed in future studies include the fact that offspring height and weight were obtained from parental report. Finally, it is also worthwhile to highlight that the risk of overweight and obesity at age 7 years was only 1.21 times higher (95% CI: 1.01, 1.50). Further studies should also focus on more detailed assessment of body composition and metabolic outcome.
Evidence that up-regulation of microRNA-29 contributes to postnatal body growth deceleration

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Mol Endocrinol 2015;29:921–932

Summary: To improve the understanding of growth and its cessation, the investigators hypothesized that the brake on growth is orchestrated by microRNAs. Bioinformatic analysis identified the miR-29 family and expression microarray analysis in mouse kidney and lung confirmed strongly early upregulation which was further confirmed by real-time PCR in several organs. Transfection of miR-29 mimics suppressed the function of 3 miR-29 target genes that have a growth promoting role, and this suppression was diminished by mutating the target sequences, suggesting that these genes are indeed regulated by miR-29. This miR-29 upregulation during early life may play a critical role in physiological slowing and eventual cessation of body growth.

Comments: A microRNA (miRNA) is a noncoding RNA molecule (usually containing about 22 nucleotides) that functions in RNA silencing and posttranscriptional regulation of gene expression. miRNAs are well conserved in both plants and animals, and each miRNA may have hundreds of different mRNA targets, and any one target may be regulated by multiple miRNAs. Although the first miRNA was discovered in the early 1990s, their role as biological regulators was only realized in the early 2000s. Different sets of miRNAs may be expressed in different cell types, and abnormal miRNA expression is also implicated in disease states. miRNAs may also play an important role in the regulation of growth plate chondrogenesis. Growth deceleration in adulthood remains a poorly understood phenomenon. On this background, the authors of this paper report their investigation of the role miRNAs as a key negative regulator of body growth. The investigators used a bioinformatics approach to identify miRNAs that were consistently upregulated in multiple organs of growing mice. This analysis identified that miRNA29 was markedly associated with upregulation, and this was associated with a downregulation of predicted target genes for miRNA29a, -b, and -c. The investigators also found that miR-29a, -b, and -c act on the 3’-UTR regions to inhibit gene expression for 3 growth-promoting genes that are downregulated with age: Igf1, Mest, and Imp1. The investigators’ additional finding that Igf1 expression was downregulated with age in the kidney, heart, and lungs, and not upregulated in the liver, suggests that if miRNA29 is important in the age-related decline in growth, its effects on different organs may be mediated through multiple targets.
Early weight gain, linear growth, and mid-childhood blood pressure: a prospective study in Project Viva

Perng W, Rifas-Shiman SL, Kramer MS, Haugaard LK, Oken E, Gillman MW, Belfort MB
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Hypertension 2016;67:301–308

Summary: The prevalence of hypertension has been reported to be increasing and it is possible that this may be related to low birth weight and rapid early childhood weight gain. Data from participants of a large ongoing study were utilized to examine the relationship of anthropometric data over the first 4 years of life with blood pressure during later childhood. Each additional z score gain in BMI during birth to 6 months and 2–3 years was associated with 0.8 and 1.6 mm Hg higher systolic blood pressure, respectively. This was not related to birth size. Reduction in gain of excess adiposity during early life may reduce midchildhood blood pressure.

Linear growth and fat and lean tissue gain during childhood: associations with cardiometabolic and cognitive outcomes in adolescent Indian children

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Summary: To identify critical windows in childhood when there may be a link between gain in body fat, lean mass, and linear growth with cardiometabolic risk in adolescence, an adolescent birth cohort born to Indian mothers and which had longitudinal body composition assessment received detailed cardiometabolic assessment. Greater fat gain during mid-to-late childhood was associated with higher systolic blood pressure and insulin resistance at adolescence. However, greater growth (linear, fat or lean) over the first 2 years did not influence cardiometabolic risk factors or cognitive function.

Comments: While there is consensus that early life growth patterns are linked to long-term risk of conditions such as hypertension and cardiovascular disease in adulthood, it is unclear whether hypertension in childhood and adolescence has any link to early growth. The study by Perng et al. used a preexisting birth cohort to perform a longitudinal study to investigate whether there was an association between gain in BMI and linear growth during 4 childhood age intervals, birth to 6 months, 6 months to 1 year, 1–2
years, and 2–3 years, with blood pressure during mid-childhood. While a number of associations were observed on univariate analysis, following adjustment for confounders, change in BMI SDS from birth to 6 months and 2–3 years were each associated with higher mid-childhood systolic blood pressure. For each SDS increment, the magnitude of association was larger for the later period (1.40 [0.12, 2.68] vs. 0.73 [0.06, 1.39] mm Hg). There was no association of this with birth size. The authors concluded that although the magnitude of the effect of gain in BMI is small, from a public health point of view and perhaps when combined with a wider picture of adverse of cardiometabolic risk factors, targeting weight gain at these opportune windows may influence long-term outcome.

The study by Krishnaveni et al. examines the same concept in a different way by exploring the temporal relationships of changes in lean and fat mass components to adolescent cardiometabolic and cognitive outcome. This study suggests that factors that increase linear, fat, and lean growth in infancy have no adverse cardiometabolic effects in this population. However, factors that increase fat gain in mid-to-late childhood may increase cardiometabolic risk without any benefit to cognitive abilities.

References

The prevalence of obesity is increasing alarmingly to epidemic proportions in children and adolescents in both developed [1] and developing countries [2]. Obesity is known to occur as a result of genetic, environmental, lifestyle, and behavioral influences [3]. Early life may be a “critical period” when appetite and regulation of energy balance is programmed, with lifelong consequences for obesity risk. Childhood obesity is widely recognized as a risk factor for development of comorbidities such as type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, and metabolic syndrome in childhood or later life.

Dietary energy intake is a major environmental risk factor which has been the focus of numerous studies. The studies reviewed below have reported that promoting longer breastfeeding duration in high birth weight newborns may decrease their risk of developing obesity, and that the consumption of high volumes of cow milk in late infancy may increase the risk for later obesity. Research has also shown that the content of food in later life, such as protein, salt, and dietary fiber intake, can influence the tendency to become obese. Therefore, interventions in early feeding practices may help prevent childhood obesity.

Another study reported that the fat mass and obesity-associated (FTO) genotype effects can be attenuated with lower protein intake. Some of the studies evaluated the impact of meals and frequency of snack consumption on the risk of adiposity, and also evaluated the dietary patterns and dietary quality associated with a higher cardiometabolic risk. Few studies have revealed an association of hypovitaminosis D with cardiometabolic risk factors.
Finally, unhealthy eating behavior and obesity have been related to a sedentary lifestyle, particularly screen time. With increased consumption of “screen media” and social networking especially among adolescents, it seems that there is an association between the use of social networking sites and unhealthy eating behavior. This chapter reviews a selection of important articles published between July 2015 and June 2016 focused on the relation between nutrition, obesity, and metabolic syndrome in childhood and in young adults.

### Key articles reviewed for this chapter

**Longer breastfeeding duration reduces the positive relationships among gestational weight gain, birth weight and childhood anthropometrics**
*J Epidemiol Community Health* 2015;69:632–638

**Effects on childhood body habitus of feeding large volumes of cow or formula milk compared with breastfeeding in the latter part of infancy**
Hopkins D, Steer CD, Northstone K, Emmett PM

**Associations between human milk oligosaccharides and infant body composition in the first 6 mo of life**
Alderete TL, Autran C, Brekke BE, Knight R, Bode L, Goran MI, Fields DA

**The effect of a pro-breastfeeding and healthy complementary feeding intervention targeting adolescent mothers and grandmothers on growth and prevalence of overweight of preschool children**
Schwartz R, Vigo Á, de Oliveira LD, Justo Giugliani E

**Usual dietary energy density distribution is positively associated with excess body weight in Mexican children**
Aburto TC, Cantoral A, Hernández-Barrera L, Carriquiry AL, Rivera JA
*J Nutr* 2015;145:1524–1530

**Associations of reward sensitivity with food consumption, activity pattern, and BMI in children**
De Decker A, Sioen I, Verbeken S, Braet C, Michels N, De Henauw S
*Appetite* 2016;100:189–196
Clustering of lifestyle behaviours and relation to body composition in European children. The IDEFICS study

A high-protein breakfast prevents body fat gain, through reductions in daily intake and hunger, in “breakfast skipping” adolescents
Leidy HJ, Hoertel HA, Douglas SM, Higgins KA, Shafer RS
*Obesity (Silver Spring)* 2015;23:1761–1764

High salt intake: independent risk factor for obesity?
Ma Y, He FJ, MacGregor GA
*Hypertension* 2015;66:843–849

Dietary fiber intake and its association with indicators of adiposity and serum biomarkers in European adolescents: the HELENA study

Impact of an early-life intervention on the nutrition behaviours of 2-y-old children: a randomized controlled trial

An early feeding practices intervention for obesity prevention
Daniels LA, Mallan KM, Nicholson JM, Thorpe K, Nambiar S, Mauch CE, Magarey A
*Pediatrics* 2015;136:e40–e49

Dietary intake, FTO genetic variants, and adiposity: a combined analysis of over 16,000 children and adolescents
*Diabetes* 2015;64:2467–2476
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<th>Changes in dietary intake during puberty and their determinants: results from the GINIplus birth cohort study</th>
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<td><em>BMC Public Health</em> 2015; 15: 841</td>
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<th>Decreasing the number of small eating occasions (&lt;15% of total energy intake) regardless of the time of day may be important to improve diet quality but not adiposity: a cross-sectional study in British children and adolescents</th>
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<th>Stabilization of overweight prevalence and improvement of dietary habits in French children between 2004 and 2008</th>
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<th>Identification of a dietary pattern associated with greater cardiometabolic risk in adolescence</th>
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<th>Vitamin D status is associated with cardiometabolic markers in 8–11-year-old children, independently of body fat and physical activity</th>
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<th>Associations between the use of social networking sites and unhealthy eating behaviors and excess body weight in adolescents</th>
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Longer breastfeeding duration reduces the positive relationships among gestational weight gain, birth weight and childhood anthropometrics

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J Epidemiol Community Health 2015;69:632–638

Background: Gestational weight gain (GWG) may have a substantial impact on intrauterine nutrition and growth, and disease susceptibility in later life, but the relationship between GWG and childhood growth remains controversial. Little is known about whether breastfeeding duration and timing of introduction of solid foods mediates the pathway from GWG to childhood growth, especially linear growth.

Aims: The aims of this study were to (1) investigate whether birth weight and infant feeding practices (i.e., breastfeeding duration and age at introduction of solid foods) mediate the relationship between maternal GWG and childhood growth, and (2) compare the direct and indirect associations of GWG with childhood growth via structural equation modelling.

Methods: A cross-sectional study of anthropometric status of infants/children aged <6 years was conducted across 8 study sites in the National Children’s Study Formative Research in Anthropometry in the USA from 2011 to 2012. Mother-offspring dyads were recruited (n = 1,634) with the following eligibility criteria: mothers aged 18–49 years and noninstitutionalized, and offspring who were aged 0–5.9 years, healthy, of the same ethnicity and living with the mother, and who had not suffered from any illness associated with weight loss within the past week. Child anthropometrics included age- and sex-specific z scores for weight for age (WAZ), height/length for age (HAZ), weight for height/length (WHZ), and BMI for age (BMIZ), as well as ulnar length, which is a marker for limb growth. Structural equation modelling was used to calculate standardized path coefficients and total, direct, and indirect associations of GWG, birth weight, and infant feeding practices with child anthropometrics.

Results: Maternal GWG had a positive indirect association with all anthropometrics mediated via birth weight, whereas longer breastfeeding duration reduced the positive associations of GWG and birth weight with WAZ, WHZ, and BMIZ in non-Hispanics (β = –0.077, –0.064, and –0.106, respectively). Longer breastfeeding duration and introducing solid foods at a later age were positively associated with ulnar length (β = 0.023 and 0.030, respectively) but not HAZ, suggesting a distinct association, for the first time, with limb growth.

Conclusions: The findings suggest that promoting longer breastfeeding duration among women with excessive GWG who had high birth weight newborns may mitigate the potential for their offspring to develop obesity. In addition, the findings reinforce the importance of promoting appropriate GWG and preventing high birth weight, which are positively associated with childhood anthropometrics.

Comments: Obesity seems to develop as early as in utero. The association between GWG and an offspring’s obesity has been shown to be positive, null, or U-shaped. Maternal GWG has been shown to be an independent predictor of total adiposity and body fat distribution in the offspring during infancy [4]. Low-birth-weight (<2,500 g) newborns born to mothers with low GWG may have undergone intrauterine malnutrition and show rapid catch-up growth and an early adiposity rebound, leading to obesity later in life. High birth weight (>4,000 g), which is used as a marker of intrauterine overnutrition,
has also been described to be associated with an increased risk of obesity. Breastfeeding is able to attenuate the negative effects of other perinatal factors, even those related with genetic susceptibility [5]. The observed results emphasize the need of promoting an adequate GWG and prolonged breastfeeding early in life.

**Effects on childhood body habitus of feeding large volumes of cow or formula milk compared with breastfeeding in the latter part of infancy**

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**Background:** There is considerable ongoing debate regarding the effects of early growth and nutrition on the development of childhood obesity and its associated health risks. Little is known about the effects of the infant diet after the introduction of complementary foods on subsequent growth and obesity.

**Aims:** To evaluate the consumption of different types of milk in the latter part of infancy and their effects on energy intake, subsequent growth, and BMI, with particular focus on the consumption of cow milk and the volume of bottle-fed milk consumed.

**Methods:** Subjects were from the Children in Focus (CIF) substudy, which included a 10% convenience sample of children taking part in the larger Avon Longitudinal Study of Parents and Children (ALSPAC) that involved 14,000 pregnant women and their subsequent offspring. The current study was restricted to singleton children born at term (≥37 weeks of gestation) with dietary information at 8 months of age (n = 1,112). Food records collected at 8 months of age were used to define the following 5 mutually exclusive feeding groups on the basis of the type and amount of milk consumed: breast milk (BM), <600 mL formula milk/day (FM low), ≥600 mL formula milk/day (FM high), <600 mL cow milk/day (CM low), and ≥600 mL cow milk/day (CM high). Weight, height, and BMI were measured at 14 time points from birth to 10 years of age, and SD scores (SDS) were calculated. Dietary energy and macronutrient intakes were available at 7 time points. Associations between milk groups and average daily energy and macronutrient intakes and milk volumes were also investigated with the use of linear regression with adjustment for sex only.

**Results:** There were marked dietary differences between the milk groups at 8 months of age, some of which persisted to 18 months of age. CM high children were heavier than BM children from 8 months to 10 years of age with weight differences ≥0.27 SDS and an average of 0.48 SDS (after adjustment for maternal education, smoking, and parity). The maximum weight difference was at 18 months of age (p ≤ 0.0001). CM high children were taller at some ages (p < 0.01) and had greater BMI SDS from ≥8 months of age. FM high children were heavier and taller than were BM children from 8 to 37 months of age.

**Conclusions:** The findings of this study demonstrated that the rate of growth in childhood may be influenced by both the type and volume of milk fed in infancy. The feeding of high volumes of cow milk in late infancy is associated with faster weight and height gain than BM feeding. These effects on body habitus may persist through childhood.
A recently published meta-analysis and systematic review has documented that rapid weight gain during the first year of life was identified as having a strong independent association with subsequent childhood overweight, with breastfed infants having 15% lower odds of childhood overweight than nonbreastfed infants [6]. Hopkins et al. hypothesized that weight gain was being stimulated by a failure to downregulate energy intake from solids when large amounts of bottle milk were being ingested. Their results indicate that this effect was the case for cow milk with average daily excess energy intake close to 740 kJ and 72% more protein being consumed in the CM high infants than in the BM-fed infants at 8 months of age. Higher energy and protein intakes were also shown in the diets of infants fed high volumes of formula milk. Intake of nonmilk energy was lower in the 2 high-volume compared with the low-volume bottle milk groups, but not enough to completely compensate for the energy from the higher milk intakes.

The mechanism by which breastfed infants tend to be leaner than nonbreastfed infants may be related to the lower protein content of BM than of cow milk (which contains 19.8% of its energy from protein) and lower than some types of infant formula. A previous study already reported that infant formula with a lower protein content reduces BMI and obesity risk at later ages [7]. At least in part, it is possible that cow milk intake or high protein infant formula in late infancy may have an influence on rapid growth in infants and young children via the enhanced secretion of insulin and insulin-like growth factor I.

The American Academy of Pediatrics stresses the need to avoid introduction of cow milk as a main drink before 12 months of age. This study’s findings strengthen this recommendation since it showed that not only the energy intake in the first months of life may impact the risk for later obesity, but also the type and volume of milk fed in later infancy may influence the rate of growth in childhood. Therefore, parents should be advised about the appropriate volume of milk to offer their children once complementary feeding is established.

**Associations between human milk oligosaccharides and infant body composition in the first 6 mo of life**

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**Note:** This article is also discussed in the chapter by Lind et al. [this vol., pp. 118–133].

**Aims:** To investigate if differences in components of human milk oligosaccharides (HMOs) influence weight gain and body composition in the first 6 months of life and if this elucidates the possible link between breastfeeding and weight gain during infancy.

**Methods:** Twenty-five term infants, breastfed for 6 months, and their mothers were prospectively recruited. Breast milk was analyzed for HMO composition by high-pressure liquid chromatography; infant length and weight were measured and body composition (percentage fat, total fat, lean
mass) was assessed by dual-energy X-ray absorptiometry, all at 1 and 6 months of age. Multiple linear regression was used for investigating associations between HMOs and growth and body composition parameters, with maternal prepregnancy BMI, pregnancy weight gain, and infant age and sex as covariates.

**Results:** Each 1-μg/mL increase in lacto-N-fucopentaose I (LNFPI) was associated with a 0.40-kg lower infant weight \((p = 0.03)\), whereas higher HMO diversity and evenness were associated with lower total and percentage fat mass at 1 month. At 6 months, each 1-μg/mL increase in LNFPI was associated with a 1.11-kg lower weight \((p = 0.03)\) and a 0.85-g lower lean mass \((p = 0.01)\); each 1-μg/mL increase in LNFPI was associated with a 0.79-g lower fat mass \((p = 0.02)\), whereas disialyl-lacto-N-tetraose and LNFPII were associated with a 1.92-g \((p = 0.02)\) and 0.42-g \((p = 0.02)\) greater fat mass, respectively. At 6 months, each 1-μg/mL increase in fucosyl-disialyl-lacto-N-hexaose and lacto-N-neotetraose was associated with 0.04% higher \((p = 0.03)\) and 0.03% lower \((p < 0.01)\) body fat, respectively.

**Conclusions:** Specific HMO components in mother’s milk are diversely associated with infant growth and body composition.

**Comments** This relatively small study \[8\] provides several statistically significant associations with potential clinical relevance. Breast milk prebiotic oligosaccharides may be related to the differences in microbiota between breastfed and classic infant formula-fed infants. The addition of prebiotics to infant formula reduces the difference in gastrointestinal microbiota between formula-fed and breastfed infants, along with differences in stool consistency and defecation frequency. Regression analysis of HMO and microbiota can be used for prediction of infant fecal bacterial genera from HMO profiles \[9\]. Further studies are needed to determine whether the supplementation of formulas with defined HMOs could induce modification of infant gut microbiota towards that of breastfed infants. Additionally, several bioactive components including HMO contribute toward immunologic balance.

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**The effect of a pro-breastfeeding and healthy complementary feeding intervention targeting adolescent mothers and grandmothers on growth and prevalence of overweight of preschool children**

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**Aims:** The prevalence of overweight and obesity in childhood is in some studies associated with the duration of breastfeeding (BF) and the age at introduction as well as composition of complementary feeding. This study assessed the effect of a successful pro-BF and healthy complementary feeding intervention in adolescent mothers and maternal grandmothers, on growth and prevalence of overweight and obesity in children at preschool age.

**Methods:** A total of 323 adolescent mothers, their infants, and the cohabitating infants’ maternal grandmothers were randomized to either the intervention group receiving counseling sessions on BF and healthy complementary feeding at the maternity ward and at home (7, 15, 30, 60, and 120 days after delivery), or control. This intervention successfully prolonged BF. These children were
reevaluated between 4 and 7 years of age with anthropometric assessment and collection of data on dietary habits. Data were analyzed using multivariate Poisson regression with robust estimation. 

**Results:** Mean maternal age at inclusion was 17.5 years. Of the initial randomized cohort, 47.3% of the intervention group and 52.7% of the control group participated in the final evaluation. Intervention prolonged exclusive BF (median [IQR]: 2.9 [1.0–4.7] vs. 1.3 [0.6–3.0] months; \( p < 0.01 \)) and postponed introduction of complementary feeding (median [IQR]: 5 [4–6] vs. 4 [4–6] months; \( p < 0.004 \)); however, there was no difference in the quality of the complementary feeds. At the age of 4–7 years, BMI for age and height for age were not different between the intervention and the control groups, and neither was the prevalence of overweight (39 vs. 31% respectively; \( p = 0.318 \)). Additionally, no significant between-group differences in dietary habits were detected, and regression analysis did not identify significant risk factors.

**Conclusions:** Although the intervention modestly prolonged the duration of exclusive BF and slightly delayed the onset of complementary feeding, it had no impact on growth or prevalence of overweight/obesity at 4–7 years of age.

**Comments**

This study targeted one of the most vulnerable populations with multiple socioeconomic and social risk factors [10]. This is consistent with several larger studies performed in socially unprivileged environments. Despite the proven importance of prolonged BF, short-term interventions are unlikely to induce long-term differences in dietary/lifestyle habits, as was demonstrated in this study. Additionally, with no continuous involvement, half of the participants were lost to follow-up. Finally, no data on physical activity or other lifestyle determinants were collected. It is therefore obvious that prolonged, sustained, and combined dietary and lifestyle interventions along with society-induced modifications are needed for a successful diminution of the increasing childhood obesity trend [11].

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**Usual dietary energy density distribution is positively associated with excess body weight in Mexican children**

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**Aims:** Dietary energy density (DED) is positively associated with body weight in adults, but data in children are inconclusive. This study compared usual DED distributions of nonoverweight versus overweight or obese (OW/O) Mexican children.

**Methods:** Data from the 2012 Mexican National Health and Nutrition Survey (ENSANUT 2012) included 24-h recall food diaries (24HR) from 2,367 children aged 5–11 years, with a random sample (\(\sim\)10%) of repeated 24HR measures to estimate usual intake distributions (minimizing intake variability between days) by using the Iowa State University (PC-Side) method. Implausible dietary reports were identified using specific sex and age group cutoff points of \(\pm 1 \) SD of the ratio of reported energy intake (rEI) and predicted energy requirements (pERs) multiplied by 100 (rEI/pER \(\times 100 \)). Information on physical activity was obtained in a subsample of children aged \(>10 \) years. Multivariate linear regression models were used (adjusting for sex, age, region, rural or urban residence, socioeconomic conditions, maternal education, and energy from beverages) to evaluate the
relation between DED and BMI, and to compare results with and without PC-Side adjustment and with restriction to plausible reporters. 

**Results:** The survey identified 35.1% of the children in the sample to be OW/O. The usual DED mean was ∼175 kcal/100 g (95% CI: 132, 225), with only 2.5% of the study sample having a DED <125 kcal/100 g, which is suggested for healthy diets, in both the complete sample and the plausible reporters subsample. More boys underreported than girls, and more girls overreported than boys. Regression model adjusted by PC-Side and for potential confounders showed higher DED in OW/O relative to nonoverweight children for both plausible reporters (9.7 kcal/100 g; \( n = 1,452; \ p < 0.0001 \)) and the complete sample (7.9 kcal/100 g; \( n = 2,367; \ p < 0.0001 \)). In addition, the difference in energy from beverages was also significant (\( p < 0.001 \)) between the groups. The usual DED difference in plausible reporters translates into 88 additional kilocalories in daily energy intake in OW/O children. In the absence of PC-Side adjustment, the difference was significant for plausible reporters (\( p < 0.05 \)) but not for the complete sample (\( p > 0.10 \)). A greater than usual DED was found in urban areas compared to rural areas. No difference was observed for sex, age, socioeconomic conditions, and maternal education.

**Conclusions:** A positive association between usual DED and OW/O was found in Mexican children, also when controlled for confounders. The association was stronger when only plausible reporters were considered. Systemic strategies for reducing energy density in the diet of Mexican children are needed and may be effective.

**Comments**

This large and well-designed survey [12] demonstrated that overweight and obese children eat food with almost 10 kcal/100 g more energy compared to normal-weight children, after adjusting for intraindividual variance and several covariates as well as restricting analysis to plausible reporters. This confirms data from similar surveys in the USA and UK. The study is, however, cross-sectional and cannot demonstrate the causality of the relation between DED and weight of children. Interestingly, a recent fMRI study demonstrated that brain regions implicated in inhibitory control and appetite regulation are activated in response to food portion size and energy density in children [13]. A global strategy focusing on dietary energy density reduction may be effective and, if sustained over a longer period, contribute to the reduction in current childhood obesity trends.

**Associations of reward sensitivity with food consumption, activity pattern, and BMI in children**

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**Aims:** Significant associations between BMI and the consumption of energy dense foods and sugar-and artificially sweetened beverages in children are demonstrated. Additionally, BMI in children is also significantly associated with increased screen time and decreased physical activity (PA). Not all children exposed to these obesogenic factors exhibit weight-related risk behaviors and become overweight. Individual reactivity to the food environment depends on reward sensitivity (RS), which is the propensity to engage in motivated approach behavior in the presence of environmen-
tal triggers associated with the reward. The study aimed at investigating RS associations in a large general population cohort of children aged 5.5–12 years.

**Methods:** A sample of 443 Flemish children (50.3% boys) aged 5.5–12 years from the longitudinal Children’s Body Composition and Stress (ChiBS) study was selected. Cross-sectional data on palatable food consumption frequency (Children's Eating Habits Questionnaire – Food Frequency Questionnaire), screen time, physical activity, parental education level, and measured length and weight were collected. The drive subscale of the “Behavioral Inhibition/Behavioral Activation Scales” (BIS/BAS) was used as a measure of RS. Three linear regression models were conducted with RS as predictor and the consumption frequency of fast food, sweet food, and sweet drinks as dependent variables.

**Results:** A significant positive association of RS was demonstrated with the consumption frequency of fast food and sweet drinks and the z score of BMI. The models predicted that children at a mean age of percentile 10 of RS consume fast food on average 4.89 times a week and sweet drinks on average 6.95 times a week, as compared to percentile 90 of RS where they consume fast food on average 5.85 times a week and sweet drinks on average 8.42 times a week. RS explicated additional variance to that related to palatable food consumption frequency, screen time, physical activity, and parental education level, rendering the measurement of RS an added value to the assessment of weight-related behavior indicators.

**Conclusions:** Children with higher RS are more attracted to fast food and sweet drinks and thus more vulnerable to developing unfavorable eating habits and overweight. Interindividual differences in RS should be included in strategies of future childhood obesity prevention campaigns.

**Comments** Behavioral drives investigated in this cohort [14] were recently also described in an adolescent cohort [15]. The message that an important part of the pediatric population is more sensitive to environmental pressures, such as unhealthy nutrition and various screens, should be conveyed to and heard by governments and lawmakers responsible for appropriate legislation that can protect this population at increased risk. This also includes advertising, the food industry, computer games, and the television industry. Ultimately, only changes in the entire society can modify the environmental pressure to the extent required for protection of the population with an increased reward sensitivity.
Clustering of lifestyle behaviours and relation to body composition in European children. The IDEFICS study

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**Aims**: Lifestyle behaviors leading to energy imbalance must be addressed in successful comprehensive approaches for obesity prevention. Patterns of health behavior are independently associated with increased obesity in children and adolescents. The aims of this study were to identify clustered lifestyle behaviors (nutritional, physical activity, and sedentary indicators) and to investigate the association between behavioral clustering patterns and body composition in a European cohort of children 2–9 years old.

**Methods**: From September 2007 to June 2008, 16,864 children from preschools and primary schools in Italy, Estonia, Cyprus, Belgium, Sweden, Hungary, Germany, and Spain were recruited. 16,228 (96%) of these children fulfilled the inclusion criteria (complete information on sex, height, and weight). Those with complete information on diet, physical activity, sedentary behaviors, and body composition (n = 11,674, 49.2% female) were included in the analysis. Fruit, vegetable, and sugar-sweetened beverage (SSB) consumption were assessed using the proxy administered food frequency section of the Children’s Eating Habits Questionnaire (CEHQ-FFQ). A standardized self-reported parental questionnaire was used for information on children’s physical activity (PA; hours and minutes of participation in sport club activities per week) and sedentary behavior (hours of TV/DVD/video viewing separately for weekdays and weekends). All analyses were stratified by sex. A 2-step analysis was used with a combination of hierarchical and nonhierarchical clustering. One-way analysis of variance was used to compare characteristics between clusters. Binary logistic regression analysis was used for estimating the odds ratio (OR) and 95% CI for the z scores of each body composition indicator.

**Results**: Analysis identified 6 behavioral clusters (C1–C6) separately in boys and girls. C1 included children with a high level of PA, C2 included children with a high level of sedentary behavior, C3 reported a high level of PA and sedentary behaviors, C4 included high SSB consumption, C5 reported low SSB consumption and low level of sedentary activities, and C6 included high fruits and vegetables and low SSB consumption as well as a low level of sedentary behaviors. In both sexes, clusters characterized by a high level of PA (C1 and C3) included a large proportion of older children, whereas clusters characterized by low SSB consumption (C5 and C6) included a large proportion of young children. Children in clusters C2 and C3 (high sedentary) had statistically signifi-
cant higher BMI \textit{z} score, waist circumference \textit{z} score, and skinfold sum \textit{z} score (for boys and girls; \( p < 0.05 \)) compared to C1 and C4–C6. Significant associations in logistic regression between derived clusters and BCI were observed only in boys; C2 (high sedentary activities and low PA) had increased BMI \textit{z} scores (OR = 1.33; 95\% CI: 1.01, 1.74) and waist circumference \textit{z} scores (OR = 1.41; 95\% CI: 1.06, 1.86).

\textbf{Conclusions:} Clusters characterized by high sedentary behavior, low fruit and vegetable consumption, high SSB consumption, and low PA were the most obesogenic in this cohort of European children.

\textbf{Comments} This large publicly funded European study [16] supports the key messages of the primary prevention program developed in course of the IDEFICS study, which focused on lowering sedentary time and increasing PA and fruit and vegetable consumption as the main targets of the intervention. However, social [11] and/or personal determinants [14, 15] may considerably lessen the positive effects on behavior in the pediatric population. Therefore, individualized and targeted programs are needed to adequately address the total young population at increased risk for obesity. As stated previously, only programs involving the whole society on different social levels, including advertising, media, education, and regulative bodies, can bring long-term success.

\textbf{A high-protein breakfast prevents body fat gain, through reductions in daily intake and hunger, in “breakfast skipping” adolescents}

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\textbf{Background:} Breakfast has been touted as an essential part of the diet to prevent and/or treat obesity. The increased frequency of skipping breakfast has occurred concomitantly with the increased rise in obesity, raising the question as to whether breakfast and its content plays a causal role. \textbf{Aims:} To evaluate the longer-term effects of consuming a normal-protein (NP) versus high-protein (HP) breakfast on appetite control, food intake, and weight management in overweight “breakfast skipping” adolescents. Specific outcomes related to weight management included changes in body weight and body composition, daily food intake, and indices of appetite control. \textbf{Methods:} Adolescents (\( n = 57; \text{age:} 19 \pm 1 \text{ years; BMI:} 29.7 \pm 4.6 \)) completed a 12-week randomized controlled trial in which they consumed either a 1,464-kJ NP breakfast (13 g protein) or a HP breakfast (35 g protein), or continued to skip breakfast (CON). Pre- and poststudy appetite, food intake, body weight, and body composition were assessed. \textbf{Results:} In comparing the before and after change in fat mass between groups, HP prevented the gain in fat mass over the 12 weeks versus CON (\( p = 0.02 \)), whereas NP did not. No significant differences were detected between NP and HP. Similar findings were also observed with changes in the percent of body fat. HP led to reductions in daily intake versus CON (\( p = 0.03 \)), whereas NP did not. In addition, HP tended to have a reduction in daily intake versus NP (\( p = 0.06 \)). HP also had a greater reduction in carbohydrate consumption versus CON (\( p = 0.01 \)) and compared to NP (\( p = 0.01 \)). Carbohydrate consumption between CON and NP was not different. HP also had a greater reduction in fat consumption versus CON (\( p = 0.02 \)), whereas NP did not. Only the HP group experienced reductions in daily hunger versus CON (\( p < 0.05 \)).
**Conclusions:** The daily addition of a HP breakfast in breakfast-skipping adolescents with overweight/obesity prevented the gain in body fat over 12 weeks compared to skipping breakfast, whereas NP breakfasts did not. The prevention of body fat gains occurred in combination with voluntary reductions in daily intake and perceived hunger. These data suggest that an HP breakfast might influence weight management through improvements in body composition and energy intake regulation in overweight young people.

**Comments**

A previous study [17] reported that European adolescents who regularly consume breakfast had lower body fat content, and that regular breakfast consumption was associated with higher cardiorespiratory fitness in adolescents, and with a healthier cardiovascular profile, especially in males. Yannakoulia et al. [18] showed that non-obese young adults’ energy intake was significantly lower after a Mediterranean-type breakfast (high in fiber) compared to a Western-type breakfast, whereas no energy compensation was made throughout the day. Furthermore, those who had the Mediterranean-type breakfast also reported lower values in the desire to eat.

However, there is a paucity of data from long-term intervention studies assessing whether the addition of breakfast improves weight management in those who habitually skip breakfast. Further, it is unclear as to whether the type of breakfast consumed influences these outcomes.

The current study found that the daily consumption of a high-protein breakfast prevented a gain in body fat over 12 weeks compared to those who continued to skip breakfast, with reductions in daily hunger and daily food intake with a high-protein breakfast. Thus, these data suggest that although the daily addition of a high-protein breakfast does not lead to weight loss, it appears to prevent body fat gain, potentially through reductions in hunger and daily food intake. Maybe a high-protein breakfast has metabolic effects that explain the changes in fat mass despite the lack of changes in weight. However, as this study includes a relatively short duration of the intervention (12 weeks), a study of longer duration would potentially provide stronger support for the role of breakfast on weight management.

Finally, we may assume that a high-protein and high-fiber diet may have even a greater impact on lower eating desire and lower energy intake. Nevertheless, it is unclear as to whether the daily consumption of a high-protein breakfast is feasible in a free-living environment.

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**High salt intake: independent risk factor for obesity?**

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**Background:** It is well established that high salt (1 g salt = 0.4 g sodium) intake is the major cause of hypertension and accordingly leads to cardiovascular diseases. Recently, several lines of evidence have also shown that high salt intake is associated with an increased risk of obesity.

**Aims:** To determine whether there is a direct association between salt intake and obesity, independent of energy intake in children and adults.
**Methods:** Data from the National Diet and Nutrition Survey Rolling Program (NDNS RP) years 1–4 (September 2008 to December 2011) was used. The NDNS RP was a rolling cross-sectional study aimed at assessing the nutritional status of the general UK population aged ≥1.5 years using a 4-day diary. Among the persons who participated in the NDNS RP core survey, 458 children (52% boys; age: 10 ± 4 years) and 785 adults (47% men; age: 49 ± 17 years) who had valid weight and height measurements as well as a complete 24-h urine collection were included in the primary analysis. The secondary analysis included 67 children and 117 adults who had a complete 24-h urine collection and who also participated in the Doubly Labeled Water (DLW) substudy, which measured energy expenditure in free-living individuals and also provided body fat mass and lean mass. Salt intake was assessed by 24-h urinary sodium.

**Results:** Compared with the participants in the lowest salt intake tertile, those who consumed more salt tended to be men, older children, younger adults, have more energy intake, and have a larger BMI and waist circumference. Children who had higher salt intake had slightly less physical exercise. Both BMI and waist circumference increased from the lowest to the highest tertile of salt intake (both \(p\) for trend < 0.001) after adjusting for age, sex, ethnic group, household income, physical activity, total energy intake, and misreporting in children. A similar trend was also observed in adults with additional adjustment for alcohol consumption, smoking, and education level. In children, a 1-g/day increase in salt intake was associated with a 28% increase in the risk of overweight or obesity (OR = 1.28; 95% CI: 1.12–1.45; \(p = 0.0002\)). The association was almost identical when total energy intake was replaced with the consumption of sugar-sweetened beverages (OR = 1.28; 95% CI: 1.12–1.47). In adults, a 1-g/day increase in salt intake was associated with an increase in the risk of overweight or obesity by 26% (OR = 1.26; 95% CI: 1.16–1.37; \(p < 0.0001\)).

**Conclusions:** The study demonstrated a significant association between salt intake and various measures of adiposity both in children and adults, independent of energy intake or sugar-sweetened beverage consumption.

**Comments**

Several lines of evidence have shown that high salt intake is associated with an increased risk of obesity, which may be mediated by the fact that high salt intake stimulates thirst and increases fluid intake, thereby increasing sugar-sweetened beverage consumption, especially among consumers of sugar-sweetened beverages. The association between salt and obesity may also be partially caused by excessive consumption of processed food that is high in both calories and salt. However, increasing evidence suggests that there may be a direct link between salt intake and obesity, independent of total energy intake. A cross-sectional study conducted in adolescents revealed a positive relationship between dietary salt intake and subcutaneous abdominal adipose tissue, as well as leptin, independent of energy intake [19]. Prospective cohort studies in adolescents [20] have shown that baseline salt intake was positively associated with an increase in the percentage of body fat, independent of energy intake. Thus, higher salt intake seems to result in greater deposition of fat, suggesting that in some way salt alters body fat metabolism. In adults, a high sodium diet is associated with hypertension, insulin resistance, dyslipidemia, and hypoadiponectinemia, and with increased urinary cortisol and its metabolites. High salt intake also predicts metabolic syndrome status, suggesting an additive mechanism in obesity-related metabolic disorders [21]. The current study’s strengths include (1) the use of salt intake measured by complete 24-h urinary sodium excretion mainly verified by para-aminobenzoic acid, which is the most accurate method for assessing salt intake and better than reliance on food frequency reports, and (2) the assessment of the misreporting of dietary energy intake with adjustment for energy intake.
Since it is well established that a reduction in salt intake lowers blood pressure, this study demonstrates that salt reduction strategies may be useful also in childhood obesity prevention efforts.

**Dietary fiber intake and its association with indicators of adiposity and serum biomarkers in European adolescents: the HELENA study**

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**Background:** Dietary fiber (DF), classified into water-soluble fiber (WSF) and water-insoluble fiber (WIF), has been considered a leading dietary factor in the prevention and treatment of obesity and its concomitant chronic diseases over the past 4 decades. Recent longitudinal studies have shown that a high consumption of DF beneficially affects body composition and inflammatory markers in children.

**Aims:** To assess total energy-adjusted DF, WSF, and WIF intakes in European adolescents participating in the Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS). Associations between energy-adjusted DF, WSF, and WIF intakes and adiposity-related indicators (BMI z score, body fat percentage [BF%], waist-to-hip ratio [WHR], waist-to-height ratio [W/H]) and serum biomarkers (lipid profile, CRP, glucose, insulin and leptin) were examined.

**Methods:** The study was conducted between 2006 and 2007, and included 1,804 adolescents aged 12.5–17.5 years (47% males) from 8 European cities, completing 2 nonconsecutive computerized 24-h dietary recalls.
**Results:** Mean total DF intake was 20 g/day (range: 8.4–84), and mean energy-adjusted DF intake was 8.4 g/1,000 kcal (3.3–21). Mean WSF and WIF intakes were 6.5 g/day (2.8–34) and 14.5 g/day (5.7–49), respectively. Mean DF intake (20 g/day) of the sample met the European Food Safety Authority recommendation, but was below those of the World Health Organization and of the Institute of Medicine. Males had significantly higher intake of energy, DF, WSF, and WIF ($p < 0.001$ for all), but lower energy-adjusted DF intakes than females ($p < 0.001$). Older adolescents had significantly higher intakes of DF, WSF, and WIF than their younger peers ($p < 0.003$). Overweight and obese females had less mean total and energy-adjusted DF intakes compared to underweight and normal-weight peers. No significant differences were observed in total and energy-adjusted DF intakes among BMI categories in males and in the age groups. On the one hand, BF% was positively associated with energy-adjusted WSF and WIF intakes, and W/H and LDL cholesterol were positively associated with energy-adjusted WSF; on the other hand, serum fasting glucose was inversely associated with energy-adjusted WSF intake, respectively.

**Conclusions:** Average total and energy-adjusted DF intakes were below the WHO recommendations. The results indicate that energy-adjusted WSF and WIF are positively related to BF%, W/H, and LDL cholesterol, but inversely related to serum glucose. Although few associations were found, WSF and WIF may play a beneficial role in DF by preventing insulin resistance and its concomitant diseases, due to low glycemic index diets. However, DF intakes can be positively related to adolescents’ BF%.

**Comments**

Results from the NHANES 2003–2006 data showed that the food sources are predominantly foods that are low in dietary fiber but consumed at high levels. From the age of 2–18 years, the risk for overweight/obesity decreased by 17% in children in the medium tertile of fiber density intake compared to the lowest tertile ($p = 0.043$) and by 21% between the highest compared to the lowest tertile ($p = 0.031$). There was also a protective effect of being in the medium tertile of dietary fiber density ($p < 0.001$) on impaired glucose metabolism. These results indicate a beneficial effect of higher fiber density in children’s diets [22].

WSF delays small bowel absorption, which can subsequently reduce cholesterol absorption due to viscous solutions in the gastrointestinal tract. In addition, fermentation of WSF can produce gases and short-chain fatty acids, causing longer-lasting satiety, lowering the glycemic index of foods with retarded absorption due to viscosity effects, and consequently slowing down acute insulin response. WIF, on the other hand, can increase the bulkiness of stool and fecal mass, thereby shortening the transit time due to nondigestibility. The findings of the current study show that energy dense, low-nutritious foods were consumed in higher amounts than healthy foods such as vegetables and fruits in adolescents. Overweight adolescents had even lower total, energy-adjusted DF intakes than underweight and normal-weight participants (females in particular).

However, the positive associations of BF% and W/H found with WSF and WIF in this study contradicts other studies [23–25], indicating that a high consumption of WSF, including fruit- and vegetable-derived DF and WIF, such as cereal-derived DF, benefits body composition and also improves blood lipids, glucose, and insulin sensitivity due to low glycemic index diets.

In the current study, serum fasting glucose concentration was inversely associated with energy-adjusted WSF. However, LDL cholesterol was found to be positively associated with energy-adjusted WSF intake, while evidence shows that increasing the consumption of DF may protect against high serum total cholesterol, triglycerides, LDL cholesterol, and C-reactive protein concentrations, and improve glucose concentrations in adults. Potential confounding factors that may explain the effect of DF in-
take on the contradictory outcome measurements include Tanner stage, and the small sample size for blood sample collections involved in the current study could result in weak linear relationships between DF intakes and serum biomarkers. The study's limitations include information only being collected for 2 days and the 24-h dietary recall method, which does not allow accurate assessments of infrequently consumed foods. Moreover, accuracy of collected data relies on the individual's memory of the past 24 h and might, therefore, be biased toward underreporting.

Impact of an early-life intervention on the nutrition behaviours of 2-y-old children: a randomized controlled trial

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Background: Obesity is highly prevalent in the great majority of countries all over the world. In New Zealand, despite an extensive well-child health service, 30% of 2- to 4-year-old children are overweight or obese. This suggests that additional intervention is necessary to establish healthy nutrition-related behaviors.

Aims: The aim of this study was to assess the effect of an intervention from 0 to 18 months of age on food and nutrient intake, eating behaviors, and parental feeding practices in 18- to 24-month-old children.

Methods: The Prevention of Overweight in Infancy (POI) study was a randomized controlled trial undertaken in Dunedin, New Zealand, between 2009 and 2012. Women booking into the Queen Mary Maternity Unit, Dunedin Hospital (the only birthing center in the city of Dunedin [population 120,000]), were eligible to participate if they were at least 16 years of age, able to communicate in English or Te Reo Maori (the indigenous language of New Zealand), and planning to live in the Dunedin area for the next 2 years. Exclusion criteria applied after birth were prematurity (born before 36.5 weeks of gestation) and identification of a congenital abnormality or a physical or intellectual disability likely to affect feeding, physical activity, or growth. In total, 802 families with healthy infants were randomly allocated to 1 of 4 groups: Usual Care (UC); Food, Activity, and Breastfeeding (FAB); Sleep; or FAB and Sleep (Combination). All groups received standard “well-child” care. The FAB intervention comprised 7–8 additional contacts for education and support around breastfeeding, food, and activity. The Sleep intervention comprised 2 additional contacts for guidance about sleeping habits. Combination families received both interventions. A validated food-frequency questionnaire assessed food intake at 2 years. A questionnaire assessed eating behaviors and parental feeding practices at 18 and 24 months.

Results: At 2 years, there were no statistically significant differences in food and nutrient intake or eating behaviors in the groups receiving the FAB intervention (FAB, Combination; 325 children) compared with the groups that did not (Sleep, UC; 341 children). With the use of a 5-point scale, small but statistically significant differences in parental feeding practices were observed in the groups receiving the FAB intervention: greater child control over eating (difference: 0.14; 95% CI: 0.02, 0.26) and less pressure to eat (difference: 0.18; 95% CI: 0.04, 0.32) at 18 months, as well as greater encouragement of nutrient-dense foods at 24 months (difference: 0.16; 95% CI: 0.03, 0.30). No statistically significant differences were observed between the groups who received the sleep
intervention (Sleep, Combination; 313 children) and those that did not, except higher meat intake in the former (11 g/day).

**Conclusions:** Additional education and support for parents from birth did not improve nutrition behaviors in this population at 2 years of age.

**Comments**

Rapid infant weight gain between birth and 2 years have a 2- to 3-fold increased risk of obesity [26]. Food preferences and eating patterns are established during infancy and continue into childhood and beyond [27]. Parents play a critical role in the development of food preferences and eating behaviors. It is well documented that obesity interventions beginning in school-age children or adolescents have had limited success. This has been attributed, at least in part, to these interventions beginning after lifestyle factors, such as dietary intake and physical activity, are well established and therefore difficult to modify. Building on top of these accepted concepts, the current intervention was performed; however, it was not successful in terms of improving lifestyle behaviors. New strategies should be developed to optimize parenting practices in order to be more effective in terms of influencing children’s behaviors.

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**An early feeding practices intervention for obesity prevention**

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**Background:** Complementary feeding practices that promote self-regulation of intake and development of healthy food preferences have been positively associated with healthy child eating patterns and growth.

**Aims:** The objective of this study was to report long-term outcomes of the NOURISH randomized controlled trial, which evaluated a universal intervention commencing in infancy to provide anticipatory guidance to first-time mothers on “protective” complementary feeding practices that were hypothesized to reduce childhood obesity risk.

**Methods:** A consecutive sample of first-time mothers (aged ≥18 years) with healthy term infants (>35 weeks’ gestation, ≥2,500 g birth weight) and who could read and speak English was approached on the postnatal wards of 7 maternity hospitals in 2 Australian cities, Brisbane and Adelaide. They were recontacted when their infant was on average 4 months old, at which time those consenting to full enrollment completed baseline assessment and were subsequently independently randomized to intervention or control conditions. Six hundred and ninety-eight mothers (mean age: 30.1 years, SD = 5.3) with healthy term infants (51% female) were enrolled. Mothers were randomly allocated to usual care or to attend 2 education modules. The intervention comprised 2 modules commencing when the children were aged 4–7 and 13–16 months. Each module involved 6 group sessions of 1- to 2-h duration, conducted over 12 weeks. Outcomes were assessed 5 times: baseline (infants 4.3 months), 6 months after module 1 (infants 14 months), 6 months after module 2 (infants 2 years), and at 3.5 and 5 years of age. Maternal feeding practices were self-reported using validated questionnaires. The BMI z score was calculated from measured child height and weight. Linear mixed models evaluated intervention (group) effect across time.
Results: Retention at age 5 years was 61%. Across ages 2–5 years, intervention mothers reported less frequent use of nonresponsive feeding practices on 6 of 9 scales. At 5 years, they also reported more appropriate responses to food refusal on 7 of 12 items (p ≤ 0.05). No statistically significant group effect was noted for anthropometric outcomes (BMI z score: p = 0.06) or the prevalence of overweight/obesity (control 13.3% vs. intervention 11.4%, p = 0.66).

Conclusions: Anticipatory guidance on complementary feeding resulted in first-time mothers reporting increased use of protective feeding practices. These intervention effects were sustained up to 5 years of age and were paralleled by a nonsignificant trend for lower child BMI z scores at all postintervention assessment points.

Comments The practical way of feeding infants (“feeding practices”) determines their eating patterns [28]. The protective effects of breastfeeding, including development of a healthy body composition, are clear. Complementary feeding has received little attention and the available research on this topic is still scarce. Healthy food preferences may be developed by exposing infants to a wide variety of textures and limiting exposure to sweet, salty, and fatty foods. Parental feeding practices are potentially modifiable targets for early obesity prevention interventions. This strategy was implemented in the current intervention study and its long-term effect assessed. Modest results were obtained, but the approach is promising and should also be evaluated in terms of changes in lifestyle behaviors.

Dietary intake, FTO genetic variants, and adiposity: a combined analysis of over 16,000 children and adolescents


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Background: Common single nucleotide polymorphisms (SNPs) located in the first intron of the gene associated with fat mass and obesity (FTO) are the first adiposity/BMI-associated variants identified through genome-wide association studies with the largest influence on BMI in children and adolescents. Previous data support a role for FTO variation in influencing food intake.

Aims: The objective of this study was to examine (1) whether the FTO rs9939609 variant (or a proxy SNP) is associated with dietary intake of total energy and macronutrients (protein, carbohydrate, and fat), and (2) whether dietary intake influences the association between the FTO variant and BMI in children and adolescents.

Methods: The current analysis included cross-sectional data on 16,094 children and adolescents (15,352 whites, 478 African-Americans, and 267 Asians) aged 1–18 years from 14 studies. Dietary intake (total energy, protein, carbohydrate, and fat) was assessed using validated food frequency questionnaires (4 studies), multiple-day dietary/food records (3 studies), multiple-day 24-h recalls (4 studies), dietary records and 24-h recalls (1 study), diet history determined by consulting and information system (1 study), and a brief-type self-administered diet history questionnaire (1 study).

Results: The BMI-increasing allele (minor allele) of the FTO variant was associated with increased total energy intake (effect per allele = 14.3 kcal/day [95% CI: 5.9, 22.7]; \( p = 6.5 \times 10^{-4} \)), but not with protein, carbohydrate, or fat intake. We also found that protein intake modified the association between the FTO variant and BMI (interactive effect per allele = 0.08 SD [0.03, 0.12]; \( p \) for interaction = 7.2 \times 10^{-4}); the association between FTO genotype and BMI was much stronger in individuals with high protein intake (effect per allele = 0.10 SD [0.07, 0.13]; \( p = 8.2 \times 10^{-10} \)) than in those with low intake (effect per allele = 0.04 SD [0.01, 0.07]; \( p = 0.02 \)).

Conclusions: These results suggest that the FTO variant that confers a predisposition to higher BMI is associated with higher total energy intake, and that lower dietary protein intake attenuates the association between FTO genotype and adiposity in children and adolescents.
The mechanism by which FTO polymorphisms influence adiposity is unclear. In some human studies, the adiposity-related allele of FTO has been reported to be associated with increased food, total energy, fat, or protein intake, suggesting that dietary intake mediates this association. However, the previously described associations have not been replicated in other studies.

There is an increasing interest in examining whether lifestyle behaviors influence the associations between FTO variants and adiposity. There is evidence that physical activity reduces the effect of FTO on body composition in adolescents [29]. In relation with dietary intake, the most relevant finding of this study is that low protein intake attenuates the association between FTO genotype and adiposity in children and adolescents. In order to prevent the development of obesity, this result emphasizes children should comply with the current recommendations on protein intake.

Changes in dietary intake during puberty and their determinants: results from the GINIplus birth cohort study

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Background: Understanding changes in dietary intake during puberty could aid the mapping of dietary interventions for primary prevention of nutrition-related chronic diseases.

Aims: The study aim was to examine overall changes in intakes of 17 different food groups representative of total dietary intake as well as macronutrients and antioxidant vitamin, during this time period, to evaluate the stability of individuals’ intakes over time, and to determine whether specific changes in diet can be predicted by parental education, family income, child education, BMI, pubertal onset, and screen time sedentary behavior.

Methods: The present analysis was based on data collected at the 10- and 15-year follow-ups of the ongoing German birth cohort study GINIplus (German Infant Nutritional Intervention Plus Environmental and Genetic Influences on Allergy Development). Healthy full-term newborns (n = 5,991) were recruited from obstetric clinics in 2 different regions of Germany (Munich and Wesel). Infants were allocated to the study intervention arm (randomized to 1 of 3 hydrolyzed formulae or to conventional cow milk) or to the nonintervention arm. Dietary data (n = 1,232) were obtained from food frequency questionnaires at the 10- and 15-year follow-ups of the GINIplus birth cohort study. Intakes of 17 food groups, macronutrients, and antioxidant vitamins were described by (1) paired Wilcoxon rank-sum tests, comparing average intakes at each time point, and (2) Cohen’s κ “tracking” coefficients, measuring stability of intakes (maintenance of relative tertile positions across time). Further, associations of changes (tertile position increase or decrease vs. tracking) with parental education, family income, child education, pubertal onset, BMI, and screen time were assessed by logistic regression and multinomial logistic regression models stratified by baseline intake tertile.
**Results:** Both sexes increased average intakes of water and decreased starchy vegetables, margarine, and dairy products. Females decreased meat and retinol intakes and increased vegetables, grains, oils, and tea. Males decreased fruits and carbohydrates and increased average intakes of meat, caloric drinks, water, protein, fat, polyunsaturated fatty acids (PUFAs), vitamin C, and α-tocopherol. Both sexes presented mainly “fair” tracking levels (κw = 0.21–0.40). Females with high (vs. low) parental education were more likely to increase their nut intake (OR = 3.8; 95% CI: 1.7, 8.8), and less likely to decrease vitamin C intakes (0.2 [0.1, 0.5]), while males were less likely to increase egg consumption (0.2 [0.1, 0.5]) and n-3 PUFAs (0.2 [0.1, 0.5]). Females with a higher (vs. low) family income were more likely to maintain medium whole-grain intakes (0.2 [0.1, 0.7] for decrease vs. tracking, and 0.1 [0.0, 0.5] for increase vs. tracking) and were less likely to decrease vitamin C intakes (0.2 [0.1, 0.6]). Males with high education were less likely to increase sugar-sweetened foods (0.1 [0.1, 0.4]). Finally, BMI in females was negatively associated with decreasing protein intakes (0.7 [0.6, 0.9]). In males, BMI was positively associated with increasing margarine (1.4 [1.1, 1.6]) and vitamin C intakes (1.4 [1.1, 1.6]), and negatively associated with increasing n-3 PUFAs.

**Conclusions:** Average dietary intakes changed significantly from childhood to adolescence. Dietary intake changes were most frequently associated with the socioeconomic environment, where females with a high socioeconomic status tended towards healthier dietary behaviors. Associations with child education and BMI were also observed for some food groups and nutrients, while no effect was seen between intake changes and screen time or pubertal onset. These results support the rationale for dietary interventions targeting children, and suggest that sex-specific subpopulations, e.g., low socioeconomic status, should be considered for added impact.

**Comments**

Understanding food intake patterns during the transition from childhood to adolescence is relevant for the guidance of public health actions for the prevention of nutrition-related chronic diseases. Evaluating which factors may determine dietary changes could help to identify possible subpopulations as targets for dietary interventions. Diet quality has been shown to follow a socioeconomic gradient. Studies examining the impact of socioeconomic status on adolescents’ and children’s food intake have suggested high consumption of high-fat and high-sugar foods, and low consumption of fruits and vegetables, in individuals from disadvantaged groups [30].

The maintenance of food intake consumption over time is referred to as “dietary tracking”. The presence and strength of dietary tracking reflect the level of stability in an individual’s long-term eating patterns. Results from the present study and others previously reported in the literature show tracking levels of dietary patterns from childhood to adolescence, which include fruit and vegetables, total energy, macronutrients, meat, and oils, are weak to moderate. This further emphasizes the need for longitudinal studies in this topic given its relevance in the development of public health nutrition strategies. This will be especially important in order to improve dietary habits in vulnerable groups.
Decreasing the number of small eating occasions (<15% of total energy intake) regardless of the time of day may be important to improve diet quality but not adiposity: a cross-sectional study in British children and adolescents

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Background: Many epidemiological studies conducted in children and adolescents have shown an inverse association between eating frequency (EF) and snack frequency (SF) and adiposity measures.

Aims: The aim of the present study was to examine the relationship of meal frequency (MF) and SF frequency with food and nutrient intakes, diet quality, and adiposity measures in British children and adolescents using different definitions of meals and snacks.

Methods: The present cross-sectional study was based on data from the National Diet and Nutrition Survey (NDNS) for children aged 4–10 years (n = 818) and adolescents aged 11–18 years (n = 818). Based on data from a 7-day weighed dietary record, all eating occasions were divided into meals or snacks on the basis of contribution to energy intake (≥15 or <15%) or time of the day (morning, noon, evening hours, or other).

Results: Positive associations were found between measures of MF and SF and energy intake, except for MF based on energy contribution in children. SF was associated with lower intakes of cereals, fish, meat, protein, PUFA, starch, and dietary fiber; with higher intakes of soft drinks, confectionery, and total sugar; and with a lower diet quality. MF based on time, but not based on energy contribution, was associated with lower intakes of fish, protein, polyunsaturated fatty acid, and starch; higher intakes of confectionery and total sugar; and lower diet quality (only in children). In both children and adolescents, after adjustment for age, sex, social class, and physical activity, all measures of MF and SF showed no association with adiposity measures.

Conclusions: The present study demonstrated that MF and SF was differentially associated with dietary intake when meals and snacks were defined on the basis of the contribution to total energy intake, but not on the basis of time. Therefore, decreasing the number of small eating occasions (<15% of total energy intake) regardless of the time of day may be important to improve diet quality. However, all measures of MF and SF showed no association with adiposity measures in both children and adolescents.

Comments: Well-designed studies on the association between EF and measures of body fatness have shown mixed findings. In a 10-year prospective study of girls, less-frequent eating at baseline (9–10 years of age) predicted a greater gain in BMI and waist circumference. Conversely, another prospective study of girls aged 8–12 years showed that higher EF (≥6 times/day), compared with moderate EF (≥4 to <6 times/day), was associated with higher increase in BMI z score between 8–12 and 11–19 years of age.

The present results in the British children and adolescent population demonstrated that the percent of energy in SF and the timing of snack and meal intake frequency, but not the energy content in MF, were similarly associated with unfavorable dietary intake patterns, suggesting that decreasing the number of small eating occasions (<15% of total energy intake) regardless of the time of day may be important to improve the diet quality. However, all measures of meal and SF showed no association with BMI z score.
Recently, the same group [31] published their results of the association between EF and adiposity in a cross-sectional study in US children aged 6–11 years \( (n = 4,346) \) and adolescents aged 12–19 years \( (n = 6,338) \) participating in the National Health and Nutrition Examination Survey in 2003–2012. They found that higher SF and EF, but not MF, were associated with higher risks of overweight and abdominal obesity in children, whereas associations varied in adolescents, depending on the definition of meals and snacks.

Obviously, if the content of the snacks is mainly based on sweets, it may have an impact on the body weight. We have to recognize that MF and SF based on time may be problematic because eating patterns vary according to lifestyle as well as the cultural environment. Therefore, since both studies were cross-sectional, prospective studies are needed to establish the observed associations.

### Stabilization of overweight prevalence and improvement of dietary habits in French children between 2004 and 2008

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**Background:** Since the 2000s, a study carried out on representative samples of French children has shown that overweight prevalence on a national scale seems to have stabilized at about 16%. A multidisciplinary public health program called Nutrition, Prevention and Health for children and teenagers was launched in 2004 in Aquitaine (Southwest France) to improve the diet and physical activity of children and adolescents and to stabilize the prevalence of childhood obesity. Before launching the program, a study was conducted in 2004–2005 among 7.5- to 10.5-year-old children in order to guide the intervention and to provide baseline data on dietary habits, lifestyle, and overweight and obesity prevalence. Four years later, the study was repeated in order to evaluate the impact of the program on children’s lifestyle.

**Aims:** To describe changes in overweight and obesity prevalence and dietary behavior among 7.5- to 10.5-year-old children in Aquitaine from 2004 to 2008, and to assess the impact of the program on this evolution.

**Methods:** Two cross-sectional surveys were conducted in 2004 (“before program” sample, \( n = 1,836 \)) and 2008 (“after program” sample, \( n = 3,483 \)) on representative samples of primary schools randomly selected in Aquitaine. Data were collected on gender, age, weight, and height. Stratification variables were the district, the size of the school, the area of residence (urban or rural), and the zone category (low socioeconomic or not low socioeconomic). Data were collected by means of a questionnaire completed by the school nurse in the presence of the child. Multivariate analyses were used to assess the effect of the regional program intervention on the evolution of overweight and obesity prevalence and eating habits independently.

**Results:** The response rate of schools was 89.0% in 2004/2005 and 92.4% in 2008/2009. Four years after the prevention program, eating habits had changed globally. After adjustment of the model for age, residential area and socioeconomic status of the area of residence, the prevalence of overweight including obesity \((OR = 1.05; 95\% CI: 0.89, 1.23; p = 0.56)\) and of obesity \((OR = 0.99; 95\% CI: 0.71, 1.39; p = 0.96)\) was found to have stabilized and eating habits had improved with increased intake of light afternoon meals \((OR = 1.38; 95\% CI: 1.13, 1.69; p = 0.002)\), and decreased snacking
in the morning (OR = 0.50; 95% CI: 0.45, 0.57; \( p < 0.001 \)) and nibbling (OR = 0.81; 95% CI: 0.70, 0.93; \( p < 0.001 \)).

**Conclusions:** The findings of this study reinforce the relevance of implementing public health programs such as the Aquitaine program, and they underline the importance of implementing and pursuing interventions in primary schools in order to achieve consistent behavioral changes, regarding their eating habits in order to stabilize or decrease the prevalence of overweight.

**Comments**
The stabilization in overweight and obesity reported in the present study is consistent with other recent studies from other European countries and the USA, China, and Australia [32–34]. Actions undertaken on the basis of the nutrition program in Aquitaine could be responsible for the stabilization of overweight and the improvement in dietary behavior among 7.5- to 10.5-year-old children in Aquitaine. Besides promoting healthy dietary habits, other actions undertaken in Aquitaine, such as early detection of overweight and encouraging a physically active lifestyle, could also have played a part.

One limitation of the present study is the fact that lifestyle habits were not assessed, especially physical activity and sleep, which are recognized as factors for obesity in children. However, the multivariate analysis was adjusted for characteristics known to have an influence on overweight prevalence: age (increase in overweight prevalence with age), area of residence (higher prevalence of overweight among rural children), and especially socioeconomic status of the living zone.

These findings reinforce the relevance of implementing public health programs, and they underline the importance of implementing and pursuing interventions in primary schools in order to achieve consistent behavioral changes.

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**Identification of a dietary pattern associated with greater cardiometabolic risk in adolescence**

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*Nutr Metab Cardiovasc Dis 2015;25:643–650*

**Background:** A number of studies have examined prospective relationships between single food groups and cardiometabolic risk factors in children and adolescents. However, foods and nutrients are not consumed in isolation. Few studies have examined dietary patterns in relation to cardiometabolic risk factors among adolescents. Energy-dense, high-fat, and low-fiber diets may contribute to obesity in young people; however, their relationships with other cardiometabolic risk factors are unclear.

**Aims:** In this study, the associations between an “energy-dense, high-fat, and low-fiber” dietary pattern (DP) and cardiometabolic risk factors, and the tracking of this DP in adolescence were examined.
**Methods:** Data was sourced from participants in the Western Australian Pregnancy (Raine) Cohort Study. The original cohort comprised 2,900 pregnant women who were recruited into a trial at King Edward Memorial Hospital (Perth, Western Australia) to examine ultrasound imaging from 1989 to 1991. A total of 2,868 babies born to 2,804 mothers who remained with the study formed the Raine cohort and were followed up at regular intervals after birth. At 14 and 17 years, dietary intake and anthropometric and biochemical data were measured and z scores for an energy-dense, high-fat, and low-fiber DP were estimated using reduced rank regression. Associations between DP z scores and cardiometabolic risk factors were examined using regression models. Tracking of DP z scores was assessed using the Pearson correlation coefficient.

**Results:** A 1-SD unit increase in DP z score between 14 and 17 years was associated with a 20% greater odds of high metabolic risk (95% CI: 1.01, 1.41) and a 0.04-mmol/L higher fasting glucose in boys (95% CI: 0.01, 0.08) and 28% greater odds of a high waist circumference (95% CI: 1.00, 1.63) in girls. An increase of 3 and 4% was observed for insulin and HOMA (95% CI: 1, 7), respectively, in boys and girls for every 1-SD increase in DP z score and independently of BMI. The DP showed moderate tracking between 14 and 17 years of age (r = 0.51 for boys, r = 0.45 for girls).

**Conclusions:** An energy-dense, high-fat, and low-fiber DP is positively associated with cardiometabolic risk factors and tends to persist throughout adolescence.

**Comments** Cardiometabolic risk factors, such as obesity, high systolic blood pressure, dyslipidemia, impaired glucose tolerance, and vascular abnormalities, develop early in life and track during childhood and adolescence into adulthood. Several studies have examined associations between single food groups and cardiometabolic risk factors in children and adolescents [35]. Very often, food consumption studies focus on individual foods or nutrients. However, due to the fact that diet is multidimensional and complex, recent research has focused on dietary patterns. Dietary patterns consider a variety of food and nutrient intakes and account for the combined effects of foods and nutrients eaten together. Results observed in this study are promising in order to try to avoid the development of cardiometabolic manifestations; however, these results should be confirmed in randomized controlled trials in adolescents.

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**Dietary glycaemic index and glycaemic load among Australian children and adolescents: results from the 2011–2012 Australian Health Survey**

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**Aims:** Some evidence suggests that diets with low glycemic index (GI) and/or glycemic load (GL) are associated with better health and decreased risk of type 2 diabetes mellitus and cardiovascular disease. The aim of this analysis was to assess current dietary GI and GL and identify the main food sources contributing to the dietary GL of Australian youths in different age groups.

**Methods:** The cohort (n = 2,651) was selected using a stratified multistage area sample of private dwellings, with a response rate of 77%. Trained interviewers conducted face-to-face interviews with an adult member of the index household. Information on the dietary consumptions of food, bever-
ages, and the use of supplements using a computer-assisted, multiple-pass 24-h recall method was collected. Dietary intake data were translated into nutrient intake using the AUSNUT 2011–2013 database. A Bonferroni post hoc test for one-way ANOVA was applied for comparisons between age groups. Linear regression was used to analyze trends across age groups.

**Results:** The mean BMI of the cohort was 19.0 (SD 3.8), similar in boys and girls (19.0 [SD 3.8] vs. 19.0 [SD 3.7]; \( p = 0.936 \)), with 18.1 and 5.1% considered overweight and obese, respectively. The mean dietary GI and GL were 55.5 (SD 5.3) and 137.4 (SD 50.8), respectively. Linear trends of dietary GI and GL, energy intake, and energy from fat increased with age (all trends \( p < 0.001 \)). Bread and bread rolls (14.7%), cereal-based dishes (10.5%), and ready-to-eat breakfast cereals (6.8%) were the top 3 contributors to dietary GL, accounting for nearly 40% of the dietary GL on a per capita basis. Cereal-based dishes, potatoes, sweetened beverages (all trends \( p < 0.001 \)), and pastas (\( p = 0.001 \)) contributed increasingly with increased age. Participants aged 14–18 years also had higher intake of sweetened beverages and lower intake of pome fruit than those aged 9–13 years. Australian children and adolescents in 2011–2012 had an increase in GI and GL from 54 to 56 and from 133 to 137, respectively, when compared with data from the 2007 ANCNPAS.

**Conclusions:** Australian children and adolescents appear to consume foods with a lower GI than UK children. High-GI “core” foods such as white breads and breakfast cereals accounted for the majority of the dietary GI and GL, although sugar-sweetened beverages also contributed significantly. Efforts to lower the dietary GI and GL of Australian children and adolescents by exchanging high-GI foods for low-GI alternatives within core and noncore foods may improve diet quality.

**Comments**

This fairly recent Australian national survey [36] provides data for designing specific dietary interventions for the pediatric population. However, as so-called core foods are responsible for most of the GI and GL, gigantic efforts are needed to modify eating habits deeply rooted in the common culture. Replacing white breads and breakfast cereals with whole-grain products, fruits, and vegetables may again require a long-term intervention involving all layers of the society with a coordinated action of medical, educational, social, sports, media, and legislative partners.

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**Healthy eating index and metabolically healthy obesity in U.S. adolescents and adults**

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*Prev Med 2015;77:23–27*

**Background:** Obese individuals are more likely to have multiple abnormal cardiovascular risk factors present, but not all obese individuals exhibit this cardiometabolic phenotype. However, it is not known whether diet quality differs between metabolically healthy obesity (MHO) and metabolically abnormal obesity (MAO) in adolescents and adults.

**Aims:** The purpose of the current analysis was to determine whether diet quality, measured by total and component Healthy Eating Index 2005 (HEI-2005), differs between MHO and MAO in a nationally representative US sample of adolescents and adults.
Methods: Data from 2 National Health and Nutrition Examination Surveys (NHANES 2007–2008; 2009–2010) were used for adolescents 12–18 years of age and adults 19–85 years of age. Obese adolescents (≥95th BMI percentile) and adults (≥30) were identified. MHO was defined as <2 abnormal cardiometabolic risk factors (elevated blood pressure, triglycerides, glucose, low HDL cholesterol, or on medications). Dietary intake was measured via 1 in-person 24-h recall collected using the USDA’s Automated Multiple Pass Method. HEI-2005 scores were calculated from 24-h recall data. General linear regression models determined whether HEI-2005 scores differed between MHO and MAO after controlling for age, race, gender, NHANES wave, BMI, physical activity, and health status by age group (12–18, 19–44, and 45–85 years).

Results: Compared with MAO, MHO adolescents ($n = 133$) had higher total HEI-2005 scores, higher milk scores, and higher scores from calories from solid fats, alcohol beverages, and added sugars. MHO women 19–44 years ($n = 240$) had higher total HEI-2005, higher whole fruit, higher whole grain, and higher meat and bean scores compared with MAO. No significant differences were observed between MHO and MAO for HEI-2005 total scores in men 19–44 years, or adults 45–85 years.

Conclusions: MAO and MHO cardiometabolic profiles are characterized by differences in HEI-2005 total and component scores, though these vary by age group and appear limited to a few specific dietary components. Results suggest potential intervention targets which may improve cardiometabolic risk in the presence of obesity. These results also show the importance of prevention/intervention beginning earlier in the life course as dietary intake only seemed to show differences in adolescents and women 19–44 years.

Comments: Available research comparing dietary intake of MHO and MAO suggests no differences; however, this research has been restricted to the evaluation of macronutrient and micronutrient composition or to single foods. Diet quality indices are useful tools to assess the overall quality of the diet. Examining dietary intake quality allows a more comprehensive examination of a person’s dietary intake that reflects a balance, variety, and equilibrium in the combination of foods and beverages. Despite the use of a single 24-h dietary recall, results obtained in this study suggest MHO adolescents had higher milk scores than MAO. It seems that consumption of dairy products is associated with a low cardiometabolic risk in adolescents [37]. These findings are promising in terms of future prevention strategies and should be tested in randomized control trials in this specific population group.

Low serum vitamin D levels are associated with increased arterial stiffness in youth with type 2 diabetes

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Diabetes Care 2015;38:1551–1557

Background: Adult studies have shown that low vitamin D (25(OH)D) concentrations is an independent risk factor for arterial stiffness. Similar studies have not been conducted in youth with type 2 diabetes mellitus (T2DM).

Aims: The purpose of this study was to examine the association between serum 25(OH)D levels and arterial stiffness in obese youth with and without T2DM. It was hypothesized that 25(OH)D would
be inversely correlated with arterial stiffness indices, including pulse wave velocity (PWV), augmentation index (AIx), and brachial distensibility (BrachD).

**Methods:** The population for this analysis was drawn from individuals who participated in the Cardiovascular Disease in Adolescents with Type 2 Diabetes (T2CVD) study at Cincinnati Children’s Hospital Medical Center from 2004 to 2010. The T2CVD study consisted of 3 groups: 221 individuals with T2DM, 250 obese individuals without T2DM, and 261 lean individuals (nonobese individuals without T2DM). All participants were between 10 and 24 years old at recruitment. 25(OH)D, PWV, AIx, and BrachD were measured in 190 youth with T2DM, 190 obese control subjects without T2DM, and 190 lean control subjects without T2DM. Multivariate analyses were conducted to elicit the independent association between 25(OH)D and arterial stiffness indices by group.

**Results:** The mean age was 17.9 ± 3.4 years, 55% were African-American, and 34% were male. The mean 25(OH)D levels were 21.27, 14.29, and 14.13 ng/mL in lean individuals, obese individuals, and obese individuals with T2DM, respectively (p < 0.01). PWV, AIx, and BrachD worsened from lean to obese to T2DM (p < 0.01). General linear models found that the 25(OH)D level was independently associated with PWV in lean individuals and with AIx in the group with T2DM such that a 3 ng/mL increase in 25(OH)D was associated with an AIx decrease of 1% (baseline AIx = 5.7 ± 12.0%).

**Conclusions:** 25(OH)D is inversely associated with some measures of arterial stiffness in lean adolescents and obese adolescents with T2DM, but not in obese normoglycemic adolescents. Future studies are needed to determine if supplemental 25(OH)D is important for cardiovascular health.

**Comments**
Adolescents with T2DM and obese youth have shown greater arterial stiffness than their lean counterparts, suggesting an increased risk for a premature onset of cardiovascular diseases. Vitamin D deficiency has been associated with different components of the metabolic syndrome. Studies in healthy, obese, and T2DM adults have found that low serum 25(OH)D levels are associated with increased arterial stiffness. The current study confirms these findings in adolescents with T2DM, emphasizing the need for early detection and adequate management of these patients. The public health relevance of these results derive from the very high prevalence of vitamin D deficiency: 13.0% of the 55,844 European individuals included in a recent study had serum 25(OH)D concentrations <30 nmol/L on average in the year, and the prevalence was 40.4% according to an alternate suggested definition of vitamin D deficiency (<50 nmol/L) [38].

**Vitamin D status is associated with cardiometabolic markers in 8–11-year-old children, independently of body fat and physical activity**

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*Br J Nutr* 2015;114:1647–1655

**Background:** Vitamin D status in childhood has been inversely associated with cardiometabolic risk markers such as glucose, insulin, and blood pressure. Relations between vitamin D status and cardiometabolic risk markers may be mediated or confounded by fat mass, which in turn may be associated with vitamin D status through sequestration of vitamin D in adipose tissue or through...
poorer diets and less sun exposure in overweight subjects leading to lower vitamin D status. Therefore, adjustment for the potential confounding effects of fat mass is important when evaluating associations between vitamin D status and cardiometabolic health.

**Aims:** To investigate the associations between vitamin D status and cardiometabolic risk markers, and to investigate whether these associations were independent of objectively measured fat mass index (FMI) and physical activity.

**Methods:** This cross-sectional study included a large cohort of Danish 8- to 11-year-old school children, and used baseline data from 782 children participating in the Optimal Well-Being, Development and Health for Danish Children through the Healthy New Nordic Diet (OPUS) School Meal Study, with assessment of vitamin D status (serum 25(OH)D) and measurements of blood pressure, fasting plasma glucose, homoeostasis model of assessment-insulin resistance, plasma lipids, inflammatory markers, anthropometry and fat mass by dual-energy X-ray absorptiometry, and physical activity by 7-day accelerometry.

**Results:** Serum 25(OH)D concentrations ranged from 15 to 132 nmol/L and concentrations ≤50 nmol/L were observed in 28.4% of the children, whereas 2.4% had concentrations <25 nmol/L. About half of the children had taken vitamin D-containing supplements during the dietary registration week. Boys were older; spent more time on moderate-to-vigorous physical activity; had higher intakes of energy, protein, vitamin D, and Ca; and higher serum 25(OH)D than girls. In addition, girls had higher FMI and higher values of most cardiometabolic markers compared with boys. Each 10-nmol/L 25(OH)D increase was associated with lower diastolic blood pressure \((p = 0.02)\), total cholesterol, LDL cholesterol, and triglyceride \((p \leq 0.001\) for all lipids), and lower metabolic syndrome score \((p = 0.01)\). Adjustment for FMI did not change the associations. The association with blood pressure became borderline significant after adjustment for physical activity \((p = 0.06)\).

**Conclusions:** Vitamin D status was negatively associated with a number of cardiometabolic markers in Danish school children with low prevalence of vitamin D deficiency; apart from blood pressure, the associations were independent of body fat and physical activity.

**Comments**

Vitamin D status is different in various populations. The global epidemic of vitamin D deficiency also has a potential impact on several chronic diseases in both children and adults. A growing body of evidence supports this study’s findings of an inverse association of vitamin D levels with the components of metabolic syndrome and other cardiovascular markers also in other young populations in the USA [39], Iran [40], and Saudi Arabia [41].

This inverse association is considered to be attributable to several underlying mechanisms. It is assumed that vitamin D deficiency may activate the renin-angiotensin-aldosterone system; in turn, its upregulation would increase blood pressure levels. It is also suggested that chronic vitamin D deficiency may cause secondary hyperparathyroidism, and an increased PTH level may have a role in increasing blood pressure. Other suggested mechanisms for vitamin D impact on blood pressure include regulation of vascular tone by 1,25(OH)D by facilitating Ca influx to the muscle cells and direct effects on vascular endothelium and smooth muscle cells through regulation of transcription of endothelial nitric oxide synthase, which has been demonstrated in vitro. It has also been demonstrated that the active metabolite of vitamin D, 1,25(OH)\(_2\)D, can upregulate lipoprotein lipase in vitro, thereby potentially playing a beneficial role in lipoprotein metabolism.

Vitamin D deficiency is assumed to cause β-cell dysfunction and to increase the risk of diabetes. It may play an important role in insulin resistance and glucose metabolism. This potential role of vitamin D may be related to inherited gene polymorphisms, involvement of immunoregulatory function, stimulating inflammation, and other molecular functions that result in increased insulin resistance.
In the current study, vitamin D status was negatively associated with a number of cardiometabolic markers in Danish school children; apart from blood pressure, the associations were independent of body fat and physical activity, which may be explained by the above mentioned mechanisms.

Finally, the optimal level of serum vitamin D is under debate, and there is no definite cutoff for its normal level in different populations. It is essential that normal values be determined according to each population’s characteristics, risk factors, and environmental conditions.

Suggestions to compensate for the very high prevalence of hypovitaminosis D include controlling environmental factors, increasing dietary intake, fortifying food, and giving supplements.

**Associations between the use of social networking sites and unhealthy eating behaviors and excess body weight in adolescents**

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**Background:** Adolescence is a time when healthy behaviors are being learnt and adopted. Unhealthy eating behaviors such as breakfast skipping and consumption of sugar-sweetened beverages (SSB) have been associated with obesity. Sedentary activities such as watching television or playing video games are well known to impact energy expenditure, but also lead to poor eating habits and increased energy intake.

**Aims:** To investigate the association between time spent using social networking sites (SNS) and unhealthy eating behaviors (breakfast skipping, consumption of SSB, and energy drinks) and overweight and obesity among adolescents.

**Methods:** Data for this study were derived from the 2013 cycle of the Ontario Student Drug Use and Health Survey (OSDUHS), a cross-sectional school-based, biennial province-wide survey of 7th to 12th grade students (n = 9,858). The survey had a student participation or response rate of 63%. Breakfast consumption was assessed by asking students on how many of the last 5 school days did they have breakfast at home, on the way to school, or at school before classes. Students were asked about the frequency of SSB and energy drink consumption, and about the number of daily hours spent on social media websites. BMI was calculated based on self-reported height and weight.

**Results:** The majority (81.5%) of students reported daily use of SNS and 10.7% reported using them on an irregular basis. After adjustment for age, sex, ethnicity, subjective SES, parental education, alcohol, tobacco and cannabis use, and BMI, multivariate logistic regression analyses revealed that adolescents who use SNS were at greater odds of skipping breakfast and consuming SSB and energy drinks, and that these associations generally increased in a dose-response manner with time spent using SNS. However, there was no evidence of a significant association between use of SNS and BMI before or after adjusting for all the covariates and unhealthy eating behaviors.
Conclusion: The present study provides evidence that the use of SNS is associated with greater odds of unhealthy eating behaviors among adolescents. However, it did not provide evidence of an association between the use of SNS and excess weight.

Comments

SNS such as Facebook, Twitter, and MySpace may be good places to reach and engage youth with healthy eating and active living messages. Research has shown that sedentary activity, particularly screen time, is associated with obesity and unhealthy eating behaviors such as consumption of SSB and energy drinks among adolescents and adults. SNS are now being used as a tool for delivering health care programs and services, education, research, intervention, and even treatment. SNS have enormous mass appeal and have become omnipresent in the daily life of many adolescents. As the amount of time adolescents spend online has increased, problematic use of SNS potentially leads to negative health consequences.

Food advertising plays an important role in food choices and preferences among youth. With the increasing popularity of SNS, junk food industries have turned to these Web-based platforms and target young consumers in their marketing campaigns. A possible explanation of the link between the use of SNS and skipping breakfast is related to the displacement of other activities. It is possible that an increase in the amount of time spent on SNS directly decreases the amount of discretionary time available for eating breakfast. SNS may also be a type of sedentary behavior that is not associated with increased body weight among adolescents.

Recent results provide evidence that the use of SNS was also associated with increased alcohol consumption among adolescents [42]. Another study that examined the relation between problematic Internet use and overweight/obesity among adolescents in 7 European countries found an association of problematic Internet use with overweight/obesity [43].

This study’s limitations include the cross-sectional design and the data that were based entirely on self-reports and may be subject to recall bias. Moreover, the use of single questions to measure the outcome variables (i.e., breakfast skipping, consumption of SSB and energy drinks) may raise potential issues related to reliability and confounding by unmeasured variables (e.g., depressive symptoms, body image). Also the external generalizability of findings may be limited to the sample studied.

However, the results of the above mentioned studies together with the study of Sampasa-Kanyinga et al. suggest the importance of planning future studies using a longitudinal design, and the importance of formulating preventive public health policies that target physical health, education, and sedentary online lifestyle early in adolescence.

Given the popularity of SNS among youth, promoting healthy eating and active living via these Web-based platforms may provide a potentially potent force to ongoing efforts.
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Health professionals involved in child care are convinced nowadays that nutrition in early life (the general concept of the so-called 1,000 days) is of paramount importance not only on growth patterns and development in infancy, but also on many health outcomes later in life. In the present chapter we focus on 19 articles related to nutrition in preterm and term infants.

Premature babies are at high risk of inadequate nutritional intake, and emphasis is placed on amino acid and lipid regimen in parenteral nutrition, the relationship between energy intake and risk for retinopathy, vitamin D intake and metabolism, donor breast milk and severe infections and mortality, lipid absorption and use of recombinant bile salt-stimulated lipase, DHA supplementation, and visual function and eating difficulties in early childhood.

Term infants, i.e., approximately 90% of the population of newborns in industrialized countries, were not left out. During the last year, very interesting data were published on highly controversial topics, such as the use of hypoallergenic formulae in non-breastfed infants at risk for allergy (25–30% of all newborns), the long-term safety of soy-based infant formulae, protein intake and risk for overweight and obesity, and gluten introduction and the risk of celiac disease. There have also been comments on the use of fermented milks without live bacteria and the influence of antibiotic exposure on weight gain. In contrast to the large literature on breast and formula feeding, relatively little attention has been paid to the complementary feeding period, the nature of the foods given, or whether this period of significant dietary change influences later health and development. We selected 2 papers on the nutritional consequences of an increasingly popular feeding technique amongst parents, i.e., baby-led weaning,
and on follow-up data up to the age of 6 years on vegetable acceptance during early introduction of complementary foods.

As usual, more research is needed. Setting up clinical studies in the field of pediatric nutrition is difficult but indispensable. We cannot use any more observational studies and clinical experience to build up evidence-based guidelines. More randomized clinical studies and prospective population-based cohort studies are obviously needed. We hope that our comments will give the readers more “appetite” to look for more manuscripts in the field of infant nutrition and more information to prescribe the best nutritional support available for infants during the first months of life.

### Key articles reviewed for this chapter

#### Term Infants

**Allergic manifestation 15 years after early intervention with hydrolyzed formulas – the GINI Study**

Allergy 2016;71:210–219

**Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis**

BMJ 2016;352:i974

**Soy-based infant formula feeding and ultrasound-detected uterine fibroids among young African-American women with no prior clinical diagnosis of fibroids**

Upson K, Harmon QE, Baird DD
Environ Health Perspect 2016;124:769–775

**Effect of dietary protein on plasma insulin-like growth factor-1, growth, and body composition in healthy term infants: a randomised, double-blind, controlled trial (Early Protein and Obesity in Childhood (EPOCH) study)**

Putet G, Labaune JM, Mace K, Steenhout P, Grathwohl D, Raverot V, Morel Y, Picaud JC
Br J Nutr 2016;115:271–284

**Antibiotic exposure during the first 6 months of life and weight gain during childhood**

JAMA 2016;315:358–365
Fermented infant formulas without live bacteria: a systematic review
Szajewska H, Skórka A, Pieścik-Lech M

Infant feeding and risk of developing celiac disease: a systematic review
Silano M, Agostoni C, Sanz Y, Guandalini S
BMJ Open 2016;6:e009163

Gluten introduction and the risk of coeliac disease: a position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

How different are baby-led weaning and conventional complementary feeding? A cross-sectional study of infants aged 6–8 months
BMJ Open 2016;6:e010665

The lasting influences of early food-related variety experience: a longitudinal study of vegetable acceptance from 5 months to 6 years in two populations
Maier-Nòth A, Schaal B, Leathwood P, Issanchou S
PLoS One 2016;11:e151356

Preterm Infants

Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition
Am J Clin Nutr 2016;103:1443–1452

Low energy intake during the first 4 weeks of life increases the risk for severe retinopathy of prematurity in extremely preterm infants
Stoltz Sjöström E, Lundgren P, Öhlund I, Holmström G, Hellström A, Domellöf M
Arch Dis Child Fetal Neonatal Ed 2016;101:F108–F113

A comparison of 3 vitamin D dosing regimens in extremely preterm infants: a randomized controlled trial
Fort P, Salas AA, Nicola T, Craig CM, Carlo WA, Ambalavanan N

Vitamin D metabolism in the premature newborn: a randomized trial
Hanson C, Jones G, Lyden E, Kaufmann M, Armas L, Anderson-Berry A
Clin Nutr 2016;35:835–841
**Effect of pasteurisation on the concentration of vitamin D compound in donor breast milk**
Gomes F, Shaw N, Whitfield K, Koorts P, McConachy H, Hewavitharana A

**Effect of donor milk on severe infections and mortality in very low-birth-weight infants: the Early Nutrition Study randomized clinical trial**
*JAMA Pediatr* 2016;170:654–661

**Recombinant bile salt-stimulated lipase in preterm infant feeding: a randomized phase 3 study**
*PLoS One* 2016;11:e0156071

**Long-term effect of high-dose supplementation with DHA on visual function at school age in children born at <33 wk gestational age: results from a follow-up of a randomized controlled trial**
Molloy C, Stokes S, Makrides M, Collins CT, Anderson PJ, Doyle LW

**Eating difficulties in children born late and moderately preterm at 2 y of age: a prospective population-based cohort study**
Johnson S, Matthews R, Draper ES, Field DJ, Manktelow BN, Marlow N, Smith LK, Boyle EM
Allergic manifestation 15 years after early intervention with hydrolyzed formulas – the GINI Study

von Berg A¹, Filipiak-Pittroff B¹, Schulz H²,³, Hoffmann U²,⁴, Link E⁵, Sußmann M², Schnappinger M², Brüseke I², Standl M², Krämer U⁵, Hoffmann B⁵,⁶, Heinrich J²,³, Bauer CP⁴,⁷, Koletzko S⁸, Berdel D¹; GINIplus Study Group
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Allergy 2016; 71:210–219

Background: There are few data on the long-term impact of hydrolyzed formulas on allergies. The objective of the study was to assess the association between early intervention with hydrolyzed formulas in high-risk children and allergic outcomes in adolescence.

Methods: GINI trial participants (n = 2,252) received 1 of 4 formulas in the first 4 months of life as a breast milk substitute if necessary: partial or extensive whey hydrolysate (pHF-W, eHF-W), extensive casein hydrolysate (eHF-C), or standard cow milk formula (CMF). Associations between these formulas and the cumulative incidence and prevalence of parent-reported physician diagnosed asthma, allergic rhinitis (AR), and eczema, as well as spirometric indices and sensitization, were examined using generalized linear models.

Results: Between 11 and 15 years, the prevalence of asthma was reduced in the eHF-C group compared to CMF (odds ratio [OR] = 0.49, 95% CI: 0.26–0.89), which is consistent with the spirometric results. The cumulative incidence of AR was lower in eHF-C (risk ratio [RR] = 0.77, 95% CI: 0.59–0.99), and the AR prevalence was lower in pHF-W (OR = 0.67, 95% CI: 0.47–0.95) and eHF-C (OR = 0.59, 95% CI: 0.41–0.84). The cumulative incidence of eczema was reduced in pHF-W (RR = 0.75, 95% CI: 0.59–0.96) and eHF-C (RR = 0.60, 95% CI: 0.46–0.77), as was the eczema prevalence between 11 and 15 years in eHF-C (OR = 0.42, 95% CI: 0.23–0.79). No significant effects were found in the eHF-W group on any manifestation, nor was there an effect on sensitization with any formula.

Conclusion: In high-risk children, early intervention using different hydrolyzed formulas has variable preventive effects on asthma, allergic rhinitis, and eczema up to adolescence.

Comments: This study reports on the 15-year-follow-up of the well-known GINI (German Infant Nutritional Intervention; government sponsored) trial, which was initiated in 1995 to investigate the preventive effects of 3 different hydrolysates compared to regular cow milk infant formula on allergy development in children at high risk of allergy [1]. The main strengths of this study are the original large sample size of 2,252 children, randomization and allocation concealment, and fair participation at 15 years of age (ITT: 61.1%; PP: 66.0%). The limitations are the unblinding of formulas when the youngest...
child turned 3 years of age, and the fact that the assessment of the formula effect is based on a parental report of a physician’s diagnosis, and not on a clinical examination in the study center. The results of the 15-year follow-up of the GINI trial confirm that the previously reported preventive effects of the eHF-C and pHF-W formulas on eczema are sustained until adolescence. During the last years of follow-up, fewer emergences of AR and asthma were related to the use of certain hydrolysates, mainly eHF-C. The effect in the eHF-C formula group on asthma is consistent with the spirometric results. The findings with respect to the respiratory allergies should be interpreted with caution until confirmed in future studies. None of the formulas had an influence on IgE sensitization.

Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis

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Background: Dietary exposure in infancy may influence the risk of allergic and autoimmune disease, with a specific concern that early exposure to cow milk protein in the form of infant formula could trigger the onset of allergic or autoimmune disease. The aim of the study was to determine whether feeding infants with hydrolyzed formula reduces their risk of allergic or autoimmune disease.

Methods: Systematic review and meta-analysis. Two authors selected studies by consensus, independently extracted data, and assessed the quality of included studies using the Cochrane risk of bias tool. Data sources were MEDLINE, EMBASE, Web of Science, CENTRAL, and LILACS. Eligibility criteria for selecting studies were prospective intervention trials of hydrolyzed cow milk formula compared with another hydrolyzed formula, human breast milk, or a standard cow milk formula, which reported on allergic or autoimmune disease or allergic sensitization.

Results: Thirty-seven eligible intervention trials of hydrolyzed formula were identified, including over 19,000 participants. There was evidence of conflict of interest and high or unclear risk of bias in most studies of allergic outcomes, and there was evidence of publication bias for studies of eczema and wheeze. Overall there was no consistent evidence that partially or extensively hydrolyzed formulas reduce the risk of allergic or autoimmune outcomes in infants at a high preexisting risk of these outcomes. Odds ratios for eczema at age 0–4, compared with standard cow milk formula, were 0.84 (95% CI: 0.67–1.07; I² = 30%) for partially hydrolyzed formula, 0.55 (0.28–1.09; I² = 74%) for extensively hydrolyzed casein based formula, and 1.12 (0.88–1.42; I² = 0%) for extensively hydrolyzed whey-based formula. There was no evidence supporting the use of a partially hydrolyzed formula to reduce the risk of eczema nor the conclusion of the Cochrane review that hydrolyzed formula could prevent allergy to cow milk.

Conclusion: These findings do not support current guidelines that recommend the use of hydrolyzed formula to prevent allergic disease in high-risk infants.
Comments

Hydrolyzed formulas contain cow milk proteins (CMPs) that are subjected to chemical and enzymatic hydrolysis to reduce the molecular weight, the peptide size, and, consequently, the allergenicity of the proteins. Efficacy and safety should be established especially for CMP-hydrolyzed formulas because factors such as the protein source, hydrolysis method, and degree of hydrolysis that depend on the manufacturer contribute to differences among hydrolysates. Given the heterogeneity of their composition, a general recommendation on the use of hydrolyzed formula in allergy prevention seems to be as inappropriate and incoherent as a general recommendation on the use of probiotics for allergy prevention or a general recommendation for treating pneumonia with antibiotics, regardless of the type of probiotic or antibiotic.

In its opinion on the essential composition of infant and follow-on formulae, the European Food Safety Authority (EFSA) [2] stated that clinical studies are necessary to demonstrate if and to what extent a particular formula reduces the risk of developing short- and long-term clinical manifestations of allergy in at-risk infants who are not breastfed.

Recommendations on the use of hydrolyzed formulae in allergy prevention should not be based on pooling data from different formulae with different protein sources, hydrolysis method, and degree of hydrolysis. In nonbreastfed infants at risk for allergy, hydrolyzed formulae with documented safety and efficacy should be the preferred choice [3].

Soy-based infant formula feeding and ultrasound-detected uterine fibroids among young African-American women with no prior clinical diagnosis of fibroids

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Environ Health Perspect 2016;124:769–775

Background: Early-life soy phytoestrogen exposure (genistein) has been shown in rats to increase uterine fibroid incidence in adulthood through an epigenetic pathway. Two large epidemiologic cohorts have provided some support for increased fibroid risk with infant soy formula feeding in women. However, both cohorts relied on self-report of clinically diagnosed fibroids. The aim of this study was to evaluate the relationship between infant soy formula feeding and ultrasound detected fibroids.

Methods: The Study of Environment, Lifestyle and Fibroids (SELF) is an ongoing cohort study of 1,696 African-American women 23–34 years of age with baseline ultrasound screening to detect and measure fibroids ≥0.5 cm in diameter. Questionnaire data on soy formula feeding during infancy was ascertained for 1,553 participants (89% based on mother’s report), of whom 345 were found to have fibroids. The association between soy formula feeding and fibroid prevalence and tumor number was estimated using log-binomial regression. Among those with fibroids, we compared fibroid size between soy formula-exposed and unexposed women using multivariable linear regression.

Results: There was no association between soy formula feeding and fibroid prevalence. However, exposed women with fibroids had significantly larger fibroids than unexposed women with fi-
broids. On average, soy formula feeding was associated with a 32% increase in the diameter of the largest fibroid (95% CI: 6, 65) and a 127% increase in total tumor volume (95% CI: 12, 358).

**Conclusion:** Our observation that women fed soy formula as infants have larger fibroids than unexposed women provides further support for persistent effects of early-life phytoestrogen exposure on the uterus.

**Comments**

Given the postnatal development of the myometrium, infancy may be a critical window for exposure to exogenous hormones. Exposition of infants to phytoestrogens contained in soy protein formula can be high, particularly if soy formula is the exclusive source of nutrition. Few data are available on the potential consequences of exposure to high doses of phytoestrogens in human infants on later sexual and reproductive development.

A study conducted in the US in adults aged 20–34 years who had participated as infants in comparative but nonrandomized feeding trials with soy protein-based infant formula or cow milk protein formula showed in 2001 [4] that women fed soy formula in infancy experienced a slightly but significantly longer duration of menstrual bleeding (by 0.37 days; 95% CI: 0.06–0.68), with no difference in self-assessed intensity of menstrual flow. The study also reported greater discomfort with menstruation (unadjusted relative risk for extreme discomfort vs. no or mild pain, 1.77; 95% CI: 1.04–3.00). Although exposure to soy formulae in the study by Upson et al. did not appear to be responsible for major health or reproductive problems, it was concluded by the ESPGHAN Committee on Nutrition (CoN) in 2008 that more information is needed on potential long-term effects of phytoestrogens [5]. The ESPGHAN CoN also concluded that “soy protein based formulae should only be used in specified circumstances because they may have nutritional disadvantages and contain high concentrations of phytate, aluminum, and phytoestrogens, the long-term effects of which are unknown. Indications for soy formulae include severe persistent lactose intolerance, galactosemia, religious, ethical, or other considerations that stipulate the avoidance of cow milk-based formulae. Soy protein formula should not be used in infants with food allergy during the first 6 months of life.” The Committee on Nutrition of the American Academy of Pediatrics stated in 2008 that “despite very limited indications for its use, soy-protein based formulas in the United States may account for nearly 25% of the formula market” [6]. More research is needed on the long-term effects of the use of soy-protein based infant formulas in early infancy.

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**Effect of dietary protein on plasma insulin-like growth factor-1, growth, and body composition in healthy term infants: a randomised, double-blind, controlled trial (Early Protein and Obesity in Childhood (EPOCH) study)**

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*Br J Nutr* 2016;115:271–284
Background: The effect of protein intake on growth velocity in infancy may be mediated by insulin-like growth factor-1 (IGF-1). This study aimed to determine the effects of formulae containing 1.8 (F1.8) or 2.7 g (F2.7) protein/100 kcal on IGF-1 concentrations and growth.

Methods: Healthy term infants were randomly assigned to receive F1.8 (n = 74) or F2.7 (n = 80) exclusively for the first 4 months of life. A group of breastfed infants (n = 84) was followed-up simultaneously as reference. Growth and body composition were measured at 0.5, 4, 6, 12, 36, 48, and 60 months of life.

Results: The IGF-1 concentrations at 4 months (primary outcome) were similar in the F1.8 (67.1 [SD = 20.8] ng/L; n = 70) and F2.7 (71.2 [SD = 27.5] ng/L; n = 73) groups (p = 0.52). Both formula groups had higher IGF-1 concentrations than the breast-fed group at 4 and 9 months of age (p ≤ 0.0001). During the first 60 months of life, anthropometric parameters in the F1.8 group were lower compared with the F2.7 group, and the differences were significant for head circumference from 2 to 60 months, body weight at 4 and 6 months, and length at 9, 12, and 36 months of age. There were no significant differences in body composition between these 2 groups at any age.

Conclusion: In formula-fed infants, although increased protein intake did not affect the IGF-1 concentration during the first 12 months of life, it did affect length and head circumference growth, suggesting that factors other than IGF-1 could play roles in determining growth velocity.

Comments: Rapid weight gain during infancy is closely associated with subsequent risks of overweight and obesity. Several studies comparing growth rates (primarily weight gain) in infants fed formula or complementary foods and those fed breast milk have suggested a positive association between high protein intake and rapid growth rate during infancy. The CHOP (Childhood Obesity Project) study, a large randomized trial [7], showed that infants fed high-protein infant formula (2.9 g protein/100 kcal) and follow-on formula (4.4 g protein/100 kcal) during their 1st year of life had significantly higher weight and weight for-length z scores (relative to the WHO standards) compared with infants fed low-protein infant formula (1.8 g protein/100 kcal) and follow-on formula (2.2 g protein/100 kcal).

In the EPOCH study including a population of healthy term infants, no impact of protein intake on the plasma hormone profile (IGF-1, insulin, and C-peptide concentrations) was observed during the first 12 months of life as opposed to the CHOP study. There was also no difference in body weight and body length at 60 months of age, again as opposed to the follow-up of the CHOP study where a high rate of lost-to-follow-up children (59%) was observed at 6 years of age [8]. The paper of Putet et al. describes very clearly the differences in study designs that may explain the discrepancies between the EPOCH study and previous studies, with a special focus on the CHOP study. In any case, the early protein hypothesis remains controversial. It seems to be too early to state that targeting dietary protein intake during infancy should be considered a valuable approach to reducing excessive early weight gain.
Antibiotic exposure during the first 6 months of life and weight gain during childhood


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JAMA 2016;315:358–365

Background: Early-life antibiotic exposure has been associated with increased adiposity in animal models, mediated through the gut microbiome. Infant antibiotic exposure is common and often inappropriate. Studies of the association between infant antibiotics and childhood weight gain have reported inconsistent results. The objective of the study was to assess the association between early-life antibiotic exposure and childhood weight gain.

Methods: Retrospective longitudinal study of singleton births and a matched longitudinal study of twin pairs conducted in a network of 30 pediatric primary care practices serving more than 200,000 children of diverse racial and socioeconomic backgrounds in the US. Children born at 35 weeks’ gestational age or older, with a birth weight of 2,000 g or more and in the 5th percentile or higher for gestational age, and who had a preventive health visit within 14 days of life and at least 2 additional visits in the first year of life. A total of 38,522 singleton children and 92 twins (46 matched pairs) discordant in antibiotic exposure were included. Exposure was systemic antibiotic use in the first 6 months of life. Weight was measured at preventive health visits from age 6 months through 7 years.

Results: Of 38,522 singleton children (50% female; mean birth weight: 3.4 kg), 5,287 (14%) were exposed to antibiotics during the first 6 months of life (mean age: 4.3 months). Antibiotic exposure was not significantly associated with rate of weight change (0.7%; 95% CI: –0.1 to 1.5%; \( p = 0.07 \), equivalent to approximately 0.05 kg; 95% CI: –0.004 to 0.11 kg of added weight gain between 2 and 5 years of age). Among the 92 twins (38% female; mean birth weight: 2.8 kg), the 46 twins who were exposed to antibiotics during the first 6 months of life received them at a mean age of 4.5 months. Antibiotic exposure was not significantly associated with a weight difference (–0.09 kg; 95% CI: –0.26 to 0.08 kg; \( p = 0.3 \)).

Conclusions: Exposure to antibiotics within the first 6 months of life compared with no exposure was not associated with a statistically significant difference in weight gain through 7 years of age.

Comments

Antibiotics promote growth in livestock, and it has been hypothesized that this occurs because of structural and functional alterations of the gut microbiome. Short-term antibiotic use can result in persistent changes in the human gut microbiome. Mice given antibiotics had altered gut microbiome composition, changed carbohydrate and lipid metabolism, and increased adiposity compared with control animals [9]. Fecal transplants in mice using stool from humans transferred the donor obesity phenotype (obese/lean) to recipient mice [10]. Previous studies reported associations between antibiotic use and obesity. A systematic review of 10 randomized clinical trials...
concluded that antibiotics had growth-promoting effects on young children from middle- and low-income countries [11]; however, given the fundamental differences observed in the structure and function of the microbiome in children with clinically significant malnutrition, these findings may not be generalizable to all children. Studies of children from industrialized countries have reported mixed results. There are many reasons to limit antibiotic exposure in children, but according to the study of Gerber et al., weight gain is likely not one of them.

Fermented infant formulas without live bacteria: a systematic review

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**Background:** Formulas which are fermented with lactic acid-producing bacteria during the production process and not containing significant amounts of viable bacteria in the final product are widely available in many countries. The aim of the authors was to review published evidence related to the safety and health effects of the administration of fermented infant formulas compared with standard infant formulas.

**Methods:** The Cochrane Library, MEDLINE, and EMBASE databases and major pediatric conference proceedings were searched for studies. Five randomized controlled trials involving 1,326 infants met the inclusion criteria.

**Results:** Compared with standard formula, the use of fermented formula resulted in a similar weight gain and length gain during the study period. Data from one randomized controlled trial, albeit large, suggest the effectiveness of fermented formula in preventing and treating acute diarrhea. Fermented formula has the potential to reduce some, albeit not well-defined, digestive symptoms. Current evidence does not support the use of fermented formula for preventing cow milk allergy.

**Conclusion:** Limited available evidence suggests that the use of fermented infant formula, compared with the use of standard infant formula, does not offer clear additional benefits, although some benefit on gastrointestinal symptoms cannot be excluded.

**Comments**

Fermented infant formulae without live bacteria needs to be differentiated from infant formulae supplemented with probiotics. The latter are defined as live microorganisms, which when given in adequate amounts confer a health benefit to the host. The ESPGHAN CoN concluded in 2007 that the available data do not allow conclusions to be drawn on the use and effects of fermented formulae for infants [12]. This systematic review shows that no negative health effects of fermented infant formulae have been demonstrated. However, the review confirms that health benefits related to the use of fermented infant formulae, if any, are very limited and not well-defined (digestive symptoms as regurgitations, hiccups, colic, and meteorism).
Infant feeding and risk of developing celiac disease: a systematic review

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Background: The hypothesis of inducing oral tolerance, via early feeding practices, to gluten in infants at genetic risk for celiac disease (CD) has long been investigated. Both prolonged breastfeeding and gluten introduction during a sensitive “window” period, in which the infant’s immune system is more likely to adapt to food antigens, have been assumed as protective factors towards the development of CD. The objective of this study was to review the evidence for the association of breastfeeding, breastfeeding duration, or the timing of gluten introduction and the later development of CD.

Methods: MEDLINE, via PubMed, EMBASE, and Web of Science were searched for studies published up to August 31, 2015 investigating the association of breastfeeding duration, breastfeeding at the moment of gluten introduction, or the timing of gluten introduction and the later development of CD. Prospective studies had to enroll infants/children at high risk of CD. For retrospective studies, participants had to be children or adults with CD.

Results: Out of 149 retrieved papers, 48 were considered in depth and 16 were included in this systematic review (9 were prospective and 2 were interventional). Duration of breastfeeding, breastfeeding at the time of gluten introduction, and delayed introduction of gluten during weaning were not effective in preventing later development of CD.

Conclusions: Currently, there is no evidence on the optimal breastfeeding duration or the effects of avoiding early (<4 months of age) or late (≥6 or even at 12 months) gluten introduction in children at risk of CD. Accordingly, no specific general recommendations about gluten introduction or optimal breastfeeding duration can be presently provided on evidence-based criteria in order to prevent CD.

Comments

Breastfeeding is the optimal way of feeding an infant for many health-related reasons, and exclusive breastfeeding for 6 months of age is recommended by the WHO [13]. This systematic review did not confirm previous findings from observational studies and did not support current recommendations [14]. Since the age of gluten introduction (anywhere between 4 and 12 months) has no effect on the prevention of CD, gluten should be introduced only as part of recommendations for introducing complementary foods in general. In children with no genetic predisposition for CD, the timing and mode of gluten introduction does not influence the risk anyhow; therefore, there is no need to introduce gluten while the infant is still being breastfed.
Gluten introduction and the risk of coeliac disease: a position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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Background: The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended in 2008, based on observational data, to avoid both early (<4 months) and late (≥7 months) introduction of gluten and to introduce gluten while the infant is still being breastfed. New evidence prompted the ESPGHAN to revise these recommendations.

Results: The risk of inducing celiac disease (CD) through a gluten-containing diet exclusively applies to persons carrying at least one of the CD risk alleles. Because genetic risk alleles are generally not known in an infant at the time of solid food introduction, the following recommendations apply to all infants, although they are derived from studying families with first-degree relatives with CD. Although breastfeeding should be promoted for its other well-established health benefits, neither breastfeeding nor breastfeeding during gluten introduction has been shown to reduce the risk of CD. Gluten may be introduced into the infant’s diet anytime between 4 and 12 completed months of age. In children at high risk for CD, earlier introduction of gluten (4 vs. 6 months or 6 vs. 12 months) is associated with earlier development of CD autoimmunity (defined as positive serology) and CD, but the cumulative incidence of each in later childhood is similar. Based on observational data pointing to the association between the amount of gluten intake and risk of CD, consumption of large quantities of gluten should be avoided during the first weeks after gluten introduction and during infancy. The optimal amounts of gluten to be introduced at weaning, however, have not been established.

Comments: This position paper from the ESPGHAN updates the previous recommendations published in 2008 [14]. The previous recommendations were based on observational studies while this very clear position paper benefits from the results of 2 large randomized clinical trials performed in Europe and published in the same issue of the New England Journal of Medicine in October 2014 [15, 16].
How different are baby-led weaning and conventional complementary feeding? A cross-sectional study of infants aged 6–8 months

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Background: Very little is known about the ability of “baby-led weaning” (BLW) to fulfill the nutritional requirements of young infants. The objective of the study was to compare the food, nutrients, and “family meal intakes” of infants following BLW with those of infants following a more traditional spoon-feeding (TSF) approach to complementary feeding.

Methods: Cross-sectional study of dietary intake and feeding behaviors in 51 age-matched and sex-matched infants (n = 25 BLW, 26 TSF) 6–8 months of age. Parents completed a questionnaire and weighed diet records on 1–3 non-consecutive days to investigate food and nutrient intakes, the extent to which infants were self-fed or parent-fed, and infant involvement in family meals.

Results: No difference was observed in energy intake, but BLW infants appeared to consume more total (48 vs. 42% energy, p < 0.001) and saturated (22 vs. 18% energy, p < 0.001) fat, and less iron (1.6 vs. 3.6 mg, p < 0.001), zinc (3.0 vs. 3.7 mg, p = 0.001), and vitamin B₁₂ (0.2 vs. 0.5 μg, p < 0.001) than TSF infants. BLW infants were more likely to eat with their family at lunch (50 vs. 86%) and at the evening meal (52 vs. 80%), respectively (both p ≤ 0.02).

Conclusions: Infants following BLW had similar energy intakes to those following TSF and were eating family meals more regularly. They had higher intakes of fat and saturated fat, and lower intakes of iron, zinc, and vitamin B₁₂.

Comments: BLW is becoming more and more popular amongst parents [17], but studies are very limited [18]. Any information on the nutritional adequacy of BLW is therefore welcome. The mean intake of fat in both groups was within the values advised by the European Food Safety Authority. Even if BLW infants had lower intakes of iron, zinc, and vitamin B₁₂, it remains to be shown by measurements of adequate biomarkers whether or not these lower intakes lead to suboptimal status in these nutrients as compared to TSF infants. The feasibility of BLW as an approach to infant feeding can only be determined in a randomized controlled trial. Such a study is urgently needed.
The lasting influences of early food-related variety experience: a longitudinal study of vegetable acceptance from 5 months to 6 years in two populations

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Background: Children’s vegetable consumption has fallen below current recommendations, highlighting the need to identify strategies that can successfully promote better acceptance of vegetables. Experimental studies have reported promising interventions that increase the acceptance of vegetables. The first, offering infants a high variety of vegetables at weaning, increased acceptance of new foods, including vegetables. The second, offering an initially disliked vegetable at 8 subsequent meals markedly increased acceptance for that vegetable. These effects have been shown to persist for at least several weeks.

Methods: We now present follow-up data at 15 months and 3 and 6 years obtained through a questionnaire (15 months, 3 years) and experimental (6 years) approaches.

Results: At 15 months, participants who had been breastfed were reported as eating and liking more vegetables than those who had been fed formula. The initially disliked vegetable that became accepted after repeated exposure was still liked and eaten by 79% of the children. At 3 years, the initially disliked vegetable was still liked and eaten by 73% of the children. At 6 years, observations in an experimental setting showed that children who had been breastfed and children who had experienced high vegetable variety at the start of weaning ate more of new vegetables and liked them more. They were also more willing to taste vegetables than formula-fed children or the no or low variety groups. The initially disliked vegetable was still liked by 57% of children.

Conclusions: This follow-up study suggests that experience with chemosensory variety in the context of breastfeeding or at the onset of complementary feeding can influence chemosensory preferences for vegetables into childhood.

Comments: Sensory experiences early in life can influence flavor preferences and food acceptance, and breastfeeding is also associated with positive effects on later eating patterns [19]. This follow-up study provides evidence that the type of milk feeding and the experience with different levels of vegetable variety during complementary feeding are associated with long-lasting effects. In addition, it shows that offering an initially disliked vegetable to infants at 8 subsequent meals was associated with an increased consumption of, and liking of, that same vegetable for up to 6 years. However, it is not possible to say whether these long-term effects were directly caused by the early experience of the infant or if subsequent behavior of the mother is also a factor. More research in the fascinating field of complementary feeding is needed. Even if this study has methodological limitations inherent to any follow-up study, it strongly suggests the positive impact of breastfeeding, variety of meals early in life, and patience with initially disliked vegetables on the size of the food repertoire later in life and consequently the variety of the diet.
Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition

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Background: Parenteral nutrition is a key component in the treatment of extremely premature neonates. Current guidelines lean towards emulsions with a higher content of amino acids and with lipids derived from fish oil.

Objective: To inspect the possible difference in impact of (1) high (immediate recommended daily intake [Imm-RDI]) versus low (incremental introduction of amino acids ([Inc-AAs]) parenteral amino acid delivery in the first 24 h of life on body composition, and (2) a mixed lipid emulsion comprised of 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil, and 15% fish oil (SMOF) compared to a soybean oil (SO)-based lipid emulsion on intrahepatocellular lipid (IHCL) content.

Methods: This was a multicenter, double-blind, randomized controlled trial. Infants born at <31 weeks of gestation were assigned to 1 of 4 groups (Inc-AA/SO, Inc-AA/SMOF, Imm-RDI/SO, or Imm-RDI/SMOF). Primary outcomes were nonadipose mass for the amino acid intervention and IHCL for the lipid intervention. Secondary outcomes were total adiposity, liver function tests, incidence of conjugated hyperbilirubinemia, weight, length, and brain volumes. Serious adverse events including sepsis and death were recorded.

Results: Outcome measures were available for 133 preterm infants. The higher amino acid content did not significantly affect nonadipose mass (adjusted mean difference: 1.0 g; 95% CI: −108, 111 g; p = 0.98). Similarly, IHCL content was not significantly affected by SMOF compared with SO (adjusted mean SMOF:SO ratio: 1.1; 95% CI: 0.8, 1.6; p = 0.58). Infants who received Imm-RDI had a higher probability than those treated with Inc-AA of having blood urea nitrogen of >7 mmol/L or >10 mmol/L, respectively (75% compared with 49%, p < 0.01; 49% compared with 18%; p < 0.01). Infants who received Imm-RDI also had a smaller head circumference at term (p = 0.02).

Conclusions: In this study, the provision of Imm-RDI of parenteral amino acids did not improve growth or body composition. SMOF containing emulsion did not reduce intrahepatic lipid accumulation.
This study reports on the effects of immediate parenteral nutrition management of preterm infants. There has been a trend in recent years to increase both amino acid and energy (lipid) intakes following recommendations of important societies such as the ESPGHAN [20]. However, studies describing long-term effects of high amounts of parenteral nutrition are scarce. There are some retrospective data showing an association with parenteral nutrient intake and neurocognitive functioning [21] and prospectively a beneficial effect in boys only at 2 years of life [22]. Short-term outcomes of high parenteral nutrient supply seem promising [23, 24], but this study asks for caution before intakes of 3.6 g/kg/day of amino acids and 2 g of lipids per kilogram per day can be implemented in routine practice. In addition, this study examined whether the provision of fish oil containing lipid emulsion had any benefit over a pure soybean lipid emulsion. No beneficial effect was obtained with the multicomponent emulsion, although a recent meta-analysis reported on reduced all-stage retinopathy of prematurity rates [25]. We definitively need at least the 2-year outcome data of this and other studies to determine whether we should change our current practice.

Low energy intake during the first 4 weeks of life increases the risk for severe retinopathy of prematurity in extremely preterm infants

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Objective: An association has been observed between poor early weight gain in preterm infants and the development of retinopathy of prematurity (ROP), but the mechanism behind this correlation is unknown. The objective of this study was to evaluate whether caloric intake and dietary macronutrient content in the first 4 weeks of life may influence the risk for severe ROP (stages 3–5).

Methods: Data were prospectively collected from a population-based cohort, including all infants born in Sweden under 27 weeks of gestation within a period of 3 years, who were all evaluated for ROP. ROP was classified and categorized according to international standards. Growth and nutrition data were retrospectively collected for each patient from hospital records.

Results: Data were available for a cohort of 498 patients, of whom 27.5% had no ROP, 17% had severe ROP, and 19.3% were treated. Higher energy, fat, and carbohydrate intakes were strongly associated with a reduction in the risk for severe ROP. In the multivariate analysis of all dietary variables evaluated, energy intake was the only independent predictor of severe ROP.

Conclusions: Low energy intake during the first 28 days of life was strongly correlated with an increased risk for severe ROP. The results suggest that securing adequate caloric intake in the first weeks of life may help to protect extremely preterm infants from developing severe ROP.

Comments: The EXPRESS study has provided the neonatal community around the world a target quality of care to aim for [26]. That the results obtained are not only depending on neonatal care but to the whole health care chain from preconception to adulthood is obvious [27]. From this observational study, many hypothesis-generating results have been obtained. This study is just one of them, showing an association of early energy intake and ROP. ROP, a neovascular disease of the retina found in very premature in-
fants, can result in life-long visual limitations. Insulin-like growth factor 1 is important for normal infant growth and retinal vascularization, and is regulated by total caloric and protein intake. Interestingly, protein or amino acid intakes did not show an association in this study while one of the leading hypotheses is that insulin-like growth factor 1 (and ω−3 polyunsaturated fatty acids) may play an important role [28]. On the other hand, another large observational study found similar results [29]. Of course, this finding must be proven in large prospective trials, especially with the recent trial in term infants and older children showing detrimental effect of early parenteral nutritional support in pediatric intensive care in mind [30].

A comparison of 3 vitamin D dosing regimens in extremely preterm infants: a randomized controlled trial

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Objectives: Preterm infants are often born with biochemical vitamin D insufficiency, due to the late placental passage of vitamin D to the fetus, occurring primarily during the third trimester. The effect of this insufficiency on early life morbidity and mortality is unknown. The aim of this study was to determine which dose of vitamin D supplementation is sufficient for obtaining normal levels of vitamin D in extremely premature infants.

Methods: A masked, randomized controlled trial including 100 infants born at 23–28 weeks of gestation. Each child was assigned to receive either placebo or 200 or 800 IU of vitamin D per day, which in addition to the routine administration of approximately 200 IU per day, resulted in an intake of 200, 400, and 1,000 IU, respectively. Primary outcome measures were serum 25(OH)D concentrations on day 28 of life, and the number of days alive and off respiratory support within the first 28 days.

Results: Vitamin D concentrations on the first day of life were <20 ng/ml in 67% of the patients. After 28 days of intervention, vitamin D levels were (median [25th–75th percentiles], ng/mL): placebo: 22 (13–47), 200 IU: 39 (26–57), 800 IU: 84.5 (52–99); p < 0.001. There was no significant difference between the groups in days alive and off respiratory support, or in other respiratory outcome measures.

Conclusions: Vitamin D deficiency at birth is present in a majority of extremely premature infants, and can be partially corrected with a 28-day supplementation of 200 IU/day, or normalized with 800 IU/day. In this study, this biochemical change was not associated with a difference in respiratory morbidity and mortality, but further research is needed to evaluate the clinical significance of these findings.
Vitamin D metabolism in the premature newborn: a randomized trial

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Objectives: The importance of maintaining adequate concentrations of vitamin D in preterm infants is generally agreed upon. However, in this age group there is a lack of information regarding vitamin D metabolites other than 25(OH)D, the commonly used biomarker of vitamin D activity. The aim of this study was to describe the concentrations of 25(OH)D$_3$, 24,25(OH)$_2$D$_3$, and 3-epi-25(OH)D$_3$ in premature infants.

Methods: Thirty-two preterm infants born at <32 weeks of gestation were randomly assigned to receive either 400 or 800 IU/day of oral vitamin D$_3$ supplementation. Circulating levels of vitamin D metabolites were obtained every 4 weeks and analyzed using a highly sensitive liquid chromatography-tandem mass spectrometry-based method.

Results: Mean serum 25(OH)D$_3$ levels at birth were deficient (17.3 ng/mL); mean 3-epi-25(OH)D$_3$ were 1.3 ng/mL and mean 24,25(OH)$_2$D$_3$ were 1.4 ng/mL. Both 25(OH)D$_3$ and 3-epi-25(OH)D$_3$ levels rose significantly over time. There was also a significant rise in the proportion of 3-epi-25(OH)D$_3$ out of total 25(OH)D$_3$ (7.2 vs. 29.7%, $p < 0.0001$ for birth vs. 8 weeks). Serum 25(OH)D$_3$:24,25(OH)$_2$D$_3$ ratios after 4 and 8 weeks were higher than the ratios described in older children and adults.

Conclusions: Vitamin D metabolism in preterm infants has unique characteristics that have not been reported in older children and adults. 25(OH)D$_3$ levels responded well to vitamin D supplementation; however, a substantial elevation in 3-epi-25(OH)D$_3$ was also observed over time. Higher than expected 25(OH)D$_3$:24,25(OH)$_2$D$_3$ ratios in premature infants may reflect immature expression of CYP24A1. The clinical relevance of these data is yet to be determined.

Effect of pasteurisation on the concentration of vitamin D compound in donor breast milk

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Objectives: Pasteurized donor human milk is considered to be the preferred source of nutrition for infants whose mothers are unable to provide breast milk, and it has several advantages over infant formulas. How pasteurization effects the concentrations of vitamin D metabolites in donor breast milk is unknown.

Methods: A total of 16 participants, who donated breast milk to the Royal Brisbane and Women’s Hospital milk bank, were recruited in this study. Milk samples were obtained before and after Hold-
The concentrations of vitamins D$_2$ and D$_3$, 25(OH)D$_2$, and 25(OH)D$_3$ were determined using liquid chromatography tandem mass spectrometry.

**Results:** The content of D$_2$, D$_3$, 25(OH)D$_2$, and 25(OH)D$_3$ in pasteurized milk samples was significantly lower than in prepasteurized milk, with $p$ values of 0.0001 for all targeted analytes. The concentrations of the vitamin D compounds in nonpasteurized milk ranged from 3.6 to 5.0 pM for vitamin D$_2$, 1.0 to 9.8 pM for vitamin D$_3$, 1.4 to 2.1 pM for 25(OH)D$_2$, and 1.2 to 9.3 pM for 25(OH)D$_3$. The concentrations of the vitamin D analogues in postpasteurized milk ranged from 3.0 to 4.0 pM for vitamin D$_2$, 0.6 to 9.5 pM for vitamin D$_3$, 1.2 to 1.7 pM for 25(OH)D$_2$, and 1.1 to 9.1 pM for 25(OH)D$_3$. The reduction in levels of vitamin D compounds attributable to the pasteurization process ranged from 10 to 20%.

**Conclusions:** Pasteurization led to a significant decline in the concentration of vitamin D metabolites in pasteurized donor breast milk.

**Comments**

Preterm infants, especially those with a gestational age below 30 weeks, are at higher risk of lower 25(OH)D levels, compared with more mature infants, as vitamin D is mostly transferred to the fetus during the third trimester. Maternal low vitamin D levels contribute as well to lower vitamin D levels in their offspring. Vitamin D is necessary for bone health and immune function, and it also is important for the saccular and alveolar stages of lung development. 25(OH)D is recognized as the biomarker of vitamin D status. Observational studies indicate that preterm infants with low 25(OH)D are at higher risk of lung disease [31], which is supported by animal studies. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition has recommended 800–1,000 IU of vitamin D per day for preterm infants, whereas the American Academy of Pediatrics recommends a dose of 200–400 IU [32, 33]. First of all, it is intriguing why almost all recommendations on nutrients are expressed on a kg/day basis and vitamin D is not. Second, those recommendations are quite distinct from each other, which usually implies that no convincing evidence is available.

The 3 papers described above are important as the beginning of a new era in vitamin D research in preterm infants. Fort et al. performed a pilot randomized controlled trial of oral vitamin D supplementation in normally fed extremely preterm infants. Of preterm infants with an average birth weight of 770 g, 67% had biochemical vitamin D deficiency with cord blood levels <20 ng/mL. Supplementation with 200, or 800 IU of vitamin D yielded intakes with the diet of about 200, 400, or 1,000 IU per day. At 28 days, the percentage of infants with blood vitamin D <20 ng/mL was 41% with placebo, 16% with 200 IU, and 0% with 800 IU, but some of the high supplementation group had relatively high vitamin D levels. Vitamin D toxicity, usually presenting as emesis, paresthesias, and hypercalcemia, was not noted.

Hanson et al. warn of an overestimation of total 25(OH)D$_3$ by a 3-epi isomer of 25(OH)D$_3$ that has been reported to be significantly elevated in preterm infants. The 3-epimer of 1α,25-(OH)$_2$D$_3$, the presumed active form of 3-epi-25(OH)D$_3$, has been shown to have a lower affinity for the vitamin D receptor than 25(OH)D$_3$, suggesting that its biological activity may be lower. Therefore, including the concentration of 3-epi-25(OH)D$_3$ may overestimate the biological potential of vitamin D status. While correcting for this 3-epimer, they compared supplementation of 400 or 800 IU of vitamin D to preterm infants with an average birth weight of approximately 1,400 g. One of the weaknesses of the study is the small sample size ($n = 32$), which continued to decrease over time as infants were discharged from the neonatal intensive care unit. The mean vitamin D level at birth was deficient (<20 ng/mL) as in Fort et al. Supplementation of both 400 or 800 IU/day normalized serum 25(OH)D$_3$, reaching mean levels >50 ng/mL in both groups. The 3-epi-25(OH)D$_3$ epimer represented only 6–8% of total 25(OH)D$_3$. 

in cord blood, but the metabolite rose quickly to 30–45% of total 25(OH)D₃ after 4 or 8 weeks of vitamin D₃ supplementation. However, we do not know the impact of this significant elevation. Of interest as well is the relatively low conversion of 25(OH)D₃ to 24,25(OH)₂D₃. Serum concentrations of 24,25(OH)₂D₃ were lower at 4 weeks than at birth in both supplementation groups despite significant increases in 25(OH)D₃ concentrations. This “lag” in the 24-hydroxylation can be related to a downregulation in CYP24A1 enzyme activity in preterm infants.

Finally, the paper by Gomes et al. shows that Holder pasteurization significantly reduces the vitamin D content of human milk. Human milk itself already has low levels of vitamin D, making supplementation necessary at all times. However, with the increasing use of own mothers’ milk or donor milk, the effect of pasteurization needs to be taken into account as well [34]. The observed effect of Holder pasteurization is limited, with losses up to 20%. Since we are discussing supplementation of either 400 or 800–1,000 IU/day, pasteurization of donor milk in itself has no significant impact on the concentrations of active metabolites in serum and should never be a reason to withhold preterm infants from human milk supplementation.

**Effect of donor milk on severe infections and mortality in very low-birth-weight infants: the Early Nutrition Study randomized clinical trial**

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**Objectives:** Maternal breast milk is superior to infant formulas in preventing infections and necrotizing enterocolitis in preterm infants. The main source of nutrition in most neonatal intensive care units is maternal breast milk, supplemented by infant formula when insufficiently available. In such cases it is unknown whether complementary human donor milk has an advantage over formula. This study aims to establish whether a supplement of donor milk on top of own mother’s milk in the first 10 days of life is more effective than formula in preventing serious infection, necrotizing enterocolitis, and mortality.

**Methods:** In this multicenter, double-blind randomized study, very-low-birth-weight infants (birth weight < 1,500 g) were recruited from 6 neonatal intensive care units in the Netherlands over a period of 29 months. The neonates were assigned to either pasteurized donor milk or preterm formula during the first 10 days of life whenever their own mother’s milk was lacking. The primary end point was the occurrence of serious infection (sepsis or meningitis), necrotizing enterocolitis, or mortality within the first 60 days of life.
Results: A total of 373 infants were eventually evaluated by intent-to-treat analysis (183 in the donor milk group and 190 in the formula group) born at a median of 28.4 weeks’ gestational age, with a median birth weight of 1,066 g. The infants’ nutrition included 89.1 and 84.5% of own mother’s milk in the donor group and formula group, respectively. The incidence of the combined outcome was similar (85 [44.7%] [formula] vs. 77 [42.1%] [donor milk]; mean difference, 2.6%; 95% CI: −12.7 to 7.4%). The adjusted hazard ratio was 0.87 (95% CI: 0.63–1.19; \( p = 0.37 \)).

Conclusions: In this study, no difference was found in the short-term outcomes evaluated of very-low-birth-weight infants receiving adjunctive pasteurized donor milk or preterm formula. Further research is needed to evaluate longer durations of intervention and long-term outcomes.

Comments: Many societies, including the ESPGHAN, state that if own mother’s milk is not available, donor milk is the best alternative [34]. In theory, human milk has a beneficial effect on various aspects of human physiology, most of which become apparent after infancy [35]. However, the statement is not supported by strong clinical evidence. Only a study performed in the early era of neonatology showed a significant effect reducing necrotizing enterocolitis (NEC) [36], whereas a more recent very small trial found an association between the use of an exclusive human milk diet and a reduction in NEC [37]. A larger study comparing donor milk with formula did not show any effect in NEC rate. The present large study shows that the additional use of donor milk in the first 10 days, when own mother’s milk is often not available, does not decrease the combined rate of sepsis, NEC, or mortality. This might be due to the effect of pasteurization as there was a huge reduction when formula was compared to own mother’s milk, or alternatively the intervention was too short (only 10 days) or the amounts of donor milk/formula that the infants received was relatively small. Clearly, the administration of small amounts of cow milk-based formula in the first 10 days following birth did not harm the infants in the postnatal phase. A similar sized trial on the use of donor milk as an add-on performed in Canada, which will be published soon, will provide more interesting data on a longer intervention period. With over 500 milk banks around the world and the relative high costs of operating such a bank, these data are necessary to support the continuation of human milk banks and expanding the number.

Recombinant bile salt-stimulated lipase in preterm infant feeding: a randomized phase 3 study

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**Introduction:** Higher growth velocity in the early life of preterm infants has a positive effect on growth and neurodevelopment. Bile salt-stimulated lipase (BSSL) is present in human milk and plays an important role in fat digestion and absorption. BSSL is absent in infant formulas and is inactivated by pasteurization of human donor milk. The objective of this study was to determine if the addition of recombinant human BSSL (rhBSSL) to formula or pasteurized donor milk promotes growth in preterm infants.

**Methods:** LAIF (Lipase Added to Infant Feeding) was a randomized, double-blind, placebo-controlled phase 3 study carried out in 54 centers in 10 European countries. Preterm infants born <32 weeks of gestation were randomized to either intervention or placebo for 4 weeks, and evaluated at 3 and 12 months. The primary outcome measure was growth velocity (g/kg/day) during the intervention period.

**Results:** Data from 410 patients were available for analysis (206 in the rhBSSL group, 204 in the placebo group), and a total of 365 infants were followed until 12 months. When looking at the whole cohort, growth velocity during intervention was not affected by rhBSSL treatment compared to placebo (16.77 vs. 16.56 g/kg/day; estimated difference: 0.21 g/kg/day; 95% CI: –0.40, 0.83), and neither were other variables assessed. However, in the subgroup of infants born small for gestational age, growth during treatment was significantly increased in the rhBSSL group compared to placebo. During intervention, the incidence of adverse events was higher in patients receiving rhBSSL.

**Conclusions:** Growth of preterm infants born small for gestational age appeared to improve with the addition of rhBSSL to the infants’ diet. Although other end points were not met and short-term safety in this study was negatively affected, these results add important information on nutrition, growth, and development in preterm infants.

**Comments**

Presentations at various meetings of a pilot study using recombinant bile salt-stimulated lipase showed very promising results with regard to weight gain rates [38]. In the present larger study, the results were disappointing. No effect of rhBSSL was shown in an adequately sized blinded randomized controlled trial. However, these data also indicate the importance of large well-conducted studies. Many interventions have been implemented based upon small trials, usually with some supportive animal data, but not vigorously tested. Especially long-term data are usually not available.

The rationale of trying to increase weight gain in preterm infants seems logical, as observational data link weight gain to improved neurocognitive outcomes [39]. Prospective studies on the causal relationship between weight gain rates and neurocognitive functioning are not available, so the question remains whether improving weight gain per se is the goal. Similarly, as rhBSSL should act by increasing fat uptake, one could question whether the increase in body fat stores and not so much lean body mass should be the goal.
Long-term effect of high-dose supplementation with DHA on visual function at school age in children born at <33 wk gestational age: results from a follow-up of a randomized controlled trial

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Background: Impairments in visual processing may be seen as long-term complications of preterm birth. Previous studies have suggested that a supplement of docosahexaenoic acid (DHA) given to preterm infants may reduce the incidence and severity of visual processing defects.

Objective: This trial aimed to assess whether children born very premature and who had received a diet fortified with high doses of DHA, did better at visual processing at 7 years of age than infants fed with standard doses of DHA.

Methods: This was a follow-up study of participants in a randomized controlled trial of preterm infants who received human milk with high-dose DHA (1% of total fatty acids). The control group received a standard dose of DHA (0.2–0.3% of total fatty acids). Stratification for gender and birth weight (above and below 1,250 g) was performed. A total of 104 seven-year-old children (49 in the high dose DHA group; 55 controls) were evaluated on several visual-processing parameters, namely visual acuity, contrast sensitivity, vernier acuity, binocular stereopsis, and visual perception.

Results: No significant differences were found between the two groups in any of the variables assessed. There was a trend favoring the control group in 12 of the 13 measures evaluated.

Conclusions: In this large follow-up study, the provision of high-dose DHA to preterm infants during the first months of life did not result in improved visual processing abilities at school age.

Comments

DHA (22:6 n-3), an omega-3 long-chain polyunsaturated fatty acid, is found in high concentrations in both the cerebral cortex and the retina. During the last trimester of pregnancy, a substantial amount of DHA is transferred from mother to fetus; thus, infants born early lack an adequate intrauterine supply of DHA at a stage when this requirement is at its greatest. Consistent with the premise that visual processes are reliant on adequate DHA concentrations early in development, very preterm children exhibit higher than expected rates of refractive errors, strabismus, amblyopia, and deficient visual perceptual skills. Consequently, a large number of trials have focused on supplementation of DHA, both during fetal life and infancy, through maternal supplementation and direct supplementation to the infant. The present article is a subset of children (from 1 of the 5 participating centers) from the original cohort who received either 1 or 0.3% DHA of their total fat intake through either a randomized formula or through supplementation of the mother. This study shows that long-term effects (school age) are not apparent in any of the subsequent visual-processing measures. Interestingly, visual acuity was enhanced in the same infants at 4 months of life [40]. Similarly, Carlson et al. [41] found only a temporary benefit for DHA supplementation in preterm infants without bronchopulmonary dysplasia who were fed formula (i.e., at 2 months, but not at 4, 6, 9, or 12 months). Could it be that maturation of visual processing is achieved faster when enough DHA is provided in early life, while
later on these functions normalize also in unsupplemented children or children who received less than the requirements? Clearly this study shows that provision of DHA in quantities higher than those found in breast milk have no long-term benefits for visual processing in either visual sensory or perceptual tasks.

Eating difficulties in children born late and moderately preterm at 2 y of age: a prospective population-based cohort study

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Background: Preterm infants born <32 weeks of gestation have a higher rate of eating difficulties than infants born at term. Data are lacking regarding the effect of late and moderately preterm (LMPT; 32–36 weeks of gestation) birth on eating disorders in the first years of life. The aim of this study was to evaluate the risk of developing eating difficulties and possible causative factors for such disturbances in LMPT infants at 2 years’ corrected age.

Methods: Participants were recruited at birth in a geographically defined region in England to form LMPT and term-born control cohorts. At 2 years’ corrected age, parents completed questionnaires regarding neurodevelopmental outcomes, and the presence of various eating problems: refusal/picky eating, oral motor problems, oral hypersensitivity, and eating behavior problems. In each category, patients with scores above the 90th percentile were defined as having eating difficulties. Data on the neonatal period were collected from hospital files, and information on sociodemographic status was collected in a maternal interview.

Results: Data were available for 651 LMPT infants and 771 term-born infants. Before adjustments, LMPT infants had higher rates of refusal/picky eating (RR = 1.53; 95% CI: 1.03, 2.25) and oral motor problems (RR = 1.62; 95% CI: 1.06, 2.47) than controls. In multivariable analysis, factors independently associated with eating difficulties were prolonged nasogastric feeding >2 weeks (RR = 1.87; 95% CI: 1.07, 3.25), behavior problems (RR = 2.95; 95% CI: 1.93, 4.52), and delayed social competence (RR = 2.28; 95% CI: 1.49, 3.48). After adjustment for these parameters, both groups had similar rates of eating difficulties.

Conclusions: Infants born late or moderately preterm have a higher risk of developing oral motor and picky eating problems at 2 years’ corrected age. However, this appears to be a consequence of specific neurodevelopmental sequelae rather than of prematurity per se.

Comments: That feeding difficulties are frequently present in infants born very preterm is well known. Prolonged exposure to nasogastric tube feeding, provision of mechanical ventilation during neonatal care, and neurodevelopmental and behavioral sequelae have all been associated with eating difficulties. Infants born late or moderately preterm (32–36 weeks’ gestational age) are usually not very ill, do not require invasive treatment, and are (usually) able to drink milk. Overall, approximately 15% of these late preterm infants and approximately 10% of term-born infants had eating difficulties at 2 years in this population-based study. These consisted predominantly of oral motor problems, such as chewing, biting, swallowing, and refusal/picky eating at 2 years’ corrected age. These difficulties were mediated by neurodevelopmental sequelae and are thus unlikely to represent a specific functional deficit after late preterm
birth, indicating a similar origin of feeding difficulties as was found in very preterm infants [42]. Screening for eating difficulties during early childhood may therefore be useful in identifying not just those in whom intervention to support feeding practices might be beneficial, but those who may have other behavioral issues or developmental morbidity.

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This chapter collects the articles that have been published between the July 1, 2015 and June 30, 2016 in the area of the relationships between nutrition and cognition. Although few new findings may be detectable in such a narrow time frame, there are nevertheless some data from follow-up studies and new hypothetical links between nutrition or nutrition-related issues (e.g., the topic of intestinal flora). The latter might still lack solid results based on sound study designs and supported by adequate statistical power, but the hypothetical background could give support to consistent observational data and then a supportive set of experimental randomized studies. In accordance with recent methodological recommendations, while in the near future we may expect less studies to arise from these new hypotheses, we may get more harmonized and homogenous methods and subjects, so as not to waste data and/or make a combined analysis difficult to be performed and interpreted (we refer in particular to the myriad of papers on the connection between long-chain polyunsaturated fatty acids [LCPUFA] and neurodevelopmental performance published in the 1990s and 2000s). The example of the studies from Australia – starting with large and consistent numbers, allowing also for a strong follow-up – should be enlarged to other nutrients beyond LCPUFA and to international networks of research beyond a single state. For the 2017 Yearbook, 4 areas of interest for the connection with the neurocognitive performance have been considered: (1) LCPUFA in pregnancy and lactation, (2) micronutrients and pregnancy, (3) the world of microbiomes, and (4) a brief paragraph on miscellanea. Overall commentaries are included for each of the 4 sections following the summaries of papers and respective commentaries within each category.
Key articles reviewed for this chapter

Long-Chain Polyunsaturated Fatty Acids, Pregnancy, and Lactation

Fatty acid composition in breastfeeding and school performance in children aged 12 years
Dalmeijer GW, Wijga AH, Gehring U, Renders CM, Koppelman GH, Smit HA, van Rossem L

Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development
Delgado-Noguera MF, Calvache JA, Bonfill Cosp X, Kotanidou EP, Galli-Tsinopoulou A
Cochrane Database Syst Rev 2015;7:CD007901

Does n-3 LCPUFA supplementation during pregnancy increase the IQ of children at school age? Follow-up of a randomised controlled trial
BMJ Open 2016;6:e011465

Association between prenatal and current exposure to selected LCPUFAs and school performance at age 7
van der Wurff IS, Bakker EC, Hornstra G, Kirschner PA, Gielen M, Godschalk RW, Kremers S, Zeegers MP, de Groot RH

Micronutrients and Pregnancy

Effects of maternal iodine nutrition and thyroid status on cognitive development in offspring: a pilot study
Thyroid 2016;26:296–305

Effects of maternal vitamin B₁₂ supplementation on early infant neurocognitive outcomes: a randomized controlled clinical trial
Srinivasan K, Thomas T, Kapanee ARM, Ramthal A, Bellinger DC, Bosch RJ, Kurpad AV, Duggan C
Matern Child Nutr 2016, DOI: 10.1111/mcn.12325

Impact of prenatal exposure to cadmium on cognitive development at preschool age and the importance of selenium and iodine
Microbiome

**Feeding the brain and nurturing the mind: linking nutrition and the gut microbiota to brain development**
Goyal MS, Venkatesh S, Milbrandt J, Gordon JI, Raichle ME
*Proc Natl Acad Sci USA* 2015;112:14105–14112

**Fetal, neonatal, and infant microbiome: perturbations and subsequent effects on brain development and behaviour**
Diaz Heijtz R

**The infant microbiome: implications for infant health and neurocognitive development**
Yang I, Corwin EJ, Brennan PA, Jordan S, Murphy JR, Dunlop A
*Nurs Res* 2016;65:76–88

Miscellanea

**Diet-induced changes in iron and n-3 fatty acid status and associations with cognitive performance in 8–11-year-old Danish children: secondary analyses of the Optimal Well-Being, Development and Health for Danish Children through a Healthy New Nordic Diet School Meal Study**
Sørensen LB, Damsgaard CT, Dalskov SM, Petersen RA, Egelund N, Dyssegaard CB, Stark KD, Andersen R, Tetens I, Astrup A, Michaelsen KF, Lauritzen L
*Br J Nutr* 2015;114:1623–1637

**The long term impact of micronutrient supplementation during infancy on cognition and executive function performance in pre-school children**
*Nutrients* 2015;7:6606–6627
Fatty acid composition in breastfeeding and school performance in children aged 12 years

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Objectives: The association between LCPUFA concentrations in infant feeding and school performance was assessed at 12 years of age within a population-based birth cohort.

Methods: School performance was compared in 277 nonbreastfed children and 157 children who had fatty acid composition of their mothers’ breast milk measured. Nonbreastfed children were fed a docosahexaenoic acid (DHA)-deprived formula. The score on a standardized achievement test and the teacher’s advice regarding a child’s potential performance level in secondary education were considered.

Results: Early high DHA intakes were associated with higher developmental scores in breastfed girls compared to the nonbreastfed girls. Among breastfed girls who received a different DHA level, each percentage point of higher content of total n-3 LCPUFA was associated with a higher developmental score. The association between LCPUFA content and teacher school advice showed a similar pattern. No association was found in boys.

Conclusion: Besides the unmeasurable role of sociodemographic and lifestyle-related factors, early and higher intakes of n-3 PUFA, especially DHA, may contribute to better school performance in girls.

Comments: It is largely accepted that breastfed infants show better cognitive outcomes compared with nonbreastfed infants. LCPUFA included in breast milk take part in the structural composition of the brain. This observational study evaluated the relationship between the content of LCPUFA in breast milk with school performance at 12 years of age.

The study is noteworthy since it reports a long-term association of a nutrient supplied in the first ages of life (DHA and LCPUFA through human milk) with school performance later on, and thus not using the often discussed scales of mental and psychological development. As the authors nicely underline at the end of the discussion, the socioeconomic status is a decisive variable than can rarely be separated from the breastfeeding environment in any case. Moreover, gender-related effects of LCPUFA should be explored.
Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development

Delgado-Noguera MF, Calvache JA, Bonfill Cosp X, Kotanidou EP, Galli-Tsinopoulou A
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Cochrane Database Syst Rev 2015;7:CD007901

Objectives: To assess the effectiveness of LCPUFA in breastfeeding mothers in the cognitive and physical development of their infants.

Methods: The evidence about the effect of supplementation of LCPUFA on breastfeeding mothers (including the pregnancy period) on growth and neurodevelopment of their children was reviewed. Eight randomized clinical trials were found, including a total of 1,567 women from high-income countries.

Main Results: All the studies were performed in high-income countries and the longest follow-up was 7 years. The quality of evidence was found to be moderate and low. Supplementing a mother’s diet with LCPUFA during the pregnancy and the first 4 months after birth did not improve child growth or neurodevelopment assessed through validated investigations (problem-solving ability or intelligence, psychomotor, motor, or language development). Weak evidence was found in children’s attention at 5 years of age, favoring the supplementation.

Conclusions: These results suggest that there is inconclusive evidence to support or refute the practice of giving LCPUFA supplementation to breastfeeding mothers in order to improve neurodevelopment.

Comments: This Cochrane article included 8 randomized controlled trials (1,567 women) in this systematic review which evaluated the effectiveness of LCPUFA supplementation during pregnancy and the postpartum period on neurocognitive outcomes of mothers and their offspring compared with placebo. Many specialists are proposing LCPUFA supplementation for mothers during pregnancy and lactation from the perspective of preventive nutrition. According to the conclusions of the review, with the present knowledge, there is inconclusive evidence to support or refute the practice of giving LCPUFA supplementation to breastfeeding mothers in order to improve neurodevelopment or visual acuity. This Cochrane review deserves attention since the inclusion of large numbers and the application of a rigorous methodology once more allows for the appreciation of minimal differences of doubtful meaning. As suggested by experts, this does not mean to co-opt for the old practice (in this case, not to use LCPUFA for pregnant and lactating women), but simply that everyone can be left out of any recommendation and be free to choose between the previous and the older supplementary habit.
Does n-3 LCPUFA supplementation during pregnancy increase the IQ of children at school age? Follow-up of a randomised controlled trial

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Background: A recent systematic review found a lack of high-quality data to support the long-term effects of DHA supplementation on child neurodevelopment.

Methods: Child neurodevelopment will be assessed at 7 years of age in follow-up of a multicenter double-blind randomized controlled trial of DHA supplementation in pregnancy in 2,399 Australian women with a singleton pregnancy <21 weeks’ gestation who were randomized to receive a total dose of 800 mg DHA/day or a vegetable oil placebo until birth. Within this population, around 30% of the children, both preterm and term, were selected for neurodevelopmental follow-up up to 7 years of age. According to our design, at the 7-year follow-up, a psychologist will assess the primary outcomes, IQ, attention, language, memory, and learning, with validated scales of intelligence. Caregivers will also be asked to complete specific questionnaires. Intention-to-treat analyses will be performed.

Results: The study will provide the first robust data regarding the long-term effects of maternal DHA supplementation during pregnancy.

Comments

Although several studies have shown the beneficial effects of LCPUFA supplementation during gestation on neurodevelopment of newborns, there are still unclear aspects that may confound the evidence. Most research has been inconclusive because of the presence of limitations such as smaller samples or low statistically power of the studies. For this reason, LCPUFA reference intakes are always debated. Randomized controlled trials are required to assess the possible positive effects of maternal DHA intake on cognitive ability at school age.

The investigators performed the largest randomized controlled trial in Australia (2,399 women enrolled) to assess the role of DHA supply during pregnancy on cognitive function of children at 7 years of age.

The paper does not show any result, but accurately describes the interventions, methods, and procedure. This trial, DOMInO (DHA to Optimise Mother Infant Outcome), represents a chance to make a comparison between the effects of a DHA intervention with a placebo during pregnancy given the high usage of prenatal supplements containing DHA in countries throughout the world.
Association between prenatal and current exposure to selected LCPUFAs and school performance at age 7

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Objectives: To determine the association between levels of the major LCPUFA measured at study entry, 22 weeks of pregnancy, 32 weeks of pregnancy, at partus, in umbilical cord plasma and child’s plasma at age 7, and school performance scores at age 7.

Methods: Data from the Maastricht Essential Fatty Acid Birth (MEFAB) cohort were used for this study. Developmental scores for spelling, reading, and arithmetic at 7 years of age were obtained via the school for 149, 159, and 155 children, respectively. Associations between LCPUFA levels and school performance scores were analyzed, adjusting for covariates (smoking, maternal education, sex, breastfeeding, maternal intelligence, birth weight, and BMI at 7 years of age).

Results: Significant associations between DHA level at 7 years of age and both reading and spelling were found. On the other hand, consistent significant negative associations were observed between all maternal DHA plasma levels and arithmetic scores at 7 years of age, as well as for maternal LCPUFA plasma levels at study entry and both reading and spelling scores at 7 years of age.

Conclusion: The observations from this observational study suggests prudence when considering DHA supplementation during pregnancy, and underline the needs of further observations on the long-term effects of early DHA supplementations within randomized trials.

Comments: Within the same context of the previous papers, the authors focused their attention on the effects of pre-, peri-, and postnatal exposures to LCPUFAs on school performance at 7 years of age through an observational study, not a randomized controlled trial, with many potential limitations. Seven hundred and fifty Caucasian children were enrolled from 1990 to 1994 and invited to participate in the 7-year follow-up. The observations were somewhat unexpected since positive associations were found between present LCPUFA levels of children and their abilities, while negative associations were found with the maternal plasma levels in pregnancy. This confirms the need to have more data on early intakes and later outcomes.

Overall Commentary

The common thread between the 4 papers is the correlation between early LCPUFA intake and later cognitive performance. However, we are still far from separating the effects of LCPUFA in human milk from breastfeeding itself and the environmental correlates, as well as defining the effects of LCPUFA in pregnant and lactating mothers on the later cognitive abilities and scholastic achievements. The association between diet, metabolism, biochemistry, and function still recognize in LCPUFA a wonderful issue, but the individual (inclusive of gene-related) and environmental characteristics represent variables difficult to avoid. Moreover, even if more comprehensive and objective outcome measures were considered in the follow-up, the effects of the initial differences could only partially be adjusted for.
Effects of maternal iodine nutrition and thyroid status on cognitive development in offspring: a pilot study

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Objective: The authors investigated the effects on the intelligence quotient (IQ) of children born to mothers with different levels of iodine supplementation, with or without the administration of levothyroxine (LT₄), prior to and during pregnancy.

Methods: This prospective observational study included 4 study groups, each comprising 15 mother-child pairs, identified on the basis of maternal histories of iodized salt consumption and LT₄ treatment prior to and during pregnancy. IQ tests were administered to children at 6–12 years of age with validated scales of intelligence, verbal IQ, and performance IQ.

Results: Children taking iodized salts showed advantages on the developmental scales compared to other children, and no associations were found with maternal free thyroxine concentrations at any stage of pregnancy. Overall, the prevalence of borderline or defective cognitive function was more than 3-fold higher in the children of mothers not using iodized salt than of those mothers using it.

Conclusions: Neurointellectual outcomes in children appear to be more dependent on their mothers’ nutritional iodine status than on maternal thyroid function.

Comments

It is widely agreed that an adequate iodine status is important for early-life neurodevelopment. A pilot, prospective, observational study showed that children of mothers who had never used iodized salt have presented a prevalence of borderline or defective cognitive scores. It seems that not only severe but also mild-to-moderate maternal iodine deficiency may impair neurodevelopment in the offspring. This relatively limited, well-designed study indicates that neurointellectual outcomes in children appear to be more dependent on their mothers’ nutritional iodine status than on maternal thyroid function, and it is therefore recommended to monitor the mother’s iodine status before and during gestation.

Dietary deficiency of iodine is an often unknown, unrecognized dietary issue, particularly in women of childbearing age and children.
Effects of maternal vitamin B₁₂ supplementation on early infant neurocognitive outcomes: a randomized controlled clinical trial

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Objectives: To report the effects of maternal B₁₂ supplementation on cognitive development in infants at 9 months of age on the Bayley Scales of Infant Development.

Methods: One hundred and eighty-three pregnant women received vitamin B₁₂, and 183 received placebo. The 9-month development score was available in 178 infants. There were no significant differences in maternal sociodemographic characteristics and baseline biochemical measures between infants who underwent developmental evaluation and infants who were not evaluated. There were no significant differences in any of the subscales of developmental scales between infants born to mothers who received B₁₂ supplementation (n = 78) versus placebo (n = 100). On multiple regression analysis, elevated maternal total homocysteine (tHcy) levels adjusted for major covariates were significantly negatively associated with expressive language, and in the third trimester of pregnancy with expressive language and fine motor domains.

Conclusions: In pregnant women with elevated tHcy levels and/or B₁₂ deficiencies, it may be worthwhile to study the impact of longer-term maternal supplementation on infant cognitive outcomes.

Comments: Micronutrients may play an important role in the developing brain of a child, but the debate on the measurable effects of micronutrients supplements at early age is still open.

For the first time, a randomized controlled clinical trial was performed with pregnant Indian women to investigate the impact of maternal vitamin B₁₂ supplementation on mental development in infants at 9 months of age. The results obtained are inconclusive because of the absence of a significant association between vitamin B₁₂ intakes of pregnant women and infants’ cognitive function, but lower expressive language and motor scores were found in mothers with high tHcy levels, which are considered biomarkers of functional deficiency of different vitamin B₁₂.

Further studies should be performed to investigate the impact of micronutrient supplementation during pregnancy on cognitive function of their children. In this field, it is critical to have a number large enough to get adequate statistical power and a precise functional outcome.
Impact of prenatal exposure to cadmium on cognitive development at preschool age and the importance of selenium and iodine

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Objectives: We aimed to assess the prenatal impact of cadmium, selenium, and iodine on children’s neurodevelopment at 4 years of age in 575 mother-child pairs from a prospectively followed cohort.

Methods: Exposure to cadmium, selenium, and iodine was assessed by concentrations in the mother’s urine during pregnancy (median 13 weeks). Validated scales of abilities were used to assess children’s general cognitive scores and 7 different subscales.

Results: In multivariable-adjusted regression analysis, elevated urinary cadmium concentrations were inversely associated with children’s general cognitive scores (mean change: –6.1 points [95% CI: –12, –0.33] per doubling of urinary cadmium). Stratifying by smoking status, the association was restricted to smokers. Urinary selenium was positively associated with children’s general cognitive scores, although the association was not statistically significant. Urinary iodine was not associated with children’s general cognitive scores.

Conclusion: Cadmium may adversely affect neurodevelopment, and the role of smoking deserves further studies.

Comments: The objective of this observational study was to evaluate the prenatal influence of cadmium, selenium, and iodine on cognitive development of Greek children at 4 years of age. The results suggest that higher exposure levels of cadmium in pregnant mothers may impair the cognitive function of children of preschool age. The negative association was particularly evident for the children of smoking mothers. Quite surprisingly, no association of mothers’ urinary iodine concentrations and their children’s cognitive abilities was found.

The article is of interest due to the apparent inconsistency with the previous paper on the role of iodine in pregnancy towards later child development and the major effect of cadmium, as observed in other circumstances also for lead and aluminum. While it is sometimes difficult to disentangle the role of single micronutrients, the paper suggests the need to protect the environment and the food chain in pregnancy from potentially dangerous trace elements and avoiding smoking.

Overall Commentary

The role of micronutrients in pregnancy, either positive or negative, is always considered for the development of children. While there is a recognized positive value for few nutrients (such as iron and iodine, or vitamins of the B group), most trace elements are not favorable, and the increasing concern for the negative effect of pollution on child development is partly ascribed to the excess of these components in the maternal diet during pregnancy and lactation.
Feeding the brain and nurturing the mind: linking nutrition and the gut microbiota to brain development

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Perspective: Since the human gut contains a microbial community composed of tens of trillions of organisms that normally assemble during the first 2–3 years of postnatal life, the authors propose that brain development needs to be viewed in the context of the developmental biology of this “microbial organ” and its capacity to metabolize the various diets we consume. Accordingly, the persistent cognitive abnormalities seen in children with undernutrition may be related in part to their persistent gut microbiota immaturity. Indeed, specific regions of the brain that normally exhibit persistent juvenile patterns of gene expression and are involved in various higher cognitive functions, such as the brain’s default mode network, may be particularly vulnerable to the effects of microbiota immaturity in undernourished children. Moreover, understanding the interrelationships between microbiota and brain metabolism in childhood undernutrition could also provide insights about responses to injury seen in adults.

Comments: A current topic that we have decided to include in this chapter concerns the microbiome. Findings from previous studies have clearly shown the impact of a healthy commensal gut microbiota on normal neurocognitive development. It is increasingly accepted that perturbations on normal gut microbiota may determine neurological abnormalities associated with undernutrition because of several pathways that are involved in the connection between microbial gut colonization and neural circuits. The authors tried to test these hypotheses by approaches using gnotobiotic animals that offer a way to evaluate the impact of gut microbiota from infant and children on brain metabolism, gene expression, and food biotransformation. The authors wrote, “we humans live in a microbe-dominated planet,” so feeding our gut to ensure neurocognitive development should help the ongoing evolution of our species.
Fetal, neonatal, and infant microbiome: perturbations and subsequent effects on brain development and behaviour

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Review: The human gastrointestinal tract acts like a repository of diverse and complex community of microbes, termed “gut microbiota,” that normally assemble during the first postnatal years of life. This evolution-driven process has been shown to contribute to the developmental programming of many tissues and functions of the body, with the first being the development and function of the immune system. The actions of the gut microbiota have much wider effects on the body structure and functions than originally believed, going up to the modulation of brain development and behavior. The gut microbiota may greatly impact on brain development, and disturbances in the assembly and maturation of the gut microbiota may have a long-lasting influence on the development of the overall processes of intelligence, including motor, social, and cognitive functions. Finally, a more complex metabolic link may connect microbiota and the developing brain.

Comments

This review considered recent research on the relationships of microbiome with neurodevelopment. Inadequate colonization during the early stages of life may increase susceptibility to a variety of several adverse metabolic or immune outcomes and atypical motor activity, socioemotional development, and cognitive functions in later life. Several factors that influence the assembly of the infant gut microbiota may interfere with brain development, such as mode of delivery (vaginal or caesarean delivery), infant feeding practices (breastfeeding or diet-formula feeding), use of antibiotics, and environmental factors. Moreover, maternal stress, gestational age, genetics, and infections may affect the complex community of microbes in an infant’s gut. The investigators also assessed the role of the metabolic demand of gut microbiota during brain growth, thus being in agreement with the previous paper.

The infant microbiome: implications for infant health and neurocognitive development

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The authors provide a brief overview of the microbiome and the “microbiome-gut-brain axis,” while discussing factors known to affect the composition of the infant microbiome, such as mode of delivery, antibiotic exposure, infant-feeding patterns, and present research priorities for nursing science, and clinical implications for infant health and neurocognitive development. Accordingly, the gut microbiome influences the neural pathways, playing an important role in infant development. Several factors influence colonization of the infant gut microbiome. Because of such an extensive physiological influence, infant microbial colonization patterns have the potential to impact physical and neurocognitive development and life-course disease risk.
Comments

This article briefly reviews the “microbiome-gut-brain axis” and the factors that influence microbiome composition of infants during the first years of life. It is widely accepted that gut microbiota play an important role on the brain’s regulation, but it has only been clarified in the last years that there are 3 bidirectional pathways (immunological, endocrine, and neural) connecting the brain and gut microbiome. Human studies have shown an association between autism, a neurodevelopmental disorder, and abnormal gut microbiome composition. During early life, it is very important to understand the patterns of gut microbial colonization and the mechanisms by which they may influence the psycho-neuro-immunological pathways to improve the life quality of infants and children and to maintain health throughout the lifespan.

Overall Commentary

The microbiome represents the last and promising frontier of the links between diet and development. A lot of descriptive biology, biochemistry, physiology, and pathophysiology has been described during the last 15 years, but we are still waiting for microbiome-based interventions able to reverse disorders and functions of organs out of the gastrointestinal tract and the gut, the natural residence of the microbiome. So, until this happens, we lack the cause-effect relationship required to confirm the role of microbiome in brain development and function and in health and disease.

Miscellanea

Diet-induced changes in iron and n-3 fatty acid status and associations with cognitive performance in 8–11-year-old Danish children: secondary analyses of the Optimal Well-Being, Development and Health for Danish Children through a Healthy New Nordic Diet School Meal Study

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Br J Nutr 2015;114:1623–1637

Objectives: The authors investigated whether the Healthy New Nordic Diet (OPUS) School Meal Study intervention influenced n-3 LCPUFA and iron status and, in turn, also the cognitive performance.

Methods: The study design was a cluster-randomized cross-over trial comparing school meals with packed lunch (control). At baseline and after each treatment, the main biomarkers of the iron and fatty acid status were measured together with some performance tests.

Results: The intervention improved school performance, reading comprehension, and n-3 LCPUFA status, but it did not affect serum ferritin or Hb. Low iron stores at baseline were associated with poorer school performance in girls, but with better reading comprehension in both boys and girls. Both the baseline and the intervention-induced increase in n-3 LCPUFA status were positively as-
associated with school performance, and potentially explain approximately 20% of the intervention effect.

**Conclusions:** These exploratory associations indicate that increased fish intake might explain some of the increase in reading performance and inattention in the study.

**Comments**

This cluster-randomized cross-over trial compared 3 months of meal intervention based on the Healthy New Nordic Diet with control meals where children continued to consume their routine lunch. The major dietary difference between these 2 groups was an increased fish intake.

The study deserves attention for its novelty (n-3 and iron are considered together, within the new Nordic Diet). In general, mixed findings were observed, with a complexity of interpretations. LCPUFA confirmed in general a positive role in school performance, and a poor iron status at baseline with a less efficient performance. The final consideration that fish does not contain only iron and LCPUFA but several other nutrients potentially associated with cognition, indicates a new way to look at the effects of these nutrients within a realistic dietary composition of a specific dietary pattern.

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**The long term impact of micronutrient supplementation during infancy on cognition and executive function performance in pre-school children**

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**Objectives:** To investigate the long-term cognitive and social-emotional effects of multiple micronutrient supplementation compared with iron supplementation alone, administered during infancy.

**Methods:** The study was a follow-up to an initial randomized, double-blind controlled trial in 2010 where 902 infants, 6–17 months, were equally randomized to either iron or multiple micronutrients (MMN), including zinc, for 6 months. In 2012, a subsample from the original cohort was randomly assessed for major cognitive abilities (intelligence, working memory, inhibition, and executive function). The tests showed no significant differences between the supplementation groups, though girls displayed higher scores than boys in some subscales, with boys scoring higher in some behavioral tests.

**Conclusions:** The results suggest that MMN supplementation has no long-term additional effects on cognitive function compared with iron supplementation alone.

**Comments**

Previously, most studies had evaluated the role of micronutrients on cognitive development of infants or children at school age, but only few trials had been performed in children in the preschool age. What this randomized, double-blind controlled trial adds is the assessment in this age group.

The results showed no significant differences between the 2 groups on cognitive function, even if girls had higher verbal IQ and social competency scores than boys. Moreover, boys had higher problem behavior scores than girls. These results remain inconclusive and show the difficulty of reaching conclusions on the practice of giving micronutrient supplementation during infancy.
Overall Commentary
Two different studies were examined, the first within the context of the model of a Nordic European diet and the second to assess the effects of micronutrient supplementations in children of a South American country, far from Europe. Different settings, different populations, and one suggestion that, even for brain and brain function, whole diets and whole foods should be prominent for the health of infants and children, making the concept of “sustainability” at the first place of diet.
Nutrition and Growth in Chronic Disease

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Growth failure (wasting and stunting) is common in many children with chronic disorders. These include, but are not limited to, inflammatory bowel disease (IBD), especially those with Crohn’s disease (CD), cystic fibrosis (CF), chronic kidney diseases (CKD), and juvenile idiopathic arthritis (JIA). Poor growth may lead to short stature and a reduction in adult height as seen in a subset of these patients. Suboptimal nutrition, prolonged use of glucocorticoids (GC), metabolic derangements, and chronic inflammation contribute to the underlying pathophysiology of growth failure. All these factors lead to a continuum of abnormalities in the systemic growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis, including relative GH insufficiency, GH/IGF-1 resistance due to impairment of IGF-binding proteins, downregulation of GH/IGF receptors, and/or impairment of local GH and IGF-1 signaling pathways. Targeting the inflammatory process aggressively using immunomodulators (e.g., azathioprine and methotrexate) and biologic therapy (e.g., anti-TNF drugs), minimizing the use of systemic GC, and optimizing nutrition may be associated with improvement in markers of the GH-IGF axis and are essential for ensuring normal growth and pubertal development. However, in spite of the advances in contemporary care of these diseases, many children with these conditions continue to grow slowly, and improvement in disease activity does not seem to normalize linear growth completely.
Key articles reviewed for this chapter

Inflammatory Bowel Disease

Food intake adequacy in children and adolescents with inflammatory bowel disease

Overweight and obesity in children with newly diagnosed inflammatory bowel disease

Extensive modulation of the fecal metagenome in children with Crohn’s disease during exclusive enteral nutrition
*Am J Gastroenterol* 2015;110:1718–1729

Cystic Fibrosis

Comparing the use of Centers for Disease Control and Prevention and World Health Organization growth charts in children with cystic fibrosis through 2 years of age
Zhang Z, Shoff SM, Lai HJ
*J Pediatr* 2015;167:1089–1095

Comparison of WHO and CDC growth charts in predicting pulmonary outcomes in cystic fibrosis
Machogu E, Cao Y, Miller T, Simpson P, Levy H, Quintero D, Goday PS

Early life growth trajectories in cystic fibrosis are associated with pulmonary function at age 6 years
Sanders DB, Fink A, Mayer-Hamblett N, Schechter MS, Sawicki GS, Rosenfeld M, Flume PA, Morgan WJ
*J Pediatr* 2015;167:1081–1088.e1

Evidence for a cystic fibrosis enteropathy
Adriaanse MPM, van der Sande LJTM, van den Neucker AM, Menheere PPCA, Dompeling E, Buurman WA, Vreugdenhil ACE

Nutritional status improved in cystic fibrosis patients with the G551D mutation after treatment with ivacaftor
Borowitz D, Lubarsky B, Wilschanski M, Munck A, Gelfond D, Bodewes F, Schwarzenberg SJ
Chronic Renal Failure

Long-term growth hormone treatment in short children with CKD does not accelerate decline of renal function: results from the KIGS registry and ESCAPE trial
Mehls O, Lindberg A, Haffner D, Schaefer F, Wühl E; German KIGS Board; ESCAPE Trial Group

Considerable variations in growth hormone policy and prescription in paediatric end-stage renal disease across European countries – a report from the ESPN/ERA-EDTA registry
Nephrol Dial Transplant 2016;31:609–619

Juvenile Idiopathic Arthritis

Growth in children and adolescents with juvenile idiopathic arthritis over 2 years of treatment with etanercept: results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study
Kearsley-Fleet L, Hyrich KL, Davies R, Lunt M, Southwood TR; British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study
Rheumatology 2015;54:12791285

Inflammatory Bowel Disease

Food intake adequacy in children and adolescents with inflammatory bowel disease
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Aims: The study evaluated food intake of a group of 68 children and adolescents with IBD, of whom 57 had CD.

Methods: In this cross-sectional study, the investigators performed a thorough evaluation of nutritional status (anthropometry, laboratory, and 3-day food intake record) and disease activity in 68 children and adolescents with IBD (57 with CD). Furthermore, the food intake of the children in
the IBD group was compared with the intakes of healthy children from the National Nutritional Survey and recommended daily allowances (RDA).

**Results:** Nutritional status was altogether fairly good, with only 10% of the subjects undernourished (BMI z score less than –2 SD); 3 children were stunted and only 1 was overweight. The most frequent nutritional deficiency was anemia (51%). The second most frequent nutritional deficiencies were of vitamin D (25%) and zinc (17%). Poor intake (<80% RDA) was recorded for carbohydrates (CHO) and most minerals and micronutrients, but was notably poor for calcium, magnesium, vitamin A, vitamin E, and fiber. Excessive intake (>150% RDA and in some even >200% RDA) was recorded for protein and most water-soluble vitamins.

There were significant differences in the reported intakes of the patients with IBD when compared to RDA and the National Nutritional Survey for almost all dietary components. Compared to RDA, the intake of patients with IBD was significantly poor for carbohydrates (75%, \( p = 0.016 \)), calcium (49%, \( p < 0.05 \)), magnesium (76%, \( p < 0.05 \)), vitamin A (72%, \( p < 0.05 \)), vitamin E (57%, \( p < 0.05 \)), and fiber (44%, \( p < 0.05 \)), and higher for protein (175%, \( p < 0.05 \)), iron (112%, \( p < 0.05 \)), and water-soluble vitamins (118–189%, \( p < 0.05 \)). Compared with the intakes of healthy Israeli children from the National Nutritional Survey, the intake of the IBD group was lower for calories (78%, \( p = 0.012 \)), carbohydrates (61%, \( p < 0.05 \)), magnesium (67%, \( p < 0.05 \)), vitamin C (34%, \( p < 0.05 \)), and fiber (54%, \( p < 0.05 \)), and high for B12 (141%, \( p < 0.05 \)). Of the 68 subjects, 50 ate ordinary diets, 7 children were on exclusive enteral nutrition (EEN), and 11 consumed regular food with different polymeric formula supplements. Compared to children without supplements, children on EEN and nutritional supplements (18/68) had significantly better intakes of energy (1,870 ± 755 vs. 2,267 ± 432, \( p < 0.05 \)), carbohydrates (223 ± 97 vs. 292 ± 99, \( p < 0.05 \)), and all minerals and micronutrients \( p < 0.05 \). Dietary intake was not different by disease activity (remission or relapse) or nutritional status.

**Conclusions:** In this study, undernutrition and short stature were not prevalent, but micronutrient deficiencies including iron, zinc, and vitamin D were common. The study showed that children and adolescents with IBD have peculiar food intake patterns, as some macro- and micronutrients were consumed in excess while others were exceedingly deficient in their diets. Children with IBD consuming a regular diet only had poor intake of energy, minerals, and vitamins, while the intake of children taking nutritional supplements was significantly better, especially with regard to minerals and fat-soluble vitamins. There were significant divergences in the intake of children with IBD when compared to RDA or healthy Israeli children, raising the question of what is the appropriate comparison/control group for these children.

**Comments** The usual convention in nutritional studies is to use an age- and gender-matched healthy control group, but is the intake of this control group appropriate and is it in agreement with RDA? And if not, what is the adequate comparison group? Ideally, the appropriateness of nutrient intake should be evaluated by the expected outcome: growth, biological parameters such as body composition, and sometimes nutrient blood levels. Since we do not use such parameters in the regular clinical setting and in short-term studies, we have to continue to use healthy controls for reference, while acknowledging that they are not necessarily always the perfect match.
Overweight and obesity in children with newly diagnosed inflammatory bowel disease

Pituch-Zdanowska A1, Banaszkiewicz A1, Dziekiewicz M1, Łazowska-Przorek I1, Gawronska A1, Kowalska-Duplaga K2, Iwanczak B3, Klicewicz B4, Grzybowska-Chlebowczyk U5, Walkowiak J4, Albrecht P1

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Aims: The study reported overweight and obesity rates among children with IBD at the time of diagnosis.

Methods: This retrospective study reported the anthropometry data of children and adolescents with newly diagnosed IBD at 5 academic institutions (Warsaw, Poznan, Wroclaw, Katowice, and Cracow) in Poland from 2005 to 2013. BMI categories and corresponding percentiles were as follows: ≤5th percentile, underweight; 5th–84th percentile, normal weight; ≥85th percentile, overweight; ≥95th percentile, obesity. Percentiles were evaluated using the BMI-for-age and gender percentiles charts according to the World Health Organization (WHO).

Results: The study included 675 patients, 368 with CD and 307 with ulcerative colitis (UC). Overall, 8.4% of the IBD population was overweight and obese, 4.3% in children with CD and 13.4% in patients with UC. The risk of overweight and obesity decreased with an increase in disease activity index (OR = 0.5342, p = 0.0012) for both diseases. CD patients with severe disease were at the lowest risk of being overweight/obese.

Conclusions: Overall, the prevalence of children with excess body weight with IBD was 8.4% compared to a prevalence of 20% in the population of healthy children in Poland. The incidence of overweight and obesity in IBD patients could be, therefore, a mirror of the incidence of overweight and obesity in the general population.

Comments

Nutritional status in children and adolescents with IBD is affected at several levels. Undernutrition, growth faltering/short stature, specific micronutrient deficiencies, altered body composition, and even overweight and obesity have been reported in both children and adults. The pathophysiology of these disturbances is multifactorial and includes poor food intake, nutrients’ malabsorption, increased losses, and increased needs associated with inflammation. These are augmented by disturbances of the GH/IGF axis and the use of drugs such as corticosteroids, antacids, laxatives, and nonsteroidal anti-inflammatory drugs. It seems that the prevalence of both under-and overnutrition in children and adolescents with IBD has shifted in the last years. Growth failure was present in 13–33% of patients at diagnosis and 10–29% at follow-up in studies published before 2000, but only 9.5% at diagnosis and 6.9–27% at follow-up among unselected patients with CD in studies published after 2005 [1]. However, despite improved weight and height, micronutrient status of children and adolescents with IBD is still precarious as reported in this study by Hartman et al. Furthermore, minerals and micronutrient intake was significantly poor in children on a regular diet, without any supplements. The study is a reminder that good weight and appropriate height are not guaranties of appropriate nutrient intake or micronutrient status.
Recent data also noted the presence of overweight and obesity, unknown or seldomly reported before 2000 in patients with IBD. The reported prevalence of overweight and obesity in newly diagnosed American children with IBD was 10% in CD to 20–30% in UC and even higher in adults [2]. In Scotland, Steed et al. [3] found that 18% of the IBD population was obese. The Polish study presented here found a lower prevalence rate compared to what has been reported in previous studies, probably a result of geographical variation in the incidence of overweight and obesity in the general population. Unfortunately, being overweight or obese does not make the disease less severe or easier to treat. On the contrary, the diagnosis may be delayed in overweight children, and obesity and overweight represent additional morbidity burdens for children with IBD.

Extensive modulation of the fecal metagenome in children with Crohn’s disease during exclusive enteral nutrition

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Aims: The study investigated the relationship of pediatric CD microbiota (taxonomic profile and genetic functional capacity) with intestinal inflammatory markers and changes before, during, and after induction treatment with EEN.

Methods: At most, 5 serial fecal samples were collected per patient from 23 children with active CD (11 newly diagnosed). The first sample was collected before or within 6 days of EEN initiation, 2 during EEN (at 16 and 32 days), and 1 close to the end of treatment. A final sample was collected when patients returned to habitual diet (at 63 days after EEN). In addition, 2 fecal samples were collected, at least 2 months apart, from 21 healthy children with no known family history of inflammatory bowel disease as a control group. Microbiota composition and functional capacity were characterized using sequencing of the 16S rRNA gene markers (genera, operational taxonomic unit [OTU], and oligotypes) and shotgun metagenomics (indicative of microbiota genetic functional capacity).

Results: Gut microbiota richness and evenness, was higher in controls than CD children prior to EEN (controls vs. CD: 10.23 vs. 8.00; \( p = 0.006 \)). The reduction in microbiota diversity associated with CD was similar either by OTU or genus analysis. In total, 36 genera out of 84 (43%) tested differed significantly between CD children and controls. The variability of the OTU community structure between samples was higher for CD children than healthy controls (CD vs. controls: 0.5848 vs. 0.4868; \( p < 0.001 \)). An association between age and genus community structure was observed for controls (\( p = 0.033 \)) but not CD children.
During EEN, diversity decreased at the genus level ($p = 0.037$). This became apparent even after 15 days on EEN with a minimum diversity observed by 30 days. There was a slight recovery toward the end of EEN and complete recovery to pretreatment levels when patients returned to habitual diet.

Twenty-six genera significantly correlated with calprotectin in CD children: both strongly positive and negative. Overall, OTUs predicted 78% of the variation in fecal calprotectin concentration. Genetic functional capacity using shotgun metagenomics was also different. Samples from CD patients showed more ubiquinone and lipopolysaccharide biosynthesis and the twin-arginine translocation system, whereas fatty acid biosynthesis and sulfur reduction were overrepresented in controls. Unlike relationships observed with taxa abundance, there were no significant correlations between calprotectin and relative abundance of functional modules.

**Conclusions:** The gut microbiota of CD children presented lower taxonomic diversity per individual, but higher variation between individuals perhaps attributed to variations in disease behavior. However, despite lower taxonomic bacterial diversity, a higher level of genetic functional diversity was associated with the CD microbiota prior to EEN treatment. This diverse microbial functional capacity tended to decrease during EEN to levels similar to healthy controls. These data suggest a high degree of functional redundancy, with multiple species performing similar roles in healthy children, which may be important in maintaining gut health. In active CD, this functional redundancy may be lost and then restored during EEN.

**Comments**

EEN is the first-line therapy recommended for induction of remission in children with CD. Meta-analysis of pediatric studies which have compared the effect of EEN with other treatments have shown that EEN has equivalent efficacy to corticosteroids, inducing remission in up to 80% of patients with active disease. The mechanism by which EEN induces remission has been a major topic of interest. Proposed mechanisms include direct anti-inflammatory effects, improved epithelial barrier function, and modulation of the gut microbiota. Reduced diversity and richness of the gut microbiota have been well documented in IBD patients, a condition referred as dysbiosis. Moreover, the accumulation of certain pathobionts has been reported in both patients with IBD and animal models of IBD. Several studies have investigated the effect of EEN on the gut microbiota of CD patients. Most reported on loss of diversity and richness of gut microbiota before the start of EEN and restoration of the diversity of the microbiota in CD patients to that observed in controls [4]. Furthermore, Leach et al. [5] also reported a significant and sustained EEN effect on intestinal bacterial composition and the association between the Bacteroides-Prevotella group and reduced disease activity. Kaakoush et al. [6] reported of a decrease in number of OTUs and microbial diversity in CD patients. Significantly, the number of OTU decreased dramatically upon starting EEN and this corresponded with CD remission. Recurrence of CD corresponded with an increase in OTUs. Recolonization of patients with specific microbial taxa belonging to 6 Firmicutes families was also clearly correlated with disease recurrence in their patients [6].

Using bacterial 16S rRNA genes targeting and shotgun metagenomics, Quince et al. characterized microbial community structure and genetic functional capacity in fecal samples from 23 children with active CD and 21 healthy controls. The study complements the data published earlier by Gerasimidis et al. [7]. The previous study evaluated the quantitative changes in selected bacterial groups and metabolites formerly implicated in CD. The present study investigated the association of the pediatric CD microbiota with intestinal inflammatory markers (calprotectin) and changes before, during, and after induction treatment with EEN.
Bacterial taxa were both more and less abundant in children with CD before the start of EEN. Numerous OTUs and species were less abundant in CD children, including classic commensals such as *Faecalibacterium* spp. and *Bifidobacterium* spp., but some bacteria were more prevalent in CD, including *Escherichia coli/Shigella* spp., *Streptococcus* spp., *Peptostreptococcus* spp., and *Atopobium* spp. Paradoxically, EEN induced a major reduction in the relative abundance of several species, some of which were already at lower abundance compared with controls, shifting the microbiota to an even more "dysbiotic" state. EEN treatment also induced changes in functional modules. A subset of taxa was associated with a sizable amount of the variation in fecal calprotectin. Among them, *Bifidobacterium* spp. had the strongest negative and *Atopobium* spp. the strongest positive association with calprotectin in multivariate regression analysis. The observational design of this study did not allow for the establishment of a causative association between these findings and their role in CD pathogenesis, or to hypothesize on a mechanism of therapeutic action of EEN based on the changes in the gut microbiota. Whether the clinical efficacy of EEN is related to its beneficial effects on gut microbes remains to be explored.

**Cystic Fibrosis**

**Comparing the use of Centers for Disease Control and Prevention and World Health Organization growth charts in children with cystic fibrosis through 2 years of age**

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**Aims:** Using WHO and Centers for Disease Control and Prevention (CDC) 2000 growth charts for children with CF aged 1–24 months, the study investigated: (1) the differences in weight and height status (i.e., weight-for-age percentile [WFAp], length-for-age percentile [LFAp], weight-for-length percentile [WFLp], and BMI percentile [BMIp]) on the 2 charts, (2) the prevalence of undernutrition as defined on the 2 growth curves, and (3) the WHO percentiles values equivalent to the 50th percentile of CDC BMI at 24 months.

**Methods:** z scores and percentile values were calculated using as reference the CDC’s 2000 growth charts and the WHO’s 2006 growth charts. A cutoff value of the 50th percentile of WFLp and BMIp was used to define underweight. Short stature was defined as LFAp less than the 5th percentile.

**Results:** The study cohort (n = 2,587) comprised 84% of children with CF born between 2003 and 2005 and reported in the 2008 US Cystic Fibrosis Foundation (CFF) Patient Registry.

*LFA Status by WHO and CDC Growth Charts.* In boys, the WHO LFAp was consistently below the CDC’s by an average of 8 percentiles in the first 2 years of life (WHO 13 ± 28 vs. CDC 21 ± 27 percentiles, p < 0.0001) and similar in girls. As a result, using WHO charts, more boys with CF were classified as short (LFAp <5th) compared with the CDC (WHO 35% vs. CDC 22%, p < 0.0001). Overall, 14% of the study population had short stature by WHO but normal height on CDC charts.
**WFA Status by WHO and CDC Growth Charts.** In boys, the WHO WFAp was 9 percentiles lower than the CDC's prior to 6 months of age (WHO 7 ± 24 vs. CDC 16 ± 26 percentiles, \( p < 0.0001 \)), equal at 6–7 months of age, and then remained 14 percentiles higher from 8–24 months of age (WHO 32 ± 30 vs. CDC 18 ± 26th percentile, \( p < 0.0001 \)). Similar results were observed in girls.

**WFL Status by WHO and CDC Growth Charts.** No difference in WFLp was observed in boys between the WHO and CDC references prior to age 12 months (WHO 36 ± 30 vs. CDC 36 ± 31 percentiles). At 12–24 months of age, WHO WFLp was 11 percentiles higher than the CDC's (WHO 64 ± 28 vs. CDC 53 ± 30 percentiles, \( p < 0.0001 \)). Therefore, underweight prevalence defined by WHO WFLp <50th was similar to that defined by the CDC prior to 12 months of age, but at 12–24 months of age, underweight prevalence was WHO 35% vs. CDC 46% (\( p < 0.0001 \)). Among children 12–24 months of age, 28% were underweight on CDC charts, but appeared of normal weight when using WHO charts.

**WHO WFL and WHO BMI Status.** In boys, BMIp was 13 percentiles lower prior to 6 months of age (BMIp 16 ± 27 vs. WFLp 29 ± 30 percentiles, \( p < 0.0001 \)), similar at ages 6–12 months, and 8 percentiles higher at ages 12–24 months (BMIp 72 ± 28 vs. WFLp 64 ± 28 percentiles, \( p < 0.0001 \)), compared with WFLp. As a result, underweight prevalence based on WHO BMIp <50th was higher before 6 months of age (BMIp 80% vs. WFLp 67%, \( p < 0.0001 \)), similar at ages 6–12 months (BMIp 57% vs. WFLp 56%, \( p = 0.09 \)), and lower at ages 12–24 months (BMIp 28% vs. WFLp 35%, \( p < 0.0001 \)), compared with WFLp <50th. Similar results were observed in girls with CF.

**At 24 Months of Age.** When transitioning back to CDC charts at 24 months of age, 29% of children who were short on WHO charts appeared normal on CDC charts, 27% with WHO WFLp >50th were at CDC WFLp <50th, and 30% with WHO BMIp >50th were at CDC BMIp <50th. The 50th percentile CDC BMI was equivalent to the 70th percentile WHO BMI regardless of various statures.

**Conclusions:** The use of WHO and CDC growth charts in this CF population resulted in different prevalence rates in short stature and undernutrition in the first 2 years of life, which were higher for shortness and lower for underweight by WHO growth charts, compared with CDC charts. A larger discrepancy occurred during the second year, especially for the underweight classification. When switching from WHO charts to CDC charts at 2 years of age, about one-third of children with normal weight on WHO WFL charts will appear underweight on CDC charts.

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**Comparison of WHO and CDC growth charts in predicting pulmonary outcomes in cystic fibrosis**

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**Aims:** (1) Evaluation of the association between WFA and WFL at 2 years and the percent predicted forced expiratory volume in 1 s (FEV1%) at 6 years when using the WHO versus CDC percentiles, and (2) examination of the association between weight change from ages 2–6 years and maximum FEV1% at 6 years.

**Methods:** The study used data from a cohort of CF patients registered within the CFF Patient Registry, born between 2001 and 2004, and studied for at least 6 years. All had weight and height at 2 years of age and a valid spirometric examination between the ages of 6 and 8 years. The WFA and WFL percentiles on both the CDC and WHO charts were calculated and patients were categorized...
into 3 groups: <10th percentile, >10th but <50th percentile, and >50th percentile, based on their WFA and WFL status by both the CDC and WHO growth charts.

**Results:** Complete data were available for 1,155 patients, including weight and height at 2 and 6 years of age and a valid FEV1%, and were included in the analysis.

**WFL Percentiles on WHO and CDC Growth Charts at 2 Years.** WFL percentiles were significantly higher on the WHO growth charts compared with those on the CDC growth charts (median and IQR: WHO –64.8 [41.7–84.9], CDC –48.1 [23.7–75.7], p < 0.0001).

**CDC WFL 50th Percentile and Corresponding WHO WFL 50th Percentile.** WHO WFL 50th percentile corresponding to CDC WFL 50th percentile ranged from 55.6 to 65.2 percentiles for boys, whereas for girls it ranged from 53.2 to 70.2 percentiles. Of the 450 (39%) patients categorized as being WFL >10th but <50th percentile by CDC charts, 194 (43%) were categorized as being WFL >50th percentile on the WHO charts.

**FEV1% at 6–8 Years.** WHO WFL percentile at 2 years, total duration on antibiotics before their FEV1%, and a history of *Burkholderia cepacia* complex-positive culture were significant covariates of FEV1% at 6 years. A 1-U increase in WHO WFL percentiles at 2 years of age was associated with a 0.08% increase in FEV1% at 6 years.

**Comparison of FEV1% in Patients with WFL >50th Percentile.** The FEV1% at 6 years was lower for children on the WHO WFL 50th percentile at 2 years (n = 194) versus those who were on the 50th percentile on both the CDC and WHO (n = 564) growth charts (median and IQR: 103 [94–115] vs. 107 [96–117], p < 0.05). There was no difference in FEV1% by WFA percentiles.

**Weight Change between 2 and 6 Years of Age and FEV1% at 6 Years.** Patients whose WFA was <50th percentile at age 2 years but improved to the 50th percentile by age 6 years had a significantly higher FEV1% compared with patients who remained <50th percentile at both times (median and IQR: 107 [95–118] vs. 102 [91–112], p < 0.003). Patients whose WFA was at the 50th percentile at both 2 and 6 years of age had a significantly higher FEV1% compared with patients who were below the 50th percentile at both time periods (median and IQR: 109 [99–119] vs. 102 [91–112], p < 0.0001).

**Conclusions:** Switching from the CDC to WHO growth charts showed a shift to higher percentiles by WFL status at age 2 years on the 2006 WHO growth charts, giving the impression of a better nutritional status. However, children with WFL <50th percentile on the CDC growth charts but classified on the 50th percentile on the WHO standards had a lower FEV1% compared with children reaching a WFL 50% percentile on both charts. This suggests that if clinicians were to switch to using the WHO growth charts for monitoring growth from birth to 2 years, maintaining the 50th percentile recommendation by age 2 years, they may be targeting a lower weight and the implications would be a lower FEV1% at 6 years.

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**Early life growth trajectories in cystic fibrosis are associated with pulmonary function at age 6 years**

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**Aims:** The study reported early-life (up to 6 years) growth trajectories in children with CF and the relationship with FEV1 at age 6–7 years, as well as the timing of growth trajectories changes that affects the FEV1 at age 6–7 years

**Methods:** The study included data from children with CF born between 1994 and 2005, diagnosed before 2 years of age, and followed in the CFF Patient Registry through at least 7 years of age. The change in growth indices (WFL for ages 0–2 years and BMI for ages 2–6 years) were compared with mean FEV1% predicted at 6–7 years of age. Growth trajectories before 6 years of age were classified into the following mutually exclusive categories: annualized WFL-BMI always above the 50th percentile (i.e., always meeting the CFF goal), annualized WFL-BMI that increased >10 percentile points from the first year in the study to 6 years of age, annualized WFL-BMI that was stable (i.e., <10 percentile increase or decrease from the first year in the study to 6 years of age), or annualized WFL-BMI that decreased >10 percentile points from the first year in the study to 6 years of age.

**Results:** The cohort consisted of 6,805 eligible children with CF. Children with WFL-BMI always >50th percentile had the highest FEV1% predicted at 6–7 years of age. Those in whom WFL-BMI increased >10 percentile points had significantly lower FEV1% predicted than the subjects with annualized WFL-BMI always >50th percentile, but significantly higher than subjects with WFL-BMI that was stable or decreased >10 percentile points. Subjects with WFL-BMI that decreased >10 percentile points had the lowest FEV1% predicted; this difference was statistically significant in comparison with subjects with WFL-BMI always >50th percentile and WFL-BMI that increased >10 percentile points.

Children with WFL-BMI always >50th percentile had 101.8 (95% CI: 100.1, 103.5) FEV1% predicted at age 6–7 years. Children whose WFL-BMI increased >10 percentile points had 98.3 (95% CI: 96.6, 100.0) FEV1% predicted at age 6–7 years. Children with stable WFL-BMI had 94.4 (95% CI: 92.6, 96.2) FEV1% predicted at age 6–7 years, and children with WFL-BMI that decreased >10 percentile points had 92.9 (95% CI: 91.1, 94.8) FEV1% predicted at age 6–7 years.

**Conclusions:** The study demonstrates that in children with CF, individual growth trajectories in the first 6 years of life are associated with clinically meaningful differences in FEV1% predicted at age 6–7 years, supporting the CFF recommendations of maintaining WFL-BMI >50th percentile throughout childhood, as children who met this goal through age 6 years had the best FEV1% predicted at ages 6–7 years.

**Comments**

In 2008, the CFF Subcommittee on Growth and Nutrition published their recommendation that infants and toddlers diagnosed with CF should strive to attain WFL ≥50th percentile, based on the CDC growth curves [8]. These recommendations have been reaffirmed by 2 new guidelines published in 2016 by the European Society for Clinical Nutrition and Metabolism, European Society for Pediatric Gastroenterology, Hepatology and Nutrition, and European Cystic Fibrosis Society (ESPEN-ESPGHAN-ECFS) and the American CFF guidelines for preschoolers with CF [9, 10]. The maintenance of adequate nutritional status continues to be a primary concern for patients and physicians caring for CF patients. Many studies have been published since 2008, and these have shown that children who maintain above average growth in early childhood (WFLp or BMIp ≥50th) have the best chance to preserve good lung function into adulthood and have a survival advantage over those on lower growth percentiles. All the studies published before 2015 related pulmonary morbidity and survival to WFLp or BMIp based on CDC growth reference curves [11]. Since their publication in 2006, the WHO growth standards have been adopted by most countries and have been recommended by both the CDC and AAP for use in American children less than 2 years of age. As the 2 growth charts have been constructed based on growth data of 2 kinds of populations (WHO: breastfed healthy infants; CDC: compilation of nationally representative surveys data), it was obvious from the beginning that growth evaluation
using the 2 charts will give major differences in growth percentiles even in healthy children [12].

Since the WHO growth standards are now the recommended tool for tracking anthropometric growth in all children from birth to 2 years of age, it is necessary to establish how early growth patterns on WHO growth charts correlate with pulmonary function and survival into adulthood for children with CF.

The studies from both Zhang et al. and Machogu et al. showed significant divergences in growth status definition as about one-third of children who appeared to have good/appropriate growth on WHO curves were short and/or undernourished at the transition to CDC curves at 2 years of age, the curves that were previously used for nutritional status evaluation of children with CF and on which the current nutritional guidelines are based. The findings from these 2 studies have important implications for all children with CF and their physicians, but so far no definite answer. Is it enough to maintain WFLp or BMlp above the WHO’s 50th percentile? Does this growth trajectory confer the same pulmonary function and survival advantages as ≥50th percentile WFLp or BMlp on the CDC’s growth charts for children with CF?

So far, at 6 years, according to the data presented by Machogu et al., pulmonary function, based on FEV1% predicted, was significantly better in those attaining the 50th percentile WFL at 2 years of age on both the WHO and CDC curves, versus those that met the 50th percentile on the WHO curve but were below the 50th percentile on the CDC curve. The difference they identified at 6 years was not big, but we should pursue further longitudinal studies to better understand whether growth recommendations using the WHO standards may need to be increased to confer the same longer-term benefits that are seen with CDC-based growth recommendations.

Several studies have described the association between growth indices at age 2, 3, and 4 years and FEV1 later in life. Patients with a higher WFA percentage at 4 years of age had better FEV1 from ages 6 through 18 years, fewer pulmonary exacerbations, and better survival. However, assessments of growth were taken at only 1 time point; therefore, it is not known if growth change (improvement or worsening) or the timing of these changes is important or influences long-term morbidity or survival. Using the growth data from the CFF Patient Registry, Sanders et al. showed that children with WFL-BMI always at the >50th percentile from diagnosis to age 6 years had the highest mean FEV1% predicted at age 6–7 years. Among children with WFL-BMI <50th percentile at least 1 year before age 6 years, those whose WFL-BMI increased >10 percentile points by 6 years of age had higher FEV1 at age 6–7 years in comparison with subjects whose WFL-BMI was stable or decreased >10 percentile points. These results reaffirm the close relationship between lung health and nutritional state during early childhood, which may have lifelong effects. This is in keeping with current CFF guidelines and should encourage health providers to promote optimal nutrition frequently and consistently from the earliest age.
Evidence for a cystic fibrosis enteropathy

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Aims: Serum intestinal fatty acid-binding protein (I-FABP), a cytosolic protein exclusively present in the enterocytes of the intestine and released into circulation upon intestinal injury, was used as a marker of intestinal damage, and fecal calprotectin, a marker for neutrophil activation or degradation, was used to evaluate intestinal inflammation. Correlations between these quantitative enteropathy measures and disease characteristics of CF were used to investigate whether intestinal damage/inflammation represent a potential therapeutic target for improvement of nutritional status and preservation of lung function.

Methods: The study investigated 68 CF patients and 107 controls. Levels of serum I-FABP were retrospectively determined. Fecal calprotectin was prospectively studied. Nutritional status, lung function (FEV1), exocrine pancreatic insufficiency (EPI), CF-related diabetes (CFRD), and use of proton pump inhibitors (PPIs) were obtained from medical charts.

Results: Serum I-FABP levels were significantly elevated in CF patients (486 pg/mL [270–774]) compared with control subjects (228 pg/mL [147–349], p < 0.001). In children, serum I-FABP level correlated negatively with lung function (FEV1 r = –0.734, p < 0.05, n = 11), whereas no correlation was found in adult CF patients. Serum I-FABP levels did not differ between patients with or without CFRD, EPI, Pseudomonas aeruginosa colonization, malnutrition, or PPI use. There was no correlation between I-FABP level, pancreatic enzymes replacement therapy (PERT) dosage, CRP, and fecal calprotectin levels.

Fecal calprotectin levels were elevated above the cutoff level in 40 CF patients (93%) (524 μg/g [92–905]). There was a significant inverse correlation between fecal calprotectin and lung function in adult CF patients (FEV1 r = –0.484, p < 0.05; FVC r = –0.304, p = 0.207; FEV1/VCo2 r = –0.509, p < 0.05), but not in children. In children only, weight-for-height z score was positively correlated with fecal calprotectin (r = 0.531, p < 0.05). Calprotectin levels were significantly elevated in EPI patients, in patients with CFRD, and in patients using PPIs. Fecal calprotectin levels did not differ between patients with or without P. aeruginosa colonization or with dosage of PERT. No correlation was found between sputum and fecal calprotectin levels. Sputum calprotectin levels correlated with age (r = –0.472, p = 0.05).

Conclusions: This study demonstrates that both enterocyte damage and intestinal inflammation are present in CF patients. There was a significant inverse correlation between enterocyte damage and lung function in CF children, and between intestinal inflammation and lung function in CF adults. The observed enterocyte damage was not influenced by CF-related comorbidities or medication use, whereas intestinal inflammation was associated with EPI, CFRD, and PPI use. CF enteropathy can be proposed as a future target for therapeutic interventions in order to improve the general condition and preserve lung function in patients with CF.
The presence of pancreatic insufficiency, the high demands required to cover for chronic respiratory problems, and recurrent pulmonary infections were considered for a long time to be the main determinants for CF malnutrition and poor growth. However, in spite of appropriate PERT, food intake and good pulmonary care nutritional status in many children with CF still remains suboptimal. The study of Adriaanse et al. provides evidence of CF enteropathy, comprising enterocyte damage, reflected by the abnormal serum I-FABP levels and intestinal inflammation as shown by the high fecal calprotectin levels. A study by Flass et al. [13] showed that more than 70% of pancreatic insufficient CF patients had visible intestinal inflammatory lesions on capsule endoscopy. Furthermore, they reported increased intestinal permeability in CF patients and significant differences in the fecal microbiome at the phylum and genus levels. The underlying pathophysiology for the intestinal damage and inflammation is not fully understood, but is probably related to the more acidic intestinal pH due to the lack of endogenous buffering capacity due to pancreatic insufficiency, impaired functional integrity related to CFTR dysfunction within enterocytes, or injury from exogenous pancreatic enzymes. Additional factors are malnutrition, the medication used frequently in CF patients such as PPIs and antibiotics, and the changes in intestinal microbiome and bacterial overgrowth. Notably, the observed enterocyte damage correlated inversely with lung function in CF children, suggesting that intestinal enteropathy and pulmonary dysfunction are connected in CF. Different mechanisms were proposed to explain the observed negative correlation between the CF enteropathy and lung function. The intestinal damage/inflammation resulting in bacterial translocation potentially may enhance the pulmonary inflammation leading to a decline in lung function. Otherwise, intestinal alterations due to CFTR dysfunction may result in malnutrition with consistent respiratory muscle weakness and compromised innate lung defense. Further, impaired lung function may result in splanchnic hypoperfusion and intestinal hypoxia affecting the intestine. Taken together, this may contribute to intestinal inflammation and impairment and may explain the complex interrelationship between CF enteropathy and lung function.

Nutritional status improved in cystic fibrosis patients with the G551D mutation after treatment with ivacaftor

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**Aims:** Ivacaftor is an oral CFTR potentiator shown to increase the open probability of the CFTR channel. The study reported the effect on weight and BMI after 48 weeks of treatment in the phase 3 trials of ivacaftor.

**Methods:** The study used data from 2 international, multicenter, randomized, double-blind, placebo-controlled trials that evaluated ivacaftor (Kalydeco, VX-770; Vertex Pharmaceuticals Inc., Boston, MA, USA) in patients with a confirmed diagnosis of CF and at least one G551D-CFTR mutation. The primary end point of the study was the estimated mean change from baseline through week 48 in ppFEV1. Study visits occurred at day 15, week 8, and then every 8 weeks thereafter. At each study visit, weight and height were measured, in addition to other study-related activities.

**Results:** The 2 studies included 213 patients: 105 aged 6–20 years (mean age: 12 years) and 108 patients older than 20 years (mean age: 30 years). The mean change from baseline to week 48 in body weight was 4.9 kg in the ivacaftor group compared with 2.2 kg in the placebo group (treatment difference of 2.7 kg; 95% CI: 1.14–4.29; \( p = 0.0008 \)). The ivacaftor group had an increased WFA z score at week 48 of 0.29 compared with –0.06 in the placebo group (treatment effect 0.35; 95% CI: 0.202–0.508; \( p = 0.0001 \)). By week 48, the ivacaftor group had an increase in BMI z score of 0.26 compared with –0.13 in the placebo group (treatment effect 0.39; 95% CI: 0.213–0.573; \( p < 0.0001 \)). In the older patients, the mean change from baseline to week 48 in body weight was 2.7 kg in the ivacaftor group and –0.2 kg in the placebo group (treatment difference of 2.9 kg; 95% CI: 1.35–4.47; \( p = 0.0003 \)). By week 48, the ivacaftor group had a mean increase in BMI of 0.9 compared with –0.1 in the placebo group (treatment effect 1.0; 95% CI: 0.44–1.49; \( p = 0.0003 \)).

**Conclusion:** Treatment with the CFTR potentiator ivacaftor, which increases the ion transport function of the CFTR channel, results in improved weight gain and BMI in both children and adults relative to placebo.

**Comments**

Ivacaftor is a revolutionary treatment option for CF patients with gating mutations. It has been approved recently for the treatment of patients with CF aged 6 years or older with Gly551Asp-CFTR mutations. Ivacaftor (VX-770) is an orally bioavailable CFTR potentiator that increases the probability of CFTR channel opening in recombinant cells bearing the G551D gating mutation; it enhances chloride secretion while reducing excessive sodium and water reabsorption in cultured human CF bronchial epithelial cells carrying one G551D allele. By addressing the underlying protein defect, ivacaftor may help to maintain adequate airway hydration, and may be able to modify disease progression. Borowitz et al. as well as a previously published randomized controlled trial with ivacaftor reported statistically significant improvement in pulmonary function, weight, and CFTR activity (as determined by sweat chloride) in patients carrying a G551D-CFTR mutation on at least 1 allele [14–16]. The improvement of nutritional status on ivacaftor treatment may be the result of CFTR potentiation effect on respiratory epithelia, pancreatic acini, or intestinal mucosa, and improved pulmonary and intestinal function.

It is remarkable that z scores for BMI improved rapidly in the ivacaftor group over the first 8 weeks of treatment (with sustained improvements through 48 weeks) [15]. It seems unlikely that any agent given after 6 years of age could have a significant impact on pancreatic damage, which is thought to occur earlier in life. CF therapies that improve lung function, such as tobramycin and dornase alfa, did not lead to improvements in nutritional status in published studies. Taken together, this suggests that additional mechanisms may be contributing to the nutritional effects of ivacaftor. The discovery and confirmation of the pathways through which ivacaftor affects the nutritional status should be further pursued.
Long-term growth hormone treatment in short children with CKD does not accelerate decline of renal function: results from the KIGS registry and ESCAPE trial

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Aims: This article reports the evolution of renal function for up to 5 years in short children with CKD stages II–IV enrolled in 2 large clinical studies with and without concomitant recombinant human growth hormone (rhGH) treatment.

Methods: Participants. The authors reviewed the clinical data of 2,212 short children with CKD on conservative treatment, dialysis or transplantation from 1995 until January 2012 as part of the pharmacoepidemiologic survey known as KIGS® (Pfizer International Growth Database; Pfizer Health AB, Strängnäs, Sweden). KIGS is an international registry developed with the main objective of documenting the long-term outcome and safety of Genotropin™ (Pfizer Health AB). All patients received rhGH (Genotropin™) with a mean dose of 1 ± 0.33 IU/kg per week given by daily subcutaneous injections. The patients were subdivided into 3 groups according to primary renal disease, namely, glomerulopathies, renal hypodysplasia with or without reflux, and hereditary or other renal disorders. Control patients (n = 274) were chosen from children with CKD stages II–IV, participants in the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients) trial.

Methods. The annual decline in GFR was analyzed longitudinally for 5 years and cross-sectionally for up to 10 years. Estimated GFR (eGFR) was assessed by creatinine clearance. For the rhGH group, clinical and laboratory follow-up data were analyzed at the following time points: 1 year from start (±3 months), 2 years from start (±3 months), and yearly thereafter for up to 10 years. For control patients, yearly clinical and laboratory data (±3 months) were used for follow-up until the end of the fifth year.

Results: At baseline, patients started on rhGH treatment were significantly younger and had a lower mean standardized height and eGFR compared to the controls. Ninety-seven patients on continuous rhGH treatment and 113 non-rhGH-treated controls were followed longitudinally for at least 5 years. After 5 years the mean decline in eGFR from start was −5.8 ± 15.8 mL/min/1.73 m² in the KIGS patients and −8.6 ± 13.2 mL/min/1.73 m² in the controls (ESCAPE trial) (p = 0.17).

In multivariate regression analyses, in KIGS patients’ absolute height (R² = 0.0635; negative association) and eGFR at baseline (R² = 0.0578; negative association) best explained the variance (adjusted cumulative R² = 0.1213) in eGFR. Adding rhGH dose or growth velocity to the model did not further increase the percentage of explained variation. In the ESCAPE trial patients, absolute height (R² = 0.0608; negative association) and type of primary renal disorder, glomerulonephritis versus others, (negative association) best explained the variance (adjusted cumulative R² = 0.0946) in eGFR.

Conclusions: The investigation of the long-term effects of rhGH treatment on renal function in children with CKD showed that the decline in eGFR per year in rhGH-treated patients was rather small and did not exceed the decline in non-rhGH treated controls.
Considerable variations in growth hormone policy and prescription in paediatric end-stage renal disease across European countries – a report from the ESPN/ERA-EDTA registry

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Aims: The study described the variation in recombinant growth hormone (rGH) policies in pediatric patients with end-stage renal disease (ESRD) across Europe, using data from the ESPN/ERA-EDTA registry.

Methods: Cross-sectional data on the height of children on renal replacement therapy (RRT) were retrieved from the ESPN/ERA-EDTA registry. Anthropometric, clinical, and medication-related parameters were also collected.

To study the effect of actual rGH use, the authors calculated the percentage of patients with short stature that used rGH (yes/no) during 5 years of follow-up (2007–2012, whenever available). The authors compared national GH policies with actual use of rGH with the percentage of children with a short stature defined as height SDS of $-2$ or below.

Results: Policies in rGH Use. In 21 (75%) of 28 countries, rGH was reimbursed for children with CKD. Height SDS criteria for prescribing rGH varied between $-1.88$ and $-3$ SDS and/or a stable or decrease in height SDS (stable or decrease of $>0.25$ SDS in the previous year) and/or growth velocity ($>1$ SDS decrease in growth velocity).

Differences between Policies in Relation to Height SDS and Economic Indicators (Gross Domestic Product [GDP]). GDP was significantly higher in countries with rGH reimbursement, compared with countries without rGH reimbursement (17.0, $p = 0.01$). Mean height SDS (95% CI) was significantly higher in countries where rGH was reimbursed ($-1.80; 95\% \text{ CI: } -2.06 \text{ to } -1.53$) compared with countries where rGH was not reimbursed ($-2.34; 95\% \text{ CI: } -2.49 \text{ to } -2.18; p < 0.001$).

Effect of Age Limitation of rGH Prescription. Mean height SDS was significantly lower in countries that prescribed rGH under the age of 12 months (mean height SDS: $-1.98$) versus those that allowed prescription from 12–24 months (mean height SDS: $-1.93$) and from 24 months and older ($-1.52$ SDS, $p < 0.001$). Mean final height SDS was 0.63 SDS lower ($p < 0.001$) in countries that prescribed rGH in children over 18 years when compared with countries that were not allowed to prescribe rGH in children over 18 years of age.
**Height Criteria.** Mean height SDS tended to be higher in countries that were allowed to prescribe rGH based on either height SDS or a stable/decrease in growth velocity, compared to countries that prescribed rGH based on both criteria only.

**CKD Stage.** Height SDS was significantly higher in countries that were allowed to prescribe rGH in CKD stages 4–5 ($-1.48$; $95\%$ CI: $-1.85$ to $-1.10$) or stages 3–5 ($-1.33$; $95\%$ CI: $-1.51$ to $-1.14$) when compared with countries where physicians were allowed to prescribe rGH from CKD stage 1 onwards ($-1.94$; $95\%$ CI: $-2.58$ to $-1.29$).

**Actual Provided Care.** The percentage of rGH use between 2007 and 2011 was available for 13 of the 28 countries. A total of 45.9% of dialysis and 38.9% of transplant patients had short stature (height SDS less than $-2$) and would therefore be eligible for receiving rGH. In all countries, the actual use of rGH was lower than the number of children eligible for rGH: only 26.0% of short children on dialysis and 8.9% of short transplanted patients actually received rGH. The factors that affected the decision to use rGH treatment in children with short stature were: patients refused treatment, improving nutritional intake and metabolic bone disease, suboptimal dialysis adequacy, and patients with severe uncontrolled hyperparathyroidism. There was no association between the percentage of rGH use and final height in both dialysis ($\beta = 0.02$, $p = 0.28$) and transplantation ($\beta = 0.03$, $p = 0.25$).

**Conclusions:** The study showed a considerable variation in GH policies across 28 countries in Europe. Total absence of reimbursement of rGH was associated with a more compromised final stature in children with ESRD. However, even in countries with rGH reimbursement, the actual rGH prescription in patients who were eligible for rGH was remarkably low and differed substantially among countries.

**Comments**

Short stature is highly prevalent in children with CKD whether on RRT or after renal transplant. The degree of renal dysfunction correlates with the degree of growth failure and children with ESRD on chronic dialysis have the most profound growth faltering. The Chronic Kidney Disease in Children Study (CKiD, a US registry of children with a GFR <75 mL/min/1.73 m$^2$) identified a fall in HtSDS of 0.12–0.16 for each decline of 10 mL/min/1.73 m$^2$ GFR. Infants born with CKD demonstrate more profound height deficits than those children who acquired CKD later in childhood [17]. In addition, registry studies have shown that children with CKD have progressive growth failure over time independent of renal function. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2006 Annual Report states that the heights of children are $-1.64$ SDS below the mean at the time chronic dialysis is initiated, $-1.71$ SDS after 1 year of dialysis, and $-1.84$ SDS after 2 years of dialysis [18]. The recent report published by the ESPN/ERA-EDTA registry found that 45% of children with ESRD who started dialysis before 19 years of age had a final adult height that was less than the third percentile for normal age- and sex-matched controls [19].

Growth failure in CKD has been associated with both increased morbidity and mortality. For every decrease in height SDS, mortality has been reported to increase by 14% and the more profound the deficit, the higher the mortality [20]. Children with growth failure at the time of initiation of dialysis have had increased hospitalizations and missed days of school as well as poorer school performance, lower self-esteem, and difficulties and social adaptation problems as adults [21].

There is evidence that height in children with CKD has substantially improved during the last decades. This is likely to be due to better understanding and management of the complications of CKD such as nutrition (particularly in infants), anemia, acidosis, bone disease, improvement in dialysis machines and programs, and the use of rhGH [22].
The perturbation in the GH axis in uremic children is characterized by insensitivity to GH and has been attributed to impaired GH signaling through the JAK2/STAT5 pathway, resulting in reduced transcription of IGF-1 [23]. Supraphysiologic doses of rhGH have been successful in overcoming the resistance to GH observed in children with CKD. A recent meta-analysis of 5 randomized controlled trials in children using rhGH after transplantation showed significant improvements in growth in those with poor growth without increases in rejection rates after 1 year of use [24]. A Cochrane Review analysis that included 16 studies (809 children) confirmed the effectiveness and safety of rhGH in children with CKD (8 studies) and pediatric transplant recipients (8/16) [25]. Treatment with rhGH (28 IU/m²/week) compared with placebo or no specific therapy resulted in a significant increase in HtSDS at 1 year (7 studies, 287 children: mean difference (MD) 3.88 cm/year; 95% CI: 3.32–4.44). Height velocity, though reduced, remained significantly greater than for untreated children during the second year of therapy (1 study, 82 children: MD 2.30 cm/year; 95% CI: 1.39–3.21). Compared to the 14 IU/m²/week group, there was increase in height velocity in the 28 IU/m²/week group (3 studies, 150 children: 1.18 cm/year; 95% CI: 0.52–1.84). Studies that reported median final height after long-term rhGH give remarkably consistent results. Overall, the median change in HtSDS from the start of treatment to adult height was 0.9 (range: 0.3–1.4) [26, 27]. Overall, the frequency of reported side effects of rhGH was generally similar to that of the control group. rhGH treatment has in theory the potential to induce glomerular sclerosis and progressive kidney disease. The genes for the GH receptor, IGF-1, IGF-1 receptor, and IGF-binding proteins are expressed in renal parenchyma, and GH and IGF-1 are involved in the regulation of glomerular and tubular functions [28]. In healthy adult volunteers, therapeutic doses of rhGH induced an increase of both GFR and renal plasma flow mediated by IGF-1 [29]. Glomerular hyperfiltration can result in glomerulosclerosis and progressive kidney disease, at least in rodents. The study by Mehls et al. reported the glomerular function, eGFR, evolution at 5 and 10 years in 2 cohorts of children with CKD, one treated with rhGH (KIGS registry, 367 children) compared to a control group chosen from the ESCAPE trial (274 children). Although, the overall glomerular function was not significantly different between the 2 groups, in ESCAPE patients with glomerulopathies, eGFR declined significantly in comparison to baseline and the KIGS group. The small differences in delta eGFR in renal hypo-/dysplasia and in other disorders were not significant. Baseline height and eGFR were significantly and negatively correlated with eGFR change in the KIGS group. rhGH treatment showed no association with eGFR decline. The dropout rate was slightly higher in the KIGS cohort; however, the difference did not seem to influence the validity of the main results and conclusions. The conflicting findings from studies in experimental animals, acromegalic patients, and short children on rhGH treatment may be explained by the excessive GH production/dosage resulting in high GH levels in transgenic animals and acromegalic patients. In patients with acromegaly, the mean estimated daily GH production rate exceeds the physiological rate by the order of 100-fold as compared to a 2- to 3-fold supraphysiological GH exposure at the rhGH dose used in children with CKD [30]. Moreover, in mice transgenic for GH, the production of GH is not limited to cells of the hypophyseal gland, but occurs also in parenchymal (including renal) cells [31]. Although rhGH use was found to be safe and efficacious in children with ESRD, its use is reported as limited. van Huis et al. reported on underuse of rhGH treatment in children with short stature from 28 European countries. According to each country’s cri-
The use of rhGH for eligible children with CKD on dialysis is 0, 15, and 19% in Macedonia, UK, and Lithuania, respectively, and 50 and 51.4% in Estonia and Slovenia. rhGH use in renal transplanted children was even lower. The extremely low use of rhGH after renal transplantation might have been caused by the fear of triggering rejection, although studies in transplant recipients did not show an association between the use of rhGH and transplant rejection. The national criteria for the institution of rhGH treatment were different between countries with regard to height criteria, rhGH dosage, and minimal or maximal age limits. The reasons for rhGH underuse were also variable. Total absence of rhGH reimbursement was reported in only 7 out of 28 countries (with a relatively low GDP). The reimbursement of rhGH treatment, however, did affect children’s final height outcome. Other obstacles, both physician- and patient-related, were also reported and should be addressed in order to improve the use of rhGH in children with ESRD and offer those children a chance to achieve more beneficial health outcomes.

**Juvenile Idiopathic Arthritis**

**Growth in children and adolescents with juvenile idiopathic arthritis over 2 years of treatment with etanercept: results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study**

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**Aims:** The study analyzed the growth of children with severe juvenile idiopathic arthritis (JIA) over the initial 2 years of treatment with etanercept (ETN).

**Methods:** The study reviewed the growth data of children participating in the British Society for Pediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN). Since 2004, this national prospective observational study has recruited children <16 years of age with a diagnosis of JIA starting ETN. Baseline and follow-up (6, 12, 24, and 48 months) data included patient demographics, JIA classification, details of current and past antirheumatic therapies, current disease activity captured using the JIA core outcome variables, pain visual analogue scale, height, and weight.

**Results:** Complete height data were available for 191 of 658 patients registered from 2004 to 2011. Patients were predominantly female (65%), with a median age at the start of ETN of 11.0 years (IQR: 7.3 ± 12.9). More than half of the patients were on concomitant MTX (58%) and 38% were on concomitant oral corticosteroids. Overall, disease activity score improved after 2 years and the median baseline Juvenile Arthritis Disease Activity Score (JADAS-71) was 16.2 (IQR: 10.3 ± 22.4) at baseline compared with a median JADAS-71 of 4.0 (IQR: 0.5 ± 8.0) (change $p < 0.001$) at 2 years. The mean height z score at baseline was $-0.74 ± 1.4$. Twenty-nine patients (15%) were classified as hav-
ing short stature. The mean height z score improved to −0.57 ± 1.4 after 1 year and −0.45 ± 1.4 at 2 years, an overall change of +0.29 ± 0.5 (p < 0.001). At 2 years, 18 patients (9%) were classified as having short stature and 13 (7%) were classified as having poor growth. Mean height velocity was 5.8 ± 2.4 cm/year. Mean height z scores of patients with systemic arthritis remained the lowest after 2 years, −1.45 ± 1.3. Two factors were independently associated with height: baseline height z score and corticosteroid use at baseline. For every unit decrease in baseline height z score, a 0.110-unit increase in height z score from baseline to 2 years was predicted (95% CI: 0.161–0.059, p < 0.001). For patients on oral corticosteroids at baseline, the predicted change in height z score from baseline to 2 years was 0.192 lower than for patients not on oral corticosteroids at baseline (95% CI: 0.343–0.040, p = 0.013). Although there was a weak association between lower JADAS-71 scores at 6 months and improvement in height z score at 2 years, this did not reach statistical significance (p = 0.051).

**Conclusions:** The patients with the most severe growth restriction prior to ETN had a greater capacity for growth and were able to gain more from treatment. The patients who received concurrent corticosteroids at the start of ETN treatment were mostly patients with systemic arthritis and demonstrated lower height z scores over the 2 years and less improvement. Despite suggestions that control of disease activity will lead to improved growth, the study results were unable to demonstrate a definite association between change in JADAS-71 and improved height z score.

**Comments**

Growth disorders are common among patients with JIA. These disorders range from general growth retardation to local acceleration of growth in the affected limb, and are associated with an increased production of proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6. Proinflammatory cytokines may act individually or in combination to impair child growth through systemic mechanisms and/or a local action. Whereas IL-6 affects growth mainly via systemic mechanisms altering growth hormone secretion, IL-1β and TNF-α can directly affect growth plate chondrocyte dynamics as well as longitudinal bone growth. Other factors that might contribute to growth suppression associated with childhood arthritis include the degree, extent, and duration of disease activity; age at onset; immobility; suboptimal nutrition; and corticosteroid therapy. The growth-suppressing effects of glucocorticoids appear multifactorial, with some glucocorticoid actions modifying skeletal responses to the GH/IGF-1 axis, whereas other evidence indicates a direct effect of GH on growth plate chondrocytes.

The study by Kearsley-Fleet et al. demonstrated improved height z scores and increased height velocity over the first 2 years of ETN treatment. There was also a suggestion of improved disease activity, but this did not reach statistical significance. The strongest baseline factors associated with improved growth were low height z scores at baseline, suggesting that patients with the most severe growth restriction prior to ETN had a greater capacity for growth and were able to gain more from treatment. Patients on oral corticosteroids at baseline mostly suffered from systemic arthritis and had lower height z scores over the 2 years and less improvement. This could indicate that oral corticosteroid use at baseline is a marker of disease severity or highlight the powerful growth inhibitory effects of corticosteroids.

Advances in drug treatment, especially anti-TNF drugs, have provided new means of controlling the most aggressive forms of polyarticular JIA. Two small previous studies have reported the improvement in linear growth in patients with JIA treated with ETN, mostly children with polyarticular JIA. In multivariate linear regression analyses, the improvement in the growth velocity was best in patients with the greatest growth retardation. Tynjälä et al. [32] showed that the change in inflammatory activity remained a significant predictor of growth velocity, even after glucocorticoids were taken into account. This suggests that the improvement in the growth velocity may be
accounted for by the decrease in inflammation, and not by a direct effect of biological agents on growth or on skeletal maturation. Despite suggestions that control of disease activity will lead to improved growth, the study by Kearsley-Fleet et al. was unable to demonstrate a significant relationship between disease activity and children’s growth velocity. The small number of the study group, absence of pubertal and nutritional status evaluation, strong influence of glucocorticoids effect, and existence of additional growth inhibitor cytokines may explain the results from this study.

Growth retardation resulting from the extended inflammatory process is one of the most important and permanent complications of polyarticular JIA, affecting the long-term quality of life. Normal growth is an important target in the treatment of every chronic condition during childhood. Biological drugs are powerful means for controlling the inflammation in JIA patients. Further studies should investigate the efficacy of anti-TNF medications in restoring normal growth in these children as well as the effect of anti-TNF treatment on skeletal growth and maturation.

References


Early nutrition is an important factor regulating both early and long-term growth and body composition, and therefore has important effects on the risk of later overweight and obesity. There is a lot of activity within this research area with a wealth of publications including observational studies, intervention studies, and studies focusing on the potential mechanisms behind associations between early nutrition and different aspects of growth. There has been a special interest in factors with potential mediating effects between early nutrition and later growth such as growth factors and growth-related hormones, appetite-related hormones, and factors with a potential programming effect, e.g., epigenetic programming.

For this short review we have included 11 papers which we found of special interest published during the period from July 1, 2015 to June 30, 2016. We have chosen to focus mainly on 2 areas where there has been a lot of activity and many publications: the effects of early protein intake on later overweight and obesity, and aspects of breastfeeding which can have effects on risk of later overweight and obesity.

There is strong evidence that high protein intake early in life is associated with an increased risk of later obesity. However, there are only few intervention studies and the causality and the mechanisms are still being discussed. Recently, we summarized publications from the last years on this topic [1]. We have included 5 key papers on this topic that we found of special interest.

It is still being discussed whether breastfeeding protects against later overweight and obesity. Recently, in a *Lancet* series on breastfeeding, it was concluded that there was suggestive evidence of protection [2]. This conclusion was based also on studies from low- and middle-income settings. They mention that residual confounding by socio-
economic position is a possibility, but also that breastfeeding reduced the risk by 13% in the high-quality studies. We have included 4 studies on the aspects of breastfeeding and later obesity which we found of special interest.

**Key articles reviewed for this chapter**

**Breastfeeding and Infant Growth – Contributing Factors, Nutrient Composition, and Its Role in Regulating Appetite**

**Reduced breastfeeding rates among obese mothers: a review of contributing factors, clinical considerations and future directions**
Bever Babendure J, Reifsnider E, Mendias E, Moramarco MW, Davila YR
*Int Breastfeed J 2015;10:21*

**Associations between human milk oligosaccharides and infant body composition in the first 6 months of life**
Alderete TL, Autran C, Brekke BE, Knight R, Bode L, Goran MI, Fields DA
*Am J Clin Nutr 2015;102:1381–1388*

**Appetite-regulating hormones in early life and relationships with type of feeding and body composition in healthy term infants**
Breij LM, Mulder MT, van Vark-van der Zee LC, Hokken-Koelega AC
*Eur J Nutr 2016, Epub ahead of print*

**Breast milk nutrient content and infancy growth**
*Acta Paediatr 2016;105:641–647*

**Macronutrient Intake in Early Life: Associations with Sleep and Obesity**

**Macronutrient intakes in infancy are associated with sleep duration in toddlerhood**
Kocevska D, Voortman T, Dashti HS, van den Hooven EH, Ghassabian A, Rijlaarsdam J, Schneider N, Feskens EJ, Jaddoe VW, Tiemeier H, Franco OH
*J Nutr 2016;146:1250–1256*

**Nutrient intakes in early life and risk of obesity**
Rolland-Cachera MF, Akrouf M, Pénéau S
*Int J Environ Res Public Health 2016;13:64*

**The Early Protein Hypothesis**

**Protein concentration in milk formula, growth, and later risk of obesity: a systematic review**
Patro-Gołąb B, Zalewski BM1, Kouwenhoven SM, Karaś J, Koletzko B, van Goudoever JB, Szajewska H
*J Nutr 2016;146:551–564*
Breastfeeding and Infant Growth – Contributing Factors, Nutrient Composition, and Its Role in Regulating Appetite

Reduced breastfeeding rates among obese mothers: a review of contributing factors, clinical considerations and future directions

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Abstract: Maternal obesity is associated with significantly lower rates of breastfeeding. There are increasing rates of obesity among reproductive-age women. Recent research has shown a significant impact of breastfeeding in reducing the risk of obesity in both mothers and their children. Therefore, in order to identify the factors contributing to the lower breastfeeding rates among these women, the authors performed a literature search using 3 databases covering the years from 1995 to 2014 with the search terms “breastfeeding” and “maternal obesity”. They hope that the results of their review may lead to the development of ways to increase breastfeeding in this vulnerable population.
The factors impacting early breastfeeding include mechanical factors and delayed onset of lactogenesis II, and they have critically analyzed the potential contributors to these factors. The factors impacting later breastfeeding and exclusivity include hormonal imbalances, psychosocial factors, and mammary hypoplasia. Several recent interventions have sought to increase breastfeeding duration in obese women with varying levels of success, and the authors have presented the strengths and weaknesses of these clinical trials. Many obese women do not obtain the health benefits of exclusive breastfeeding and their children are more likely to also be overweight or obese if they are not breastfed.

Further research is needed for exploring the physiological basis for the reduced rate of breastfeeding among obese women, which should be accompanied with effective interventions supported by clinical research to advance the care of obese women and their children.

Children born by obese mothers have an increased risk of later overweight and obesity. Although breastfeeding does not seem to have a strong protective effect on later obesity, it is likely that there is some protection that would be important for these children. It is therefore a problem that obese mothers have difficulties in initiating breastfeeding and breastfeed for a shorter period. This review gives a comprehensive and interesting overview of the literature on the potential causes of the lower breastfeeding rates in obese mothers and of interventions to improve breastfeeding rates. Among the factors impacting early initiating of breastfeeding, they mention the potential effect of larger breasts which has previously been mentioned as a factor which could cause difficulties in latching and positioning of the child. However, they could not find documentation for such effects. Several studies have found that the hormonal profile of breastfeeding obese mothers differs considerably from normal-weight mothers. An example is that the higher circulating leptin levels in obese mothers might interfere with the effect of oxytocin on muscle contraction in the milk ducts during breastfeeding. They also mention that high androgen levels might reduce the duration of breastfeeding, which could also be the reason why women with polycystic ovarian syndrome breastfeed for a shorter period. Insufficient glandular tissue is also mentioned as a potential cause. Animal studies found that obesity early in life had a negative impact on glandular tissue development, but there are no data to support that obese mothers have less glandular tissue. The review also identified 4 intervention studies aimed at increasing the duration of breastfeeding in obese mothers. The most effective intervention was one where the mothers were contacted regularly by a breastfeeding counselor [3]. The review concludes that there is a need to identify modifiable behavioral and physiological factors which could facilitate longer breastfeeding in obese mothers.

Associations between human milk oligosaccharides and infant body composition in the first 6 months of life

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**Background:** There is conflicting evidence whether breastfeeding decreases the risk of developing obesity in childhood. This conflict may be partially due to the differences in specific components of breast milk that may affect early development. Therefore, the authors examined whether differences in the composition of human milk oligosaccharides (HMOs) correlate with growth and body composition of infants at 1 and 6 months of age.

**Methods:** Thirty-seven mother-infant dyads were recruited when the infants were 1 month of age from the University Hospital at the University of Oklahoma Health Sciences Center; 31 of these dyads participated in the 6-month visit. Infants were still breastfed at 6 months. Data on 25 mother-infant pairs were included in the analyses. Breast milk samples and infant measures were taken at 1 and 6 months of infant age. HMO composition was analyzed by high-pressure liquid chromatography, and infant growth (length and weight) and body composition (percentage fat, total fat, and lean mass) were measured by dual-energy X-ray absorptiometry (DXA). Multiple linear regression analysis was used to measure the relationships between HMOs and infant growth and body composition.

**Results:** Higher HMO diversity and evenness at 1 month were associated with lower total and percentage fat mass at 1 month; each 1-μg/mL increase in lacto-N-fucopentaose (LNFP) I was associated with a 0.40-g lower infant weight ($p = 0.03$). At 6 months, each 1-μg/mL increase in LNFP I was associated with a 1.11-g lower weight ($p = 0.03$) and a 0.85-g lower lean mass ($p = 0.01$). At 6 months, each 1-μg/mL increase in LNFP I was associated with a 0.79-g lower fat mass ($p = 0.02$), whereas disialyl-lacto-N-tetraose and LNFP II were associated with a 1.92-g ($p = 0.02$) and 0.42-g ($p = 0.02$) greater fat mass, respectively. At 6 months, each 1-μg/mL increase in fucosyl-disialyl-lacto-N-hexaose and lacto-N-neotetraose was associated with 0.04% higher ($p = 0.03$) and 0.03% lower ($p < 0.01$) body fat, respectively.

**Conclusion:** The authors concluded that the overall composition of HMOs in breast milk appears to be related to infant growth and body composition. However, they realize that more studies should be performed in larger samples with longer follow-up.

**Comments**

Many mechanisms have been suggested for the potential protecting effect of breastfeeding against obesity in later life, such as the content of protein [4], growth factors, appetite-regulating hormones [5, 6], and free amino acids [7]. In this study the impact of the contents of the different HMOs was investigated and it appears to be the first study to investigate associations of HMOs and early growth. There is a large variation in the content of the different HMO both over time and between mothers, and the authors hypothesize that these variations in HMO composition were related to growth and body composition in early life. The results indicate that some HMO could explain part of the variation in body weight, fat mass, and lean mass in early life. The strengths of the study include direct measurement of body fat composition by DXA and not just BMI, and measurement at 2 time points. However, the sample size was very small and results were not adjusted for multiple testing. Therefore, the authors suggest future work should be conducted with more participants and later follow-up. Also, the relation to the development of the gut microbiome was discussed as part of the effect of the HMO may be due to the prebiotic properties of HMOs. Unfortunately, no stool samples were collected in this study, but they should be included in future studies to further investigate the mechanisms.
Appetite-regulating hormones in early life and relationships with type of feeding and body composition in healthy term infants

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Background: Appetite-regulating hormones (ARH) play a role in the regulation of food intake and via this also body composition. There are only a few studies examining the associations between ARH and body composition in early life.

Methods: Serum levels of ARH (ghrelin, leptin, insulin, glucose-dependent insulinotropic peptide [GIP], pancreatic polypeptide [PP], and peptide YY [PYY]) were determined in a random subgroup of 197 healthy infants at 3 months of age, and in 41 of them also at 6 months of age. The authors associated these with the type of feeding and longitudinal fat mass percentage (FM%) determined by the use of air displacement plethysmography at 1, 3, and 6 months and abdominal visceral and subcutaneous fat, using ultrasound, at 3 and 6 months.

Results: At 3 months, formula-fed infants had significantly higher serum levels of ghrelin, leptin, insulin, GIP, and PP (p = 0.026, p = 0.018, p = 0.002, and p < 0.001, respectively), and lower serum levels of PYY (p = 0.002) compared to breastfed infants. Leptin and ghrelin correlated positively with FM% at 3 months and insulin with change in FM% between 1 and 3 months (r = 0.37, p < 0.001; r = 0.23, p < 0.05; and r = 0.22, p < 0.01, respectively). Leptin at 3 months correlated with subcutaneous fat at 3 months (r = 0.23, p < 0.001), but not with visceral fat. Other ARH did not correlate with body composition measurements at any age. The study found no differences in ARH between boys and girls.

Conclusion: It was shown that there is a different profile of ARH in formula-fed infants compared to breastfed infants, indicating that lower levels of ghrelin, leptin, and insulin in breastfed infants may play a role in protecting them from developing obesity. Leptin, ghrelin, and insulin were associated with FM% or changes in FM%.

Comments: Early levels of ARHs may play a role in later development of obesity. This study provides 3-h fasting levels for a broad range of ARH including ghrelin, leptin, insulin, GIP, PP, and PYY at 3 months, and also at 6 months for a subgroup, showing a change in ghrelin, leptin, GIP, and PP during this 3-month period. There was no sex difference for any of the hormones at 3 months, which is in line with other studies except for some showing higher leptin levels in girls [8–10]. The difference according to mode of infant feeding was investigated, and for all ARH the levels differed between exclusively breastfed and exclusively formula-fed infants at 3 months. Except for PYY, the levels were higher in formula-fed infants. It is therefore likely that the hormones may be involved in the different growth patterns and the lower risk of later obesity of breastfed compared to formula-fed infants. A strength of the study is the detailed information regarding accurate adiposity measurements, including fat mass and visceral and subcutaneous fat at 2 or 3 time points during the first 6 month of life. The analyses of the relationship between the ARH and measures of growth and adiposity showed positive correlations for leptin and insulin, as well as for ghrelin, in formula-fed infants. There were no correlations for PP and GIP. This did not match the authors’ expectations as they hypothesized GIP, PP, and PYY to be inversely correlated with increase in weight.
Breast milk nutrient content and infancy growth

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Background: Human breast milk (HM) nutrient content could be related to the well-known benefits of HM in avoiding rapid infancy weight gain and risk of later obesity. In this study, the authors tested the hypothesis that infant growth may be associated with differential HM total calorie content (TCC) or macronutrient contents.

Methods: At ages 4–8 weeks, HM hindmilk samples were collected from 614 mothers participating in a representative birth cohort, with repeated infancy anthropometry. ¹H-NMR was used to measure HM triglyceride (fat), lipid analytes, and lactose (carbohydrate), while protein content was measured by the Dumas method. From these, TCC and %macronutrients were determined.

Results: The 614 HM samples were analyzed with the following results (median [IQR]): fat content: 2.6 (1.7–3.6) g/100 mL; carbohydrate: 8.6 (8.2–8.8) g/100 mL; protein: 1.2 (1.1–1.2) g/100 mL; TCC: 61.8 (53.7–71.3) kcal/100 mL. Comparing HM of mothers exclusively breastfeeding versus mixed feeding showed a higher caloric content with higher %fat, lower %carbohydrate, and lower %protein. Analyses of the association between HM nutrient content and infant anthropometric measurements showed that higher HM TCC was associated with lower 12-month BMI/adiposity and lower 3–12 months gains in weight/BMI. HM %fat was inversely related to 3- to 12-month gains in weight, BMI, and adiposity, whereas %carbohydrate was positively related to these measures. Furthermore, HM %protein was positively related to the 12-month BMI. HM composition was unrelated to maternal factors such as prepregnancy BMI, pregnancy weight gain, parity, and social status.

Conclusions: There were big variations in the macronutrient content of HM. Even though the total milk intake was not registered, it seems that HM composition could be related to infant growth.

Comments: It is well known that breastfeeding is related to lower weight gain in infancy and later risk of adiposity during childhood. It is also known that the variation in human breast milk composition is large both between mothers and for the same single mother over time. For example, the macronutrient composition change during a single breastfeeding session with increased fat content in hindmilk. Likewise, the macronutrient composition changes during the first months after delivery. However, it is not known what impacts these intra- and intermother variations in milk composition have on infant growth.

This study analyzes data from a prospective birth cohort, The Cambridge Baby Growth Study (CBGS). The cohort consists of 1,585 singleton infants (≥36 gestational weeks). Of these, 924 mothers breastfed their infant at 8 weeks and 624 mother-infant pairs.
were available with a breast milk sample and included in this analysis. Macronutrient energy composition (%E) for fat, carbohydrate, and protein was measured and total energy in kcal per 100 mL HM was calculated. There were no data on total HM intake. Interestingly, higher energy and fat content in HM at 4–8 weeks postpartum were related to lower weight gain (3–12 month) and lower BMI and skinfold thickness at 12 months. While the opposite positive relations were found for %carbohydrate, %protein was only weakly positively related to BMI at 12 months. Interestingly, there were no relationships between macronutrient content and length. The relation between %protein and higher BMI at 12 months is in accordance with results from a large intervention study showing that high-protein formula compared to low-protein formula results in higher BMI in later childhood [11]. However, it has been discussed whether the higher BMI is due to high-protein or low-fat intake. The present study could indicate that fat is at least as important as protein. An important limitation is that the total milk intake was not determined. More intervention studies are needed to clarify the influence of macronutrient intake and composition on early growth and weight.

Macronutrient Intake in Early Life: Associations with Sleep and Obesity

Macronutrient intakes in infancy are associated with sleep duration in toddlerhood

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Background: Recent evidence suggests that short sleep duration is associated with low dietary quality and higher energy intake in childhood. However, since most of this evidence is based on cross-sectional studies, the direction of the association remains unclear. Also, studies in young children are lacking.

Objective: In the present study, the authors aimed to explore the longitudinal associations of macronutrient intakes in infancy with repeated measures of sleep patterns in infants and early childhood.

Methods: The study included 3,465 children from the Generation R Study, a population-based cohort study in the Netherlands. Food intake of the infants at the age of 13 months was reported by the mothers, using food-frequency questionnaires. They also reported their child’s sleep duration.
and number of awakenings at 2 and 3 years of age. For evaluating the links of relative macronutrient intakes with sleep indexes, the authors used nutrient substitution models. They adjusted these models for sociodemographic and lifestyle factors.

**Results:** Isoocaloric substitution of fat intake by protein or carbohydrate in infancy was associated with longer total sleep duration at 2, but not 3, years of age. For each 5% increase in energy intake of either protein or carbohydrate at the expense of fat, sleep duration at 2 years of age was longer by 6 min (95% CI: 0.4, 12) and 4 min (95% CI: 2, 6), respectively. Further exploration of macronutrient subtypes indicated no consistent differences between saturated or unsaturated fat and that intake of plant compared with animal protein or tryptophan did not explain the association of higher total protein intake with longer sleep duration at 2 years of age. Replacing unsaturated with saturated fat was associated with 7 min (95% CI: –13, –1) shorter total sleep duration at 3 years of age. Macronutrient intakes were not associated with sleep consolidation.

**Conclusions:** The authors suggest that the relevance of the main findings that macronutrient composition of the diet is associated with sleep duration in young children remains to be established by further research that should study the connections of these links and find their underlying mechanisms.

**Comments**

In the Generation R cohort, a convincing association between early protein intake and later obesity was shown. The paper by Voortman et al. is one of the 11 papers commented on in this chapter. It is therefore very interesting that there is also a significant association between macronutrient intake, including protein intake and sleep duration in this cohort. However, the effect is not strong. A 5% energy increase in protein, which could be from 10 to 15% energy intake of protein, increases sleep duration by 6 min. In a subanalysis they found that substituting animal protein intake with vegetable protein was associated with longer sleep duration, suggesting that protein quality plays a role. The authors also explored the potential effect of tryptophan content in the diet. This is of interest because tryptophan is a precursor of serotonin as well as melatonin, and is positively associated with improved sleep. However, they could not confirm such an association, which might be because the tryptophan intake was only based on the data from the food-frequency questionnaire. As sleep duration was also reported by parents, the authors suggest that future studies should include detailed records of dietary intake and objective measures of sleep duration. Although there was no overall effect of fat quality, a subanalysis showed that if unsaturated fat was substituted with saturated fat, the sleep duration was 7 min shorter, suggesting that fat quality could also have an effect on sleep.

The direction of the association between diet and sleep is unknown, as pointed out by the authors. Among several potential mechanisms, the authors speculate that high protein intake through appetite-regulating hormones could increase satiety and thereby sleep duration. They suggest that future studies should include hormones that regulate appetite and satiety and that postprandial sleepiness caused by macronutrient content could be a factor.

The issue of direction was addressed in a study of children aged 8–11 years followed over a 6-month period in a school meal intervention crossover study. Being in the lowest tertile of sleep duration compared to the highest was associated with significant increase in weight, fat mass, android fat mass, and waist circumference while on a 3-month ad libitum intervention diet compared to a 3-month control diet [12]. Although these children are older, the results suggest that sleep has an effect on adiposity.
Nutrient intakes in early life and risk of obesity

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Abstract: An increasing number of studies indicate that early environmental factors influence later health. Most obese persons have had an early adiposity rebound, suggesting that factors promoting body fat development are active in the first years of life. Environmental conditions during pregnancy and early life (“the first 1,000 days”) seem to highly influence birth weight, growth velocity, and BMI trajectories. Particularly, nutritional exposure can have a long-term effect on health in adulthood. A strong contributor to the rapid increase of childhood obesity prevalence during the last decades may be the high-protein/low-fat diet often reported in young children. Metabolic programming by early nutrition could explain the development of later obesity and adult diseases.

Comments
In this short article, the authors present some interesting ideas about early nutrition and risk of later obesity. They combined the well-known early protein hypothesis with their low-fat hypothesis. The protective effect of breastfeeding on later obesity may be related to both the low-protein and high-fat content in breast milk. High early protein intake has been related to later higher BMI also in intervention studies. The mechanism could be stimulation of IGF-1 production and thereby growth, adipocyte proliferation, and earlier adiposity rebound known to be related to later obesity. The combination with early low-fat intake may reinforce the risk of later obesity as the low-fat intake may result in early low leptin levels and thereby risk of later leptin resistance and obesity. In contrast to the high-protein hypothesis supported by a big intervention study, the low-fat hypothesis is mainly supported by observational studies and therefore we need more intervention studies to confirm or reject this hypothesis.

The Early Protein Hypothesis

Protein concentration in milk formula, growth, and later risk of obesity: a systematic review

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**Background:** It is suggested that health outcome in adults is affected by the protein intake in infancy. Thus, the aim of this study was to conduct a systematic review examining the impact of infant formulas and follow-on formulas with different protein concentrations on infants’ and children’s growth, body composition, and later risk of overweight and obesity.

**Methods:** The authors searched electronic databases for randomized controlled trials (RCTs) carried out until November 2014. They chose only studies that included children aged 0–3 years who represented the general population that were fed cow milk-based infant formulas with different concentrations of protein. Lower-protein cow milk-based formulas were given to control groups (as defined by the authors). The primary outcomes were growth, overweight, obesity, and adiposity. The authors accepted for inclusion also various time points for outcomes assessment (directly after the intervention or after a different follow-up period). They also performed meta-analyses when possible.

**Results:** Results from 12 RCTs that met the inclusion criteria showed that variation in concentration of protein in formula did not affect linear growth other than a transient effect on mean length at 3 months observed in a meta-analysis of 4 studies (mean difference, –0.27 cm; 95% CI: –0.52, –0.02).

Lower mean weight and weight z scores in the group consuming lower-protein formula were reported only at 6 and 12 months. Data from 1 large RCT showed that consumption of a lower-protein infant formula may reduce BMI at 12 months of age and later (12 months, 24 months, and 6 years) and the risk of obesity at 6 years. Effects on body composition remained unclear.

**Conclusions:** The authors concluded that there is still insufficient evidence for assessing the effects of reducing the protein concentration in infant formulas on long-term outcomes. In view of the limited available evidence, more studies are needed to assess this effect. If findings in future studies confirm an effect of reducing protein intake in early life, this may lead to promising interventions for reducing the risk of overweight and obesity in children and possibly later in life.

**Comments**

This review comprehensively addresses the evidence available up until November 2014 looking into early protein intake and later risk of obesity focusing on studies on protein content in infant formula. This and other studies have focused on studying the so-called early protein hypothesis, which suggests that high amounts of early protein intake can increase the risk of later development of obesity. Insufficient evidence was available for making a firm conclusion, but this review does indicate positive effects of reducing protein intake in early life. Their suggestions for future studies include more studies with long-term outcomes which are scarce since these are difficult to perform. Future studies should preferably also include better measurements of body composition and analysis of separate effects on gender or other potential effect modifiers. A better understanding of these aspects is likely to improve our understanding of the mechanisms behind the association between early protein intake and later obesity. The present review only focuses on infant formula. However, protein intake during the complementary feeding period might play a role in the early protein hypothesis. This also highlights the need for determining the periods in which there is an increased susceptibility to negative effects of high protein intake – which is currently not known. The conclusion that more studies are needed sets the stage for the next studies which have further expanded our knowledge within this field.
Protein intake in early childhood and body composition at the age of 6 years: the Generation R Study

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**Background:** The objective of this study was to further expand on previous studies which suggest that high protein intake in infancy leads to a higher BMI in later life. The authors examined the associations between the intake of total, animal, and vegetable protein in early childhood with detailed measurements of body composition at the age of 6 years.

**Methods:** The study used the Generation R cohort, and analyses were performed in 2,911 children. The protein intake of the children was determined at the age of 1 year and assessed with a validated food-frequency questionnaire, adjusted for total energy intake. When the children were 6 years old, a thorough examination of anthropometrics and body fat (with dual-energy X-ray absorptiometry) was performed. Age- and sex-specific SD scores for BMI, fat mass index (FMI), and fat-free mass index (FFMI) was calculated.

**Results:** After adjustment for confounders, a 10-g per day higher total protein intake at 1 year of age was associated with a 0.05 SD (95% CI: 0.00, 0.09) higher BMI at age 6. This association was fully driven by a higher FMI (0.06 SD; 95% CI: 0.01, 0.11) and not FFMI (−0.01 SD; 95% CI: −0.06, 0.05). The associations of protein intake with FMI at 6 years remained significant after adjustment for BMI at the age of 1 year. Additional analyses showed that the associations of protein intake with FMI were stronger in girls than in boys (\(p\) for interaction = 0.03), stronger among children who had catch-up growth in the first year of life (\(p\) for interaction < 0.01), and stronger for intake of animal protein (both dairy and nondairy protein) than protein from vegetable sources. When performing the analysis in children with and without catch-up growth, there was a limited effect of protein intake in children without catch-up growth, while the children with catch-up growth had large effects of increase protein intake. Furthermore, they also tested whether genetic risk for obesity modified the effect of protein intake; however, this was not the case.

**Conclusions:** The results from this study further support that high protein intake in early childhood is associated with higher body fat mass, but not fat-free mass in later childhood. They also show that some subgroups might be particularly vulnerable to early high protein intake. The authors suggest that future studies should further investigate whether these changes persist into adulthood and to examine the optimal range of protein intake for infants and young children.
Dietary protein intake is associated with body mass index and weight up to 5 years of age in a prospective cohort of twins

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Am J Clin Nutr 2016;103:389–397

Objective: The authors of this study investigated whether a higher proportion of protein intake beyond the weaning period was associated with greater weight gain, higher BMI, and risk of overweight or obesity in children up to 5 years of age. Very few large epidemiologic studies have investigated this role of postweaning protein intake in excess weight and adiposity of young children. This is especially important since children in the United Kingdom, where the study cohort is from, consistently consume protein in excess of their physiological requirements.

Design: The study used participants from the Gemini cohort and consisted of 2,154 twins. The dietary intake was determined by using a 3-day diet diary when the children had a mean age of 21 months. The study collected weight and height measurements every 3 months, from birth to 5 years of age. They used longitudinal statistical models to investigate the associations between protein intake and BMI, weight, as well as height, with adjustment for age at diet diary, sex, total energy intake, birth weight/length, and rate of prior growth and clustering within families. The authors used logistic regression models to further investigate how protein intake related to later risk of overweight or obesity at 3 and 5 years of age.

Results: A total of 2,154 children had 5.7 ± 3.2 (mean ± SD) weight and height measurements up to 5 years. Total energy from protein was associated with higher BMI (β = 0.043; 95% CI: 0.011, 0.075) and weight (β = 0.052; 95% CI: 0.031, 0.074), but not height (β = 0.088; 95% CI: −0.038, 0.213), between 21 months and 5 years. Substituting percentage energy from fat or carbohydrate for percentage energy from protein was associated with decreases in BMI and weight. Protein intake was associated with a trend in increased odds of overweight or obesity at 3 years (OR = 1.10; 95% CI: 0.99, 1.22; p = 0.075), but the effect was not statistically significant at 5 years.

Conclusion: The authors further added evidence that a higher proportion of energy from protein during the complementary feeding stage is associated with greater increases in weight and BMI in early childhood. Furthermore, they showed that substituting percentage energy from protein with fat or carbohydrate both associated with lower weight gain.

Comments: These 2 birth cohort studies provide some of the much-needed evidence which was requested in the paper by Patro-Gołąb et al. These are interesting as they show that also protein intake during the complementary feeding period is important for later risk of obesity. Both at 12 months and 21 months, higher protein intake was associated with higher weight, suggesting that protein intake up to the first 2 years of life are important for later childhood weight gain.

The 2 studies also examined what dietary substitutions could be made in exchange for the high protein intake. Should it be preferred to include more fat, especially long-chain unsaturated fat or should the focus be on providing more complex carbohydrates? So far the evidence suggests it does not matter which substitutions are made based on these two studies, but this question deserves more attention. Several re-
views based on ecological data and a small observational study suggest that a high fat intake protects against later obesity [13, 14]. Furthermore, the sources of protein might matter, and the Generation R Study also found that animal protein but not vegetable protein were associated with increased BMI and fat mass; however, they found no differences between dairy protein and protein from meats. Future studies should also address the protein quality and more information is needed on specific amino acids and their role in the early protein hypothesis.

The study of Voortman et al. showed that some subgroups might be particularly vulnerable to early protein intake. An interesting finding was that the positive association of protein intake with later BMI and obesity at 6 years of age was mainly present in children that had catch-up growth. In contrast, infants without catch-up growth were not very sensitive to high protein intake. This suggests that there might be some children that are especially vulnerable to excess protein. They also examined whether children with an obesogenic genotype could be vulnerable to higher early protein intake; however, they found no interaction between protein intake and having an obesogenic genotype. Not many studies have examined the role of genotype as a potential modifying factor of early life protein intake and obesity, and more studies are needed to elucidate if this is important. The Generation R Study also found sex-specific effects of early protein intake showing that girls had stronger associations with fat mass than boys. This effect of gender was also mentioned in the paper by Pimpin et al., and fits well with a study showing sex differences in the endocrine system in response to protein intake early in life [15]. Future studies should target groups which are sensitive to high protein intake in early life. These could include infants with a certain genotype, infants that had catch-up growth, or perhaps girls.

Higher concentrations of branched-chain amino acids in breast milk of obese mothers

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Nutrition 2016;32:1295–1298

Background: There is an assumption that nutrition during fetal life and early childhood has a significant effect on increased risk of metabolic syndrome and cardiovascular diseases in adulthood. The authors also suggest that development of obesity could be speculated to be the result of high protein intake in early life, but more specifically a result of high branched-chain amino acid (BCAA) intake. The aim of this pilot study was to determine whether the pattern of breast milk free amino acid (FAA) varies between obese and normal-weight breastfeeding mothers.

Methods: One hundred breastfeeding mothers participated in this study: 50 obese and 50 controls, with similar age and parity in both groups. Breast milk samples were collected at the end of the first month of lactation and FAA concentrations were measured by ultraperformance liquid chromatography tandem mass spectrometry. Comparisons between groups were performed using a 2-tailed paired t test.
**Results:** The authors analyzed 45 breast milk samples from each group. BMI was 34.3 ± 3.9 in the obese group and 21.6 ± 1.4 in the control group ($p < 10^{-4}$). BCAA concentrations were higher in breast milk of obese mothers (95.5 ± 38.2 vs. 79.8 ± 30.9 μM; $p = 0.037$), as was tyrosine concentration (13.8 ± 7.1 vs. 10.6 ± 5.2 μM; $p = 0.016$).

**Conclusions:** The mature breast milk of obese mothers contained 20% more BCAA and 30% more tyrosine than breast milk of control mothers. Whether this exposes infants who are breastfed by obese mothers to a higher risk for obesity remains to be explored.

**Comments**

This study adds valuable knowledge regarding the role of BCAAs in the risk of obesity. First of all, the higher BCAA content found in breast milk of obese mothers could potentially pose a risk for infant obesity as high infant circulating BCAA has been implicated in obesity development through various mechanisms (see Luque et al.). However, from the current study it is not possible to determine whether this increase in BCAA content of breast milk results in higher circulating BCAA in the infants. This should be examined in more detail to determine if this might lead to BCAA-induced metabolic changes in the infants. Furthermore, the study does not report on diet or circulating levels of BCAA in the mothers, and future studies should try to uncover why this high breast milk BCAA content is seen. If this increased BCAA content in breast milk of obese mothers does impact later obesity risk, it is important to further explore the BCAA differences and how to manipulate the level.

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**Early programming by protein intake: the effect of protein on adiposity development and the growth and functionality of vital organs**

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*Nutr Metab Insights* 2016;8(suppl 1):49–56

**Abstract:** It has been suggested that breastfeeding in infancy reduces the risk of developing obesity at a later stage and that the variations in the content of protein between formula and human milk has a significant role. These have led to the introduction of the so-called early protein hypothesis, suggesting that lowering the protein supply during the first year of life has been demonstrated to decelerate weight gain and reduce obesity risk later in childhood.

This review focuses on a mechanistic approach to programmed adiposity and the effect of protein supply variations on other tissues and systems in the body, which may be mediated by branched-chain amino acids, insulin, and insulin-like growth factor 1 via the mammalian target of rapamycin.

Since new policies regarding the effect of proteins are being introduced, they also reviewed the advancement of the laws of the European regulatory as well as the recommendations by expert panels on the issue.

The authors also elaborate on different open fields, testing amino acid-modified formulas and determining the critical time window of programming, and on the long-term consequences of differences in protein intake on organ functionality among well-nourished infants.

**Comments**

This review clearly provides a summary of the mechanisms involved in the early programming effects of protein intake. They suggest that the early protein hypothesis can affect growth through various mechanisms. The link between high protein intake...
and high circulating leucine is one of the highlighted mechanisms. It is believed the higher circulating leucine stimulates insulin and IGF-1 secretion, which then affects the mammalian target of rapamycin signaling. This mechanism links high protein intake to enhanced adipogenic activity such as excessive adipogenesis. They also suggest that the general growth-stimulating effects of this pathway might also affect other tissues such as the brain and the heart. However, other mechanisms than IGF-1 and insulin-related growth signaling might be involved in the early protein hypothesis [16–18], and it is possible that multiple mechanisms are at play simultaneously. Overall, there is a growing number of articles within this field and reviews such as this do a good job of compiling the available evidence and suggesting new directions for research within this important field.

References

This chapter reviews the most recent data on malnutrition and catch-up growth published between July 1, 2015 and June 30, 2016. Catch-up growth is defined as height velocity above the expected for age that occurs after a period of growth retardation during childhood and puberty. The first paper in this chapter deals with research priorities in the field of malnutrition and highlights the most rated questions for future studies by experts (Angood et al., 2016). This is followed by research studies providing new insights into various aspects of the field: meaningful parameters for the measurement of population-level catch-up in linear growth in children (Leroy et al., 2015); new postnatal growth standards for preterm infants (Villar et al., 2015); the consequences of marginally low birth weight on weight and height in childhood (Berglund et al., 2016); important components of the malnutrition rehabilitation diet, especially proteins (Ghosh 2016; Manary et al., 2016; Stobaugh et al., 2016; Batra et al, 2016; Masarwi et al., 2016; Bortolotti et al., 2016; Semba et al., 2016), micronutrients (Shafique et al., 2016), and prebiotics (Bryk et al., 2015); and the link between the gut macrobiota and malnutrition (Blanton et al, 2016).
Key articles reviewed for this chapter

Research priorities on the relationship between wasting and stunting
Angood C, Khara T, Dolan C, Berkley JA; WaSt Technical Interest Group
PLoS One 2016;11:e0153221

Using height-for-age differences (HAD) instead of height-for-age z scores (HAZ) for the meaningful measurement of population-level catch-up in linear growth in children less than 5 years of age
Leroy JL, Ruel M, Habicht JP, Frongillo EW
BMC Pediatr 2015;15:145

Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-Up Study of the INTERGROWTH-21st Project
Lancet Glob Health 2015;3:e681–e691

Marginally low birthweight increases the risk of underweight and short stature at three and a half years of age
Berglund SK, Kriström B, Björn M, Lindberg J, Westrup B, Norman M, Domellöf M
Acta Paediatr 2016;105:610–617

Protein quality in the first thousand days of life
Ghosh S
Food Nutr Bull 2016;37(suppl 1):S14–S21

Protein quality and growth in malnourished children
Manary M, Callaghan M, Singh L, Briend A
Food Nutr Bull 2016;37(suppl 1):S29–S36

Including whey protein and whey permeate in ready-to-use supplementary food improves recovery rates in children with moderate acute malnutrition: a randomized, double-blind clinical trial
Am J Clin Nutr 2016;103:926–933

A randomized controlled trial offering higher- compared with lower-dairy second meals daily in preschools in Guinea-Bissau demonstrates an attendance-dependent increase in weight gain for both meal types and an increase in mid-upper arm circumference for the higher-dairy meal
J Nutr 2016;146:124–132
Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats
Masarwi M, Gabet Y, Dolkart O, Brosh T, Shamir S, Phillip M, Gat-Yablonski G
Br J Nutr 2016;116:59–69

Impact of qualitative and quantitative variations in nitrogen supply on catch-up growth in food-deprived-refed young rats
Clin Nutr 2016;35:669–678

Child stunting is associated with low circulating essential amino acids
EBioMedicine 2016;6:246–252

Mineral- and vitamin-enhanced micronutrient powder reduces stunting in full-term low-birth-weight infants receiving nutrition, health, and hygiene education: a 2 × 2 factorial, cluster-randomized trial in Bangladesh
Shafique S, Sellen DW, Lou W, Jalal CS, Jolly SP, Zlotkin SH
Am J Clin Nutr 2016;103:1357–1369

Effect of a mixture of GOS/FOS® on calcium absorption and retention during recovery from protein malnutrition: experimental model in growing rats
Bryk G, Coronel MZ, Lugones C, Mandalunis P, Río ME, Gualtieri AF, de Portela ML, Zeni SN
Eur J Nutr 2015;54:913–923

Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children
Science 2016;351(6275)

Research priorities on the relationship between wasting and stunting
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PLoS One 2016;11:e0153221

Background: Wasting and stunting are global public health problems affecting many millions of children. Although both result from undernutrition, share common causal factors, and frequently coexist, current policies and treatment programs approach them as separate entities. Data are lack-
ing on the physiological relationship between wasting and stunting and the impact of treatment targeted at both problems simultaneously.

**Aims:** The aim of this survey was to establish priorities for the study of the connections between wasting and stunting for future research investments.

**Methods:** The methodology was based on the Child Health and Nutrition Research Initiative (CHNRI) guidelines. Using a written questionnaire, 25 experts in nutrition, growth, and child health were asked to prioritize 30 research questions on wasting and stunting according to 3 criteria: answerability, usefulness, and impact.

**Results:** Eighteen experts (72%) completed the questionnaire. The highest rated questions were as follows: (1) “Can interventions outside of the 1,000 days, that is, at pre-school age, school age, and adolescence, lead to catch-up in height and other developmental markers?”, (2) “What timely interventions work to mitigate seasonal peaks in both wasting and stunting?”, and (3) “What is the optimal formulation of ready-to-use foods to promote optimal ponderal growth and also support linear growth during and after recovery from severe acute malnutrition?”.

**Conclusions:** Wasting and stunting should be addressed together because using a separate therapeutic strategy for each may negatively impact the overall effectiveness of treatment. High-priority research questions can guide public health trials in providing the quality evidence needed to optimize the battle against undernutrition and its consequences.

**Comments**

Wasting affects an estimated 52 million children under age 5 years, and stunting affects an estimated 165 million children [1]. The need for new nutritional interventions was highlighted in a recent paper on the worldwide progress in meeting the 2025 WHO targets for nutrition, namely, reducing and maintaining the prevalence of childhood wasting to less than 5% and reducing the number of stunted children by 40% [2].

The CHNRI study of Angood et al. was intended to establish priorities to guide future research on wasting and stunting that would result in high-impact policies and practices in the field of malnutrition. The results showed that research that directly relates to interventions and programming is the first priority. The highest-rated question, “Can interventions outside of the 1,000 days, that is, at pre-school age, school age, and adolescence, lead to catch-up in height and in other developmental markers?” was prompted by findings that there are opportunities for catch-up growth in older age groups, particularly adolescents [3], but only a few of the well-designed intervention studies have included adolescents. Further studies on catch-up growth in undernourished adolescents might prove to be a key factor in meeting nutrition targets.
Background: Early studies of undernourished children from low- and middle-income countries showed only modest, if any, population-level catch-up in absolute linear growth in the under-2-year age group. Positive changes were reported in more recent investigations based on mean height-for-age z scores (HAZ) rather than absolute height-for-age difference (HAD).

Aims: The aim of the study was to determine if population-level catch-up linear growth is evident when measured by HAD compared to HAZ.

Methods: Data from the previously published Demographic and Health Surveys, the Young Lives Study, and the Consortium on Health-Orientated Research in Transitional Societies were analyzed. HAD and HAZ were used to assess changes in growth in children aged 2–5 years.

Results: Using HAD, no catch-up linear growth was found on a population level. Furthermore, mean HAD continued to decrease between 2 and 5 years of age, suggesting a progression in stunting. Using HAZ, no change (Demographic and Health Surveys) or an increase in mean scores (some of the longitudinal data) was found. Population-level growth velocity was lower than expected in all Young Lives data sets, supporting a lack of catch-up growth.

Conclusions: The absolute height deficit in malnourished children continues to increase after 2 years of age. This finding does not challenge the critical importance of the first 1,000 days and possible interventions within this period, but it should give rise to research questions on the possible prevention of continued stunting and the potential benefit of nutritional interventions beyond 2 years of age.

Comments: The study sought to determine if there is evidence of population-level catch-up in height in children aged 2–5 years. The novelty of the study is the comparison between 2 methods of measurement: HAD, which compares the child’s height to standards, expressed in centimeters, and mean HAZ. The study was prompted by claims that HAZ may be unsuitable to measure changes in linear growth over time because it depends on standard deviations from cross-sectional data [4]. Analysis of the data from recent cohort studies of population-level catch-up growth based on mean HAZ yielded conflicting results to the decrease found using mean HAD, reflecting continued deterioration. This suggests that changes in mean HAD rather than changes in mean HAZ should serve as the basis for the meaningful assessment of population-level catch-up growth in height. HAZ can be used to assess attained growth at a given point in time and for comparisons between sex and age groups.
Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-Up Study of the INTERGROWTH-21st Project

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Lancet Glob Health 2015;3:e681–e691

Background: Monitoring postnatal growth in preterm infants is based on estimates of fetal weight from ultrasonographic scans and charts of size at birth for gestational age of values for preterm or LBW babies established from longitudinal studies of general preterm population. These charts, however, have limitations.

Methods: The INTERGROWTH-21st Project aimed to introduce other measurements of postnatal growth in preterm infants. Fetal, newborn, and postnatal growth in 8 locations worldwide, in which maternal health care and nutritional needs were met, were assessed. From these populations, the Fetal Growth Longitudinal Study selected low-risk women starting antenatal care before 14 weeks’ gestation and monitored fetal growth by ultrasonography. All preterm births from this cohort were eligible for the Preterm Postnatal Follow-Up Study which included standardized anthropometric measurements, breastfeeding or bottle-fed of expressed maternal milk, and data on morbidity, treatments, and development. To construct the preterm postnatal growth standards, we selected all live singletons born between 26 and before 37 weeks’ gestation without congenital malformations, fetal growth restriction, or severe postnatal morbidity. Analyses with second-degree fractional polynomial regression models in a multilevel framework accounting for repeated measures were performed. Fetal and neonatal data were pooled from study sites and stratified by postmenstrual age. For neonates, boys and girls were assessed separately.

Results: There were 224 preterm singleton births, of which 201 (90%) were enrolled in the Preterm Postnatal Follow-Up Study. Variance component analysis showed that only 0.2 and 4.0% of the total variability in postnatal length and head circumference, respectively, could be attributed to between-site differences, justifying pooling the data from all study sites. Preterm growth patterns differed from those for babies in the INTERGROWTH-21st Newborn Size Standards. They overlapped with the WHO Child Growth Standards for term babies by 64 weeks’ postmenstrual age. Analyses with second-degree fractional polynomial regression models in a multilevel framework accounting for repeated measures were performed. Fetal and neonatal data were pooled from study sites and stratified by postmenstrual age. For neonates, boys and girls were assessed separately.

Conclusions: The authors produced standards for postnatal growth in preterm infants and they suggest that these standards should be used for the assessment of preterm infants until 64 weeks’ postmenstrual age, after which the WHO Child Growth Standards are appropriate. Size-at-birth charts should not be used to measure postnatal growth of preterm infants.
This large-scale prospective study fills a major gap in the global repertoire of tools for monitoring the growth and progress of preterm infants. Current standards are disparate and the WHO Growth Reference Study, one of the largest global exercises for developing normative global standards [5, 6], is inadequate for assessing growth of preterm infants postnatally. The INTERGROWTH-21st study, the largest multicenter study for comparison of fetal growth in unrestricted cohorts of pregnant women across 8 countries, established these patterns of postnatal growth among preterm infants which could be used for comparison of growth, as highlighted in the subsequent study.

Marginally low birthweight increases the risk of underweight and short stature at three and a half years of age

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Aim: Marginally low birth weight is defined here as infants born between 2,000 and 2,500 g. Very few studies have been performed about the long-term health of these children. This study explored the prevalence and predictors of sustained growth restriction.

Methods: 281 marginally LBW children were followed for weight and height from birth until 3.5 years. Children with a standard deviation score (SDS) for BMI or height below –2 were considered underweight and short, respectively.

Results: The mean SDS for weight and height showed a rapid increase before 12–19 weeks of age when the most rapid weight gain was in infants born small for gestational age. However, at 3.5 years of age, 9.5% of the children remained underweight and 6.5% had short stature. In the regression models, we observed a close and significant correlation between low weight and height gains during the first 19 weeks of life and increased risks of being underweight and having a short stature at 3.5 years.

Conclusion: We found that marginally low birth weight infants initially had rapid catch-up growth. This ended before 19 weeks of age. Even though the majority showed rapid growth acceleration in infancy, there was still a significant number who remained growth restricted at 3.5 years of age (9.5% for BMI and 6.5% for height).

Comments: This study is important as it highlights the potential for linear growth faltering in even marginally preterm infants and hence the need for strategies for prevention of prematurity even in high-income settings [7]. The authors could have analyzed their data using the intergrowth standards for preterm postnatal growth in the first 12 months to further assess patterns of linear growth faltering over time.
Protein quality in the first thousand days of life

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Food Nutr Bull 2016;37(suppl 1):S14–S21

Summary: This review paper addresses the significance of protein quality during the first 1,000 days of postnatal life. The findings suggest that high-quality protein may play a role in the treatment of acute malnutrition and the prevention of stunting. The authors provide an update on the latest advancements in protein quality assessment. The Protein Digestibility Corrected Amino Acid Score (PDCAAS), a new index for evaluating protein quality, is also discussed, and its strengths and drawbacks are presented.

Protein quality and growth in malnourished children

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Food Nutr Bull 2016;37(suppl 1):S29–S36

Background: The protein quality of a given food source is determined by the amount of available essential amino acids. The 2 main indexes currently used to assess protein quality are the Protein Digestibility-Corrected Amino Acid Score (PDCAAS) or the Digestible Indispensable Amino Acid Score (DIAAS).

Aims: The aim of the study was to compare the amino acid profiles of patients with severe acute malnutrition (SAM) and acute inflammation using the PDCAAS and DIAAS, and to assess the relationship of the scores with weight gain during recovery.

Methods: Data on protein synthesis was derived from previous stable isotope studies of children with acute inflammation and SAM. The relationship between weight gain and protein quality scores was assessed using studies of SAM interventions with various foods.

Results: During recovery from SAM, protein quality scores were well correlated with the degree of weight gain. The DIAAS system adjusted for higher expected weight gain had the strongest association with the observed weight gain. In the particular physiological state of SAM with an inflammatory response, the concentrations of acute-phase proteins were higher in children receiving foods that contained the amino acids required for these proteins.

Conclusion: A balance of amino acids that matches the composition of acute-phase proteins maximizes amino acid synthesis. This study suggests that the quality of dietary protein should be evaluated in the context of the specific physiologic condition and not as an independent parameter.

Comments: The traditional assessment of protein adequacy by total protein consumption rather than protein quality has led to a significant underestimation of the risk of protein malnutrition, particularly in developing countries [8]. The complementary papers of Ghosh and Manary et al. emphasize the potential importance of high-quality protein in the prevention and treatment of malnutrition in children and summarize the recent changes in the evaluation of protein quality.
In children recovering from SAM, new tissue is created at a very rapid rate, leading to higher protein requirements than in healthy, well-fed, and age- and gender-matched children. The effect of feeding proteins of different quality on weight gain and recovery of malnourished children is not known. The DIAAS appears to better reflect the quality of protein than the other commonly used system, the PDCAAS, and is preferred by the United Nations Food and Agriculture Organization. Much work is still required to implement this measure into practice, and further studies are needed to determine the best composition (quality and source) and quantity of proteins that match the high physiological needs of children during catch-up growth.

**Including whey protein and whey permeate in ready-to-use supplementary food improves recovery rates in children with moderate acute malnutrition: a randomized, double-blind clinical trial**

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*Am J Clin Nutr 2016;103:926–933*

**Background:** The benefit of adding milk protein rather than a dairy-free source of protein to supplementary foods used to treat moderate acute malnutrition (MAM) in children remains unclear. **Aim:** The aim of the study was to compare the effectiveness of a peanut-based ready-to-use supplementary food (RUSF) containing soy protein with a novel RUSF containing whey permeate and whey protein concentrate in the treatment of children with MAM. **Methods:** A randomized, double-blind trial was conducted including more than 2,200 children from rural Malawi and Mozambique diagnosed with MAM. The children were treated with either a soy RUSF or a whey RUSF at a dose of 75 kcal/kg/day for up to 12 weeks. The primary outcome measure was recovery from MAM, defined as achieving a mean mid-upper arm circumference (MUAC) of 12.5 cm without bipedal edema within 12 weeks of therapy. Secondary outcomes were changes in MUAC, weight, and length; time to recovery; and adverse events. **Results:** The rate of recovery from MAM was significantly higher in the group fed the whey RUSF (960 of 1,144 children, 83.9%) than in the group fed the soy RUSF (874 of 1,086 children, 80.5%) \((p < 0.04)\). At the end of the study period, the whey-RUSF group had a significantly higher MUAC \((p = 0.009)\), higher gain in MUAC \((p = 0.003)\), higher mean weight-for-height \(z\) score \((p = 0.008)\), and greater weight gain \((p = 0.05)\). There were no significant between-group differences in length gain or time to recovery. **Conclusion:** Although the RUSF containing whey in this study provided a smaller amount of total protein and calories than the RUSF containing soy, it appears to be associated with a higher recovery rate and better growth. These findings support the use of dairy protein over soy in the treatment of MAM.

**Comments** This elegant, randomized, double-blind study provides the first specific evidence of an advantage of whey ingredients in RUSF used to treat MAM. Previous studies have reported positive correlations between the consumption of dairy protein and im-
proved outcomes in malnourished children [9–11], but it was unclear whether the findings were attributable to the quality of the protein or the total amount of protein consumed [12]. In the study of Stobaugh et al., malnourished toddlers receiving a whey-based 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. These findings are in line with the reviews of Ghosh and Manary et al., discussed above, emphasizing the importance of the quality and source of the protein used in the treatment of malnourished children. One innovation of this study was the use of MUAC as a primary outcome parameter instead of the standard weight-for-height z score. The change was based on reports showing that the MUAC is better suited for identifying malnourished children at highest risk of mortality [13–15].

A randomized controlled trial offering higher-compared with lower-dairy second meals daily in preschools in Guinea-Bissau demonstrates an attendance-dependent increase in weight gain for both meal types and an increase in mid-upper arm circumference for the higher-dairy meal

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J Nutr 2016;146:124–132

Background: Several therapeutic approaches to childhood malnutrition have been proposed, but the optimal regimen remains unknown.

Aims: The primary aim of the study was to investigate the effectiveness of providing a second daily meal comprised of ready-to-use supplementary foods (RUSFs) to preschool children. The secondary aim was to compare 2 RUSFs with different dairy protein content.

Methods: This is a cluster-randomized controlled trial of 533 preschool children who were provided with 1 of 2 RUSFs with different concentrations (15 vs. 33%) of dairy protein, as a second daily meal. Both the study group and wait-listed controls received the same school lunch. Each RUSF serving of 92 g contained 478 kcal and 11.5 g protein. Intention-to-treat and per-protocol analyses (>50 days of RUSF consumption) were performed. Primary outcomes were changes in the weight-for-age z score and height-for-age z score. Changes in mid-upper arm circumference (MUAC), hemoglobin, and retinol-binding protein were defined as secondary outcomes.

Results: Children who consumed an RUSF for >50 days had a significantly greater increase in weight-for-age z score (+0.40 for RUSF-15%, +0.32 for RUSF-33%) than controls (+0.24) (p < 0.01 and p < 0.05, respectively). There was a lesser decrease in MUAC in the RUSF-33% group compared to controls (20.01 vs. 20.34 cm, p < 0.05), but not in the RUSF-15% group. Children fed RUSF-15% showed a greater reduction in hemoglobin than children fed RUSF-33% (20.0 vs. 20.5 g/dL, p = 0.05).

Conclusions: The incorporation of a RUSF-based breakfast program is feasible in preschools in low-income countries and may improve weight gain in the children who consume the RUSFs regularly. The changes in MUAC and hemoglobin in children fed RUSFs suggest that increasing the dairy protein content (33% compared with 15%) may protect children from wasting and anemia.
Comments

Proteins play an essential role in the process of healthy growth and therefore constitute an important component in therapeutic diets for undernourished and malnourished children. Unfortunately, the optimal sources, optimal quantity, and manner of preparation of dietary proteins are unclear. This 3-month pilot study in 3- to 5-year-old children prone to malnutrition provides the first evidence that community interventions with RUSFs containing 33% protein from dairy sources, compared with the typical 15%, may have particular benefits in preventing wasting and anemia. However, the differences in outcome between the RUSFs were only marginal, and further studies are needed.

Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats

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Br J Nutr 2016;116:59–69

Background: Malnutrition-induced stunted growth is common in developed as well as developing countries. Occasionally, recovery is incomplete, leading to a permanent growth deficit and short stature. In most Western countries, dairy products are recommended for children during their growth period. The growth-supporting nutrients contained in milk include calcium and high-quality proteins, especially casein and whey. In newborns, milk is the sole source of nutrition and therefore must supply all the ingredients required for proper growth and development. Both human milk and cow milk, used in infant formula, contain all the essential amino acids, but they differ in the ratio of casein to whey.

Aim: The aim of the study was to determine if the type of milk protein ingested (casein or whey) influences catch-up growth.

Methods: Prepubertal rats were fed a restricted diet for 36 days followed by refeeding with an isocaloric, isoprotein diet containing either a vegetarian source of protein (standard rat chow) or an animal source of protein (milk proteins casein or whey). The groups were compared for longitudinal growth in addition to bone microarchitecture and biomechanical properties.

Results: Food restriction during the period of linear growth led to a significant reduction in weight, bone length, bone quality, and epiphyseal growth plate height. Microcomputed tomography and biomechanical tests revealed a significant reduction in cortical and trabecular bone parameters and mechanical strength. There was a general improvement after refeeding, but not all parameters were completely corrected even after 40 days. In comparison to the whey-fed rats, the casein-fed group had significantly higher body weight and greater bone thickness and strength in both the short and long term. Casein-fed rats also had a higher trabecular bone fraction in the short term than whey-fed rats, but the difference lost significance after 40 days. The effect of whey on growth was slower and was associated with maintenance of a greater epiphyseal growth plate height for a longer time.
Conclusions: Long-lasting food restriction may have deleterious effects on bone elongation and microarchitecture. Milk-based diets offer a high potential for growth. The specific milk protein used in refeeding may affect the pace of bone development.

Comments: There is an increasing body of evidence suggesting that fast catch-up growth (especially in terms of weight gain) in infancy increases the long-term risk of obesity and insulin resistance [16]. In this study of food-restricted rats, there was a dramatic differential effect of refeeding with casein or whey despite the similar amount of each protein consumed. The rats refed with casein had a significantly higher body weight than the rats refed with whey. This finding suggests that refeeding with whey may lead to similar linear growth and bone health as refeeding with casein, but with lesser weight gain. Therefore, a whey-based milk diet may circumvent long-term complications of catch-up growth. However, it is too early to translate these data to clinical recommendations.

Impact of qualitative and quantitative variations in nitrogen supply on catch-up growth in food-deprived-refed young rats

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Clin Nutr 2016;35:669–678

Background: Malnutrition remains a devastating public health problem, and improving intervention strategies is crucial. The current recommendations for refeeding lack consensus regarding the optimal molecular form of protein. Some data point to an advantage for peptides over whole proteins, but the evidence is limited.

Aims: The aim of the study was to compare the nutritional impact of peptides, partially hydrolyzed proteins, and whole proteins in refeeding of food-deprived young rats.

Methods: Healthy male rats (n = 109) were deprived of food for 2 days followed by refeeding for 2–13 days with whole chow (controls) or pediatric enteral nutrition formulas containing peptide, partially hydrolyzed protein, or whole protein. Rats were refed ad libitum or limited to 90 or 100% of basal spontaneous intake.

Results: Food deprivation resulted in a significant reduction in body and organ weight, changes in gut morphology, and a reduction in plasma citrulline, a marker of gut function. Two days of refeeding at 90% of basal intake was insufficient to restore nutritional status, regardless of the type of protein administered, whereas ad libitum refeeding was associated with improved nitrogen efficiency. After 13 days, rats fed partially hydrolyzed proteins gained significantly more weight than controls and rats fed peptide- and whole protein-containing diets. Nitrogen balance and nitrogen efficiency were significantly correlated with recovery of body weight.

Conclusions: Refeeding ad libitum has a beneficial effect on catch-up growth. Refeeding with partially hydrolyzed proteins may improve body weight gain, and a higher nitrogen supply may assist in body weight recovery.

Comments: Malnutrition in children may impair intestinal function and reduce absorption due to changes in intestinal morphology and the intestinal microbiome and an increased susceptibility to gastrointestinal infections [17]. The active uptake of hydrolyzed pro-
Proteins by the peptide transport systems may make diets based on hydrolyzed proteins more efficient for refeeding during recovery from malnutrition than diets based on whole proteins. However, data on the effects of the level of protein hydrolysis on refeeding outcome are scarce.

In this study, Bortolotti et al. used a model of 48-h food deprivation in young rats followed by oral refeeding. The most important finding was that a diet containing partially hydrolyzed protein was more effective in improving weight gain and nitrogen homeostasis than a peptide- or whole-protein-containing diet. Another important observation was that refeeding at 90% of basal spontaneous intake (which is in line with current recommendations for malnourished children) did not promote catch-up growth. Thus, it seems that refeeding efficiency may be improved by increasing energy and nitrogen supply. Further studies in malnourished children are warranted.

Child stunting is associated with low circulating essential amino acids

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EBioMedicine 2016; 6:246–252

**Background:** Stunting is considered to be the best available summary measure of chronic malnutrition and affects about one quarter of children under 5 years of age worldwide – mainly those living in low-income countries. The pathogenesis of stunting is still not fully understood. As nutritional interventions have had only modest effects in reducing stunting, the authors hypothesized children at high risk of stunting may have insufficient essential amino acids.

**Method:** The study subjects consisted of 313 children aged 12–59 months from 6 villages in rural southern Malawi. A targeted metabolomics approach was used to measure serum amino acids, glycerophospholipids, sphingolipids, and other metabolites using liquid chromatography-tandem mass spectrometry. Children underwent anthropometry.

**Results:** There were almost equal numbers of girls and boys in this study, and more than 60% of them were stunted. All 9 essential amino acids (tryptophan, isoleucine, leucine, valine, methionine, threonine, histidine, phenylalanine, and lysine), 3 conditionally essential amino acids (arginine, glycine, and glutamine), 3 nonessential amino acids (asparagine, glutamate, and serine), and 6 sphingolipids were significantly lower in stunted compared with nonstunted children. Alterations in serum glycerophospholipid concentrations were also related to stunting.

**Conclusions:** This study suggests that insufficient essential amino acids and choline in children’s dietary intake may play a role in the pathogenesis of child stunting.

**Comments** This recent study is important as it supports the notion that stunted and malnourished children may also have underlying nutrient deficits that may be amenable to treatment. Potential amino acid deficiencies have been shown to be common among...
malnourished children [18], and increased tyrosine requirements are well documented during the recovery phase of severe acute malnutrition [19]. Previous studies in formula-fed infants have also shown better growth in early infancy with higher protein intake [20], suggesting that in addition to focusing on reducing risks of environmental enteropathy [21], increased attention must be given to improving dietary quality among malnourished children with growth failure. This has special implications for appropriate complementary foods in low- and middle-income settings with food insecurity.

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**Mineral- and vitamin-enhanced micronutrient powder reduces stunting in full-term low-birth-weight infants receiving nutrition, health, and hygiene education: a $2 \times 2$ factorial, cluster-randomized trial in Bangladesh**

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*A* J* Clin Nutr* 2016;103:1357–1369

**Background:** There are many causes of stunting which include prenatal effects, inadequate postnatal nutrient intake, and recurrent infections. Infants who are born with low birth weight (LBW) are particularly vulnerable to frequent infections and malnutrition, and therefore have a high risk of stunting. More than 25% of infants born in low- and middle-income countries are born full term, but are LBW (FT-LBW). There is limited evidence on the efficacy of various specific interventions to improve growth in this group.

**Aims:** The authors studied the effects of the use of a water-based hand sanitizer (HS) independently or with a mineral- and vitamin-enhanced micronutrient powder (MNP) (22 minerals and vitamins) for prevention of infections and improvement of nutrient intake in order to reduce stunting in FT-LBW infants.

**Methods:** The study, consisting of 467 FT-LBW infants, was a prospective $2 \times 2$ factorial, community-based, cluster-randomized trial. In the first 6 months of infancy (0–5 months of age), infants from all clusters were allocated to either HS or no HS groups. In the second 6 months (6–12 months of age), infants in each of the original 2 groups were randomly reallocated to either an MNP or a no MNP group, thus forming 4 groups: (1) no HS and no MNP (control), (2) HS only, (3) MNP only, and (4) HS and MNP. All groups received the same general nutrition, health, and hygiene education (NHHE) at enrollment and throughout the 12 months.

**Results:** The use of an HS had no effect in reducing indicators of infection in the first or second half of infancy, or the likelihood of stunting at 12 months. Those who received the MNP (with or without HS) were significantly less likely to be stunted at 12 months than were the controls (OR = 0.35; 95% CI: 0.15, 0.84; $p = 0.017$).

**Conclusions:** The daily addition of a mineral- and vitamin-enhanced MNP significantly reduced stunting in FT-LBW infants in rural Bangladesh. The use of a water-based HS had no effect.

**Comments**

This important trial reported the combined effects of hand sanitation using a low-cost water-based hand sanitizer and a specially formulated micronutrient powder (22 micronutrients and minerals) in LBW infants in Bangladesh. The observation of a signifi-
Significant reduction in stunting in this high-risk population is especially notable given the high rates and risk of stunting among small-for-gestational-age infants [22]. The trial is notable in that it combined a simple hand hygiene intervention with breastfeeding support and multiple micronutrient administration in an at-risk population, and showed a large impact on stunting and no demonstrated increase in complications such as diarrhea [23] or hospitalizations [24].

**Effect of a mixture of GOS/FOS® on calcium absorption and retention during recovery from protein malnutrition: experimental model in growing rats**

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Eur J Nutr 2015;54:913–923

**Introduction:** Protein deprivation during growth results in loss of epiphyseal growth plate height and bone volume and disrupts endochondral ossification. Repair of the damage during catch-up growth requires adequate calcium intake to reach optimal peak bone mass.

**Aims:** The aim of the study was to examine the effect of GOS/FOS®, a 9:1 mixture of galacto-oligosaccharides (GOS) and long-chain fructo-oligosaccharides (FOS) known to enhance mineral absorption, on the absorption of calcium, phosphorus, and magnesium, and on bone mineralization in growing rats recovering from early protein malnutrition.

**Methods:** Rats were fed a low-protein (4%) diet for 1 week and then randomly divided into 4 groups for refeeding with diets containing normal (0.5%) or low (0.3%) levels of calcium alone or combined with 5.3% prebiotic GOS/FOS. The control groups consisted of non-protein-deprived rats continuously fed 0.5 or 0.3% calcium to days 40–50 of life.

**Results:** The control groups demonstrated an increase in body weight and length. In the intervention groups, growth was halted during the low-protein-diet phase and increased during recovery. In both groups fed GOS/FOS, there was an increase in calcium, phosphorous, and magnesium absorption, and in lactobacillus counts and β-glucosidase level, with a concomitant decrease in cecum pH and β-glucuronidase, urease, and tryptophanase levels ($p < 0.01$), regardless of the dietary calcium content. The GOS/FOS-containing diet was also associated with a decrease in the level of carboxy-terminal collagen crosslinks (CTX) and increases in femur calcium, magnesium, and phosphorus levels; bone mineral content; proximal tibia and spine bone mineral density; epiphyseal growth plate height; and hypertrophic zone thickness, stiffness, and elastic modulus.

**Conclusions:** The addition of prebiotics in the form of GOS/FOS 9:1 mixture to the rat diet results in positive colonic effects, an increase in bone mineral absorption, and improved bone development.
Comments

A high-quality diet is essential for optimal catch-up growth during recovery from malnutrition. Most studies to date have focused on the use of combinations of macronutrients and micronutrients. Prebiotics are fiber compounds that pass undigested through the upper part of the gastrointestinal tract. Their ingestion modulates the gut microbiota and induces the release of metabolic products that may improve the absorption of micronutrients (e.g., calcium, phosphorus, and magnesium), which are important components of healthy bone-growth. This elegant study is the first to offer evidence of the beneficial effects of diets containing a prebiotic mixture of GOS/FOS 9:1 on mineral absorption, gut microbiota, bone resorption, and bone retention during the catch-up growth period. The findings have important implications for nutritional therapy and warrant confirmation in malnourished children.

Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children

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Note: This manuscript is discussed also in the chapter by Grimberg et al. [this vol., pp. 1–15] and in the chapter by Prentice [this vol., pp. 165–174].

Introduction: Childhood undernutrition is a severe global health problem that causes significant morbidity and mortality, despite various interventions, by mechanisms that are not entirely clear in millions of children. Several studies have reported alterations in the gut microbiota in malnourished children.

Aims: The aim of the study was to assess the causality between childhood undernutrition and alterations in the normal development of the gut microbiota.

Methods: A model of normal postnatal gut microbiota development by age was formulated using a random forests algorithm. The algorithm was applied to bacterial 16S ribosomal RNA data sets extracted from fecal samples collected monthly from healthy Malawian children during their first
3 years of life. Age-discriminatory bacterial taxa were recognized by distinct time-dependent changes in their relative loads. On the basis of this model, a metric system was developed (microbiota-for-age z score) to define the maturation stage of fecal microbiota taken from children with different levels of undernutrition. Fecal samples collected from 6- and 18-month-old twin infants with normal growth or varying degrees of undernutrition were transplanted into young germ-free mice fed a typical Malawian diet. The gain in lean body mass was assessed by serial quantitative magnetic resonance imaging. Targeted mass spectrometry was used to assess metabolic phenotypes, and microcomputed tomography was used to assess femoral bone morphology.

**Results:** The undernourished children had immature gut microbiota. Following transplantation of the fecal samples, the recipient mice exhibited impaired growth, altered bone morphology, and metabolic abnormalities in muscle, liver, and brain. The microbiota from healthy infants of all age groups had a greater effect on growth than the microbiota from undernourished children; the most significant difference was observed between microbiota taken at age 6 months. In cohoused mice, species from the microbiota of cagemates implanted with healthy-donor fecal samples were transmitted to the microbiota of rats implanted with fecal samples from underweight/stunted donors. The resulting prevention of growth impairments in the mice was attributed to coprophagy. The bacterial species that apparently harbored the beneficial traits were cultured and introduced into recipients of microbiota from undernourished donors, leading to an improvement in growth and a decrease in metabolic abnormalities.

**Conclusion:** There appears to be a causal relationship between childhood undernutrition and gut microbiota immaturity. Growth abnormalities may be repaired with the reestablishment of the normal gut microbiota. The specific age- and growth-discriminatory taxa identified should be further investigated as potential agents for the repair and prevention of gut microbiota immaturity.

**Comments** This very well-designed and innovative set of experiments contributes several important findings that expand our understanding of the link between gut microbiota and malnutrition. Apparently, gut microbiota immaturity is not just associated with undernutrition, but is causally related to it. To assess their findings, the authors developed a random forests-based model of gut microbial community development from a serially sampled cohort of Malawian twins with a healthy growth pattern. In this manner, they were able to compute 2 related metrics: relative microbiota maturity and microbiota-for-age z score (MAZ), which significantly correlated with the chronological age of the children with healthy growth phenotypes. A significant correlation was found between MAZ at 12 months and anthropometry at 18 months, suggesting that MAZ may be useful for predicting future growth. Further studies are needed to confirm the use of this model in other populations of children from different parts of the world, different age groups, and different nutritional and health statuses.

Another important contribution of this study is the culture of 2 specific strains (*Ruminococcus gnavus* and *Clostridium symbiosum*), providing direct evidence that they improved the impaired growth phenotype associated with the impaired microbiota from the undernourished donors.

The findings of this study and the development of new models for healthy microbiota profile pave the way for future studies using similar models to design new therapeutic strategies for the prevention and treatment of malnutrition.
In this chapter, we review important articles published between July 2015 and June 2016 concerning the impact of maternal nutrition during pregnancy on intrauterine fetal growth. We carefully selected human studies, mainly of randomized controlled prospective design, along with several animal studies dealing with the effect of several nutrient supplements on fetal growth and metabolic programming. These will hopefully help in understanding the goals and intervention options for healthier offspring.

**Key articles reviewed for this chapter**

**Human Studies**

**Maternal vitamin D₃ supplementation at 50 mg/d protects against low serum 25-hydroxyvitamin D in infants at 8 wk of age: a randomized controlled trial of 3 doses of vitamin D beginning in gestation and continued in lactation**


**Maternal B vitamins: effects on offspring weight and DNA methylation at genomically imprinted domains**

McCullough LE, Miller EE, Mendez MA, Murtha AP, Murphy SK, Hoyo C

*Clin Epigenetics* 2016; 8: 8
Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh
Am J Clin Nutr 2016;103:236–249

Association between low dairy intake during pregnancy and risk of small-for-gestational-age infants
Matern Child Health J 2016;20:1296–1304

Periconceptional multiple-micronutrient supplementation and placental function in rural Gambian women: a double-blind, randomized, placebo-controlled trial

Impact of maternal nutritional status before and during pregnancy on neonatal body composition: a cross-sectional study
Pace S, Saure C, Mazza CS, Garcia S, Tomzig RG, Lopez AP, Ribarola L, Krochick GA
Diabetes Metab Syndr 2016;10:S7–S12

Intake of carbohydrates during pregnancy in obese women is associated with fat mass in the newborn offspring

Animal Studies

Maternal high fat intake affects the development and transcriptional profile of fetal intestine in late gestation using pig model
Lipids Health Dis 2016;15:90

A maternal high-energy diet promotes intestinal development and intrauterine growth of offspring
Nutrients 2016;8:258
Maternal vitamin D3 supplementation at 50 mg/d protects against low serum 25-hydroxyvitamin D in infants at 8 wk of age: a randomized controlled trial of 3 doses of vitamin D beginning in gestation and continued in lactation

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Background: A sufficient supply of vitamin D during infancy is required to maintain proper growth and normal calcium homeostasis, as well as to prevent diseases such as rickets, tooth decay, and asthma. Daily vitamin D supplementation for breastfed infants is therefore recommended by many health organizations, but carries the risk of overdose and is otherwise avoided by mothers for various reasons. This study aimed to assess an alternative: maternal supplementation during pregnancy and lactation, for its efficacy in achieving the required concentrations of infant serum 25(OH)D.

Methods: In this randomized controlled trial, 226 healthy pregnant women were assigned to receive a dose of either 10, 25, or 50 μg of vitamin D3 per day, beginning in midpregnancy (13–24 weeks of gestation) until 8 weeks postpartum. The infants in this trial did not receive any other vitamin D supplementation. At 36 weeks of gestation, and at 8 weeks postpartum, blood was drawn from both mothers and infants, and 25(OH)D levels in the different dose groups were compared.

Results: Maternal supplementation with 50 μg vitamin D3/day achieved appropriate levels of 25(OH)D levels (30 nmol/L) in 98% of the infants until the age of 8 weeks. Infants of mothers receiving doses of 10 or 25 μg vitamin D/day only achieved sufficient 25(OH)D levels at a rate of 5 and 84%, respectively. This difference between the groups was found to be significant. At 8 weeks postpartum, the maternal 25(OH)D levels were also significantly higher in the 50-μg group than the 10- and 25-μg dose groups.

Conclusions: Maternal supplementation with 50 μg vitamin D3/day was effective in preventing 25(OH)D deficiency (30 nmol/L) in 98% of breastfed infants until the age of 8 weeks. Lower doses were not similarly effective.

Comments: Vitamin D has neuroprotective and antioxidant properties [1]. In addition, vitamin D deficiency during infancy is associated with altered calcium metabolism and a risk factor for poor growth, early childhood tooth decay, asthma, and an increased risk of future diabetes. Maternal and neonatal vitamin D levels often correlate [2]. The most important outcome of the current study was that vitamin D supplementation during pregnancy led to prevention of vitamin D deficiency in almost all (98%) infants in the 50-μg group. In addition, the fact that women were randomized to several vitamin D dose groups assists in determining the optimal dose that should be supplemented during pregnancy. However, several issues need further research and clarification. First, should the dose of vitamin D be adjusted to maternal weight or BMI? In addition,
Maternal B vitamins: effects on offspring weight and DNA methylation at genomically imprinted domains

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**Background:** Nutrients participating in the one-carbon cycle (1-CC) metabolism, namely folate, choline, and the cofactors vitamins B\textsubscript{6} and B\textsubscript{12}, are essential for nucleic acid synthesis, DNA methylation, and cellular growth. Deficiencies in these nutrients during pregnancy may be associated with fetal growth restriction, low birth weight, and early-life weight gain.

**Aims:** To study the possible associations of maternal serum levels of vitamin B\textsubscript{12}, pyridoxal phosphate (PLP), 4-pyridoxic acid, and homocysteine (Hcy) with offspring weight from birth to age 3 years and the methylation patterns of 4 differentially methylated regions (DMRs) (\textit{H19}, \textit{MEG3}, \textit{SGCE/PEG10}, and \textit{PLAGL1}) previously associated with both fetal growth and development, and maternal vitamin B concentrations.

**Methods:** The participants were 496 healthy women who were already enrolled in a prospective study (the Newborn Epigenetics Study). Data collection and blood sampling were performed at enrollment and at birth, and additional data collection was performed 3 years after birth. DNA methylation at regulatory sequences of genomically imprinted genes was measured in umbilical cord blood DNA using bisulfite pyrosequencing.

**Results:** No correlation was found between maternal serum concentration of B vitamins and the newborns’ birth weight. An inverse correlation was found between maternal serum Hcy concentration and male birth weight \((p = 0.04)\). An inverse association was also found between maternal serum vitamin B\textsubscript{12} concentration and weight gain at 3 years \((p = 0.003)\). Maternal PLP levels (indicative of vitamin B\textsubscript{6} status) were associated with higher weight gain in males; there was also a positive association between higher maternal PLP levels and offspring DNA methylation at the \textit{MEG3} DMR \((p < 0.01)\).

**Conclusions:** In this large prospective study, maternal vitamin B\textsubscript{12} and B\textsubscript{6} levels in pregnancy seem to correlate with the infant’s weight gain in the first 3 years of life. PLP levels during pregnancy were correlated with methylation at the \textit{MEG3} DMR, a connection that has not yet been reported in a human prospective trial.

**Comments** Although the association between nutrients in the one-carbon pathway and offspring methylation are well-documented in animal models, there is only limited data regarding this association among humans. Nutrients involved in 1-CC metabolism are es-
essential for nucleic acid synthesis, DNA methylation, and cellular growth. These nutrients are particularly important in fetal tissue differentiation. Thus, alternation in this pathway could result in low birth weight, decreased fetal growth, and altered early-life weight gain. Understanding the association between these nutrients and offspring weight may be crucial in uncovering modifiable ways to prevent complications and downstream health effects. In the current study, although maternal vitamin B$_{12}$ concentration was not correlated with birth weight, the concentration of vitamin B$_{12}$ was associated with offspring weight gain at 3 years of age. Moreover, maternal pyridoxal phosphate concentrations were positively associated with methylation at the MEG3 DMR, and may be important for understanding the effects of prenatal nutrition on adult health outcomes. This finding highlights the importance of long-term follow-up when conducting prospective studies, as the effect of many intrauterine processes and interventions may only be apparent many years after birth.

Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh

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Note: This article is discussed also in the chapter by Prentice [this vol., pp. 165–174].

Background: In Bangladesh the prevalence of low birth weight (LBW) is as high as 37%, and high rates of small for gestational age (SGA) infants, both in weight and in length, are also reported. One of the reasons for this impairment in fetal growth is maternal undernutrition, which is also highly prevalent. The current standard of care for addressing maternal malnutrition is iron and folic acid supplementation, but a new approach for providing both micronutrients and some key macronutrients, including essential fatty acids, is the use of small-quantity (20 g/day) lipid-based nutrient supplements (LNS) for enriching home-based foods. The aim of this study was to assess the effect of LPS for pregnant and lactating women (LNS-PL) on birth anthropometric parameters.

Methods: In this randomized controlled trial, 4,011 pregnant women at <20 gestational weeks from rural Bangladesh were enrolled and randomized to receive either a daily supplement of iron and folic acid (IFA; 60 mg iron + 400 mg folic acid) or LNS-PL (20 g/day, 118 kcal) containing essential fatty acids and 22 vitamins and minerals. The primary outcomes were infant birth weight and length. Stunted growth was defined as a length $z$ score <2, and wasting was defined as a weight $z$ score <2.

Results: There was a significant difference between infants in the LNS-PL and IFA groups in birth weight (2,629 compared with 2,588 g, respectively, $p = 0.007$), weight for-age $z$ scores, head circumference-for-age $z$ scores, and BMI $z$ scores. In the LNS-PL group there was a reduced risk of stunting (18.7% compared with 22.6% in the placebo group; RR: 0.83; 95% CI: 0.71, 0.97) and small head circumference (20.7% compared with 24.9%; RR: 0.85; 95% CI: 0.73, 0.98). The prevalence of wasting was also reduced in the supplement group. The greatest effect on stunting was seen in subgroups with higher levels of food insecurity and younger maternal age.
**Conclusions:** The consumption of a lipid-based multinutrient supplement during pregnancy reduced the rate of newborn stunting, wasting, and small head circumference, especially in high-risk populations, and significantly increased most anthropometric parameters of the newborn.

**Comments**

LBW is considered one of the main health issues in low-resource societies as it is an independent predictor for neonatal morbidity and mortality. This study demonstrated that supplementation of pregnant women with LNS significantly increased many parameters including mean birth weight, birth length, and head circumference, and significantly reduced the prevalence of newborn stunting defined as birth length-for-age z score less than –2. Although this study has several strengths including its prospective nature, randomization of >4,000 women and low rate of attrition, several limitations should be kept in mind while interpreting the results. The disruption of the lipid-based nutrient supply for a period of 10 weeks compromised the ability to investigate the full potential of LNS as an intervention. In addition, women were not blinded to the type of supplement provided. Yet, the results of the current study demonstrate the positive effect of even mild nutritional change during pregnancy on neonatal outcome. Finding the proper nutrient supplementation in societies with low resources has both medical and financial benefits, especially if long-term follow-up of this cohort of offspring reveals decreased risk for morbidity later in life.

**Association between low dairy intake during pregnancy and risk of small-for-gestational-age infants**

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*Matern Child Health J* 2016;20:1296–1304

**Background:** Maternal undernutrition has been associated with poor fetal growth. As dairy products are of high calcium content, they could affect the development of the fetal skeleton. This study attempts to find an association between maternal diary consumption during the first 20 weeks of pregnancy, and the risk for the offspring being born small for gestational age (SGA).

**Methods:** A cohort of 1,175 healthy pregnant women were enrolled at their routine second trimester fetal ultrasound, performed under the local free prenatal care program. The patients were then followed until 1 month after delivery. Only normal, low-risk, singleton pregnancies were included. The information on dairy consumption was retrospectively collected using a validated food frequency questionnaire, and included information on product type and amount. Additional information such as maternal education, socioeconomic status, physical activity, BMI, smoking, and total energy consumption was also collected. SGA was defined as birth weight below the 10th percentile for gestational age.

**Results:** The average dairy intake of mothers to SGA infants was 513.9 g/day, compared to 590.3 g/day in mothers of appropriate for gestational age infants. The frequency of SGA was higher.
among women who consumed less than 3 dairy products a day, compared to women who consumed 3 or more (the recommended daily intake). An increase of 100 g/day in dairy product intake was associated with an 11% reduction in risk for giving birth to an SGA infant, adjusted OR = 0.89 (0.83, 0.96). Furthermore, it was found that consuming at least 700 g of dairy products per day would prevent 13.2% of SGA cases (2.6, 22.6), and 21.1% of the cases by an intake of 800 g/day.

**Conclusions:** Reduced dairy intake in the first half of the pregnancy is significantly associated with SGA, in a dose-dependent relation. A causal connection is conceivable, but should be studied further in the future.

**Comments**

Birth weight is an important determinant of neonatal survival and has a role in future health as diseases emerge in adult life more commonly among those with low birth weight. Inadequate maternal nutrition is one of the leading causes of fetal growth restriction. Intake of dairy products is of utmost importance since calcium metabolism is essential for fetal skeleton formation. This prospective study suggests a possible causality relation among dairy intake during pregnancy and neonatal birth weight. In addition, a positive dose-response relationship seems to exist between increasing levels of dairy intake by all pregnant women in this cohort. The known role of calcium in the proper development of fetal bone tissue and therefore the development of the whole body may serve as the physiologic mechanism for the finding of the current study. It has been also shown that the consumption of cow milk increases the blood concentration of insulin growth factor 1, which is an important determinant of growth during childhood. A high umbilical cord blood leptin level was previously demonstrated to be correlated with neonatal birth weight [3]. Unfortunately, cord insulin growth factor 1 or the levels of other hormones/adipokines were not measured in this cohort.

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**Periconceptional multiple-micronutrient supplementation and placental function in rural Gambian women: a double-blind, randomized, placebo-controlled trial**

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**Background:** Inadequate maternal intake of micronutrients such as folic acid, vitamin D, antioxidants, calcium, and iron during the preconception period could have an adverse effect on the developing placenta, leading to placental dysfunction, fetal growth restriction, and preterm birth.

**Aims:** The objective of this study was to evaluate whether or not periconceptional multiple micronutrient supplementation (MMS) could affect placental function.

**Methods:** This was a randomized, double-blind, placebo-controlled study in Gambian women (age range: 17–45 years), who were assigned either to supplementation with the UNICEF/WHO/United Nations University multiple micronutrient preparation (UNIMMAP) or to placebo. The supplement/placebo was given from recruitment until the first antenatal checkup, or continued for 1 year.
if there was no conception. The primary outcome measures were 2 indexes of vasculoendothelial and placental function (ratio of plasminogen-activator inhibitor [PAI] 1 to PAI-2 and mean uterine-artery resistance index [UtARI]) and a marker of placental transport capacity (fetal to maternal measles antibody [MMA] ratio).

**Results:** A total of 376 pregnancies from 1,156 women met the inclusion criteria, completed follow-up, and were included in the study. While no differences were found between the intervention and placebo groups in PAI-1 to PAI-2 or MMA ratios, there was a significant reduction in UtARI between 18 and 32 weeks of gestation (95% CI: 20.03, 20.00; \( p = 0.040 \)) in women who received the micronutrient supplement, indicating a reduction in placental vascular resistance.

**Conclusions:** A modest, but significant positive effect on placental vascular function was demonstrated in women receiving periconceptional MMS. Other parameters of placental development and function were not affected.

**Comments**

This pioneer study assessed the impact of periconceptional micronutrient supplementation on placental function as assessed by Doppler studies mainly of the uterine artery. Early in gestation, the uterine-artery Doppler waveform is characterized by a high-resistance profile, transforming to one of low resistance by 20–24 weeks of gestation in normal pregnancies. The persistence of high-resistance waveforms is predictive of subsequent placental-related complications, including preeclampsia, placental abruption, and fetal growth restriction. In the current study, placental vascular function was modified by periconceptional UNIMMAP supplementation. However, the therapeutic and public health implications of this finding have yet to be determined since the rate of placental-related complications was not significantly different between the study groups.

The main limitation of this study is the fact that only 8% of those who were randomly assigned to supplementation were included in the analysis of the primary outcome; thus, protection from bias afforded by randomization cannot be assumed. In addition, placental function was assessed only indirectly, with no placental histopathological examination performed.

**Impact of maternal nutritional status before and during pregnancy on neonatal body composition: a cross-sectional study**

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**Background:** Maternal obesity during pregnancy and weight gain during pregnancy are associated with higher infant birth weight. Higher birth weight, in turn, is associated with an increased risk for later metabolic syndrome and related morbidity. A higher percent of body fat mass (FM) in the newborn could be a more sensitive indicator of such risk than birth weight, but the connection between maternal parameters during pregnancy and neonatal body composition has not been studied.

**Aim:** To assess the possible relation between maternal nutritional status before conception, maternal weight gain during pregnancy, and neonatal body composition in the first hours of life.
**Methods:** During a 5-month period, consecutively born neonates in a public hospital in Argentina and their mothers were evaluated for inclusion in the study. Six hundred and four neonates and their mothers were found to be eligible, all were measured, and the mothers were interviewed. Maternal weight before pregnancy was self-reported, and maternal and neonatal weight at birth were measured. Gestational weight gain (GWG) was then calculated. Neonatal fat mass was calculated using a mathematical formula based on skinfold thickness measurement previously validated in newborns.

**Results:** Neonatal FM was positively related with maternal BMI before pregnancy, higher GWG, and a higher number of previous pregnancies. The mothers of infants with high body FM (>557 g) were more likely to be obese (72.7 vs. 35.1%, \( p = 0.005 \)), and to have gained over 18 kg during gestation (76.4 vs. 31%, \( p = 0.03 \)).

**Conclusions:** In this study, maternal obesity before pregnancy is correlated not only with neonatal birth weight, but also with neonatal fat mass.

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**Intake of carbohydrates during pregnancy in obese women is associated with fat mass in the newborn offspring**

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**Background:** Children born to obese mothers are at a higher risk for adverse metabolic outcome, both as neonates and later on in life. The aim of this study was to evaluate the relation between carbohydrate consumption during pregnancy in obese women, either with or without impaired glucose tolerance, on the offspring’s relative fat mass directly after birth.

**Methods:** A total of 222 pregnant women with a pregestational BMI of 30 already enrolled in a randomized controlled trial (Treatment of Obese Pregnant Women [TOP]) were included in this observational study. Data collection on diet was performed using a food-frequency questionnaire at 11–14 and 36–37 weeks’ gestation, representing early and late gestation. Dual-energy X-ray absorptiometry (DXA) was used to evaluate neonatal body composition and relative fat mass (RFM).

**Results:** Maternal carbohydrate ingestion during late pregnancy was significantly correlated with the offspring’s RFM (\( p = 0.006 \)), while more carbohydrates in early pregnancy only showed a relative trend to increased RFM (\( p = 0.15 \)). Stratification of the cohort according to glucose tolerance showed a stronger association between carbohydrate intake and neonatal fat mass in women with glucose intolerance (2-h glucose values >6.7 mmol/L), than in women with well-controlled glucose levels (2-h glucose values <6.6 mmol/L). Infants born to women in the highest quartile of carbohydrate intake (median: 238 g/day) had a mean adjusted value of RFM that was higher by 2.1% (95% CI: 0.6, 3.7) than those born to women in the lowest quartile of carbohydrate intake (median: 188 g/day).
**Conclusions:** Infants of obese women with a higher carbohydrate intake during late pregnancy have a relatively higher fat mass than those of obese women with a lower carbohydrate intake. The impact was higher in obese women with glucose intolerance.

**Comments** Preventive strategies for childhood obesity and identification of which women might benefit from early intervention during pregnancy are needed. Maternal glucose level, especially during late gestation is a well-known modifiable risk factor for altered neonatal birth weight [4, 5]. The relevance of maternal carbohydrate intake on anthropometric measures as well as fat mass in the offspring and its interaction with glucose tolerance was assessed in these studies. It was suggested that a reduction in carbohydrate intake to moderate levels in late pregnancy is associated with a lower fat percentage at birth in the offspring of obese women with glucose intolerance, even if the 2-h oral glucose tolerance test (OGTT) value is below the threshold for the diagnosis of gestational diabetes mellitus. In addition, pregestational maternal obesity also strongly correlated with the amount of neonatal fat mass after birth. Development and planning of preventive health policies should focus on ways to control maternal obesity and gestational weight gain and decreasing carbohydrate consumption during pregnancy in order to improve both maternal health and the health of their offspring.

**Animal Studies**

Maternal high fat intake affects the development and transcriptional profile of fetal intestine in late gestation using pig model


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*Lipids Health Dis* 2016;15:90

**Background:** Studies in animal models have shown that maternal nutrition during pregnancy may influence fetal organogenesis. This study was designed to examine the impact of a maternal high-fat diet on the development of fetal intestines by analyzing intestinal morphology, enzyme activity, and transcriptional profile.

**Methods:** Eight gilts of comparable age and body weight were randomly assigned, after insemination, into 1 of 2 groups, receiving either a high-fat diet or a control diet which was similar in all nutrient levels other than fat content. At day 90 of gestation, 2 fetuses were collected from each gilt by cesarean section. Intestinal samples were then taken for analysis of morphology, enzyme activities, RNA microarray, and gene expression.

**Results:** Fetuses from the mothers who had received the high-fat diet were of significantly higher weight at 90 days of gestation. Also significant was an increase in intestinal villous height and lactase activity. Porcine oligo-microarray demonstrated a significant difference between the groups in...
the expression of 61 genes known to participate and influence signal transduction in immune responses, cancer, and metabolism. These results were confirmed by RT-PCR analysis.

**Conclusion:** In this study, maternal high-fat nutrition during pregnancy increased fetal weight and lactase activity. It also affected the expression of genes involved in intestinal immune response and metabolism, and affected pathways associated with susceptibility to colorectal, endometrial, and breast cancer.

**Comments**

The gastrointestinal tract is an internal organ which has 2 main functions: to digest nutrients and to resist exogenous antigens. The development of the gastrointestinal tract begins at early gestation and matures rapidly in late gestation for extrauterine life. Previous studies exploring the effect of maternal obesity and overnutrition on fetal gastrointestinal tract function in mammalian animals have shown improved intestinal morphology, enzyme activities, and gene expressions on one hand, but impaired gut barrier and enhancement of gene expression of proinflammatory cytokines in offspring intestine on the other.

The current study provides possible explanations regarding the pathophysiology of previous observations. Infants with heavier birth weights have increased intestinal morphology in addition to higher lactase activity, which is needed for better degradation of lactose. This, in turn, leads to better carbohydrate absorption and subsequently increased infant growth. The current study provides bioinformatics analysis, which shows that the expression of many genes was altered in those exposed to a high-fat diet. However, the genes that were mainly affected were those involved in the process of immune response, signaling transduction, pathways in cancer, and metabolism, suggesting the inhibitory effects of maternal high-fat intake on certain biological events. Future studies should explore the potential risk and morbidity that may accompany the specific alternation in immune system.

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**A maternal high-energy diet promotes intestinal development and intrauterine growth of offspring**


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**Background:** Previous studies have implied that maternal nutrition during pregnancy may influence the development of the fetal intestine. The objective of this study was to assess the impact of maternal caloric intake during gestation both on fetal growth and on the morphology, enzymatic activity, and gene expression of the fetal intestine in a pig model.

**Methods:** Twenty gilts were randomly assigned, after mating, to 1 of 2 groups: a control group feeding on a standard control diet (based on National Research Council recommendations), and an intervention group feeding on a high-energy diet (identical to the control diet apart from a replacement of fiber with soybean oil to increase caloric intake by 13%). The feeding regimens were applied throughout gestation until delivery. The fetuses and piglets were weighed at day 90 of gestation, day 1 of life, and day 28 of life. At the same time points, an evaluation of intestinal morphology, enzyme activity, and gene and protein expressions of intestinal growth factors was performed.
Results: The body weight of the fetuses and piglets in the high-energy diet group was significantly higher than that of controls at all time points. In addition, the weight of the offspring’s small intestine (SI) was higher in the high-energy diet group at all time points. However, no differences were found in the ratio of small intestine weight to body weight between the 2 groups. In terms of intestinal morphology, an increase in villous height was found in the high-energy diet group. A significant increase in the serum concentration of insulin-like growth factor 1 receptor was also found in the intervention group. Finally, increased gene expression and protein expression of growth factors and nutrient transporters in the jejunum of fetuses and piglets were also observed.

Conclusion: In this pig model, a maternal high-energy diet resulted in larger fetuses and pups, better growth of the intestines, and improved enzymatic and metabolic function – results that may continue to affect the offspring’s metabolism later in life.

Comments
Maternal obesity or a high-fat diet can propagate the risk of metabolic syndrome to subsequent generations via nongenetic or epigenetic and metabolic mechanisms. Previous animal models have demonstrated the role of specific tissue or organs, e.g., liver, skeletal muscle, and pancreas in the subsequent development of metabolic morbidity. Yet, the role of intestinal adaptation to maternal overnutrition in the control of developmental risk of metabolic syndromes was not clear. In the present study, the dams fed a high-energy diet (HED) not only gained greater body weight, but also resulted in a higher circulating triglyceride concentration, suggesting metabolic dysfunction state of dams fed HED. During intrauterine life, glucose and amino acids are the main nutrients to provide energy for intrauterine growth. However, the piglets utilize abundant lactose in milk to provide most of the energy during the neonatal life. In the current study, the activities of both lactase and sucrase were notably increased in the small intestine of weaned piglets in the HED group, indicating that a heavier offspring from HED dams might have adaptively programed a higher digestive activity for more energy to meet the needs of neonatal growth. This observation is in accordance with the finding of the study by Che et al., which is also presented in this chapter. Several growth factors and particularly insulin growth factor 1 (IGF-1) and its receptor are important molecules to promote intestinal development and its function formation. The finding of increased serum IGF-1 concentration, as well as a higher mRNA expression level of the IGF-1 receptor in the jejunum of fetuses and neonates in the HED group, further emphasizes its role in these metabolic processes. Based on the results revealed by the present study, the intestine could be considered as a possible target to modulate the development of metabolic dysfunction in the offspring born from mothers with overnutrition during pregnancy.

Overall Commentary
Maternal nutrition affects fetal growth in many mechanisms. Nutrient supplementation during pregnancy and maintaining balanced maternal diet may improve offspring outcome. However, the impact of nutrition on fetal/offspring growth and development is attenuated by genetic, demographic, behavioral, and other factors. Thus, it should be personalized in order to achieve its maximal benefit.

Disclosure Statement
The authors report no conflicts of interest.
References


Stunting in Developing Countries

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Severe growth faltering leading to stunting is still highly prevalent in low- and lower-middle-income countries. An analysis of data from 54 such countries shows that babies are born small and then follow a remarkably uniform pattern of stunting initiated soon after birth and continuing to a nadir at 2 years of age. Despite many decades of research, the exact etiology of this growth failure remains obscure, which limits our ability to devise effective community-wide preventative strategies. Stunting is ecologically associated with a number of correlates of poverty including: generally poor diets of low diversity; food insecurity; poor water supply, sanitation, and hygiene; frequent infections and inflammation (including enteric infections that cause a persistent environmental enteropathy that may inhibit nutrient uptake); and poor parental understanding of the principles of childcare.

Among these etiological agents, the role of the gut microbiome has received special attention of late and forms the subject of the set of first research studies highlighted here. The second set focuses on more translational aspects of immediate public health relevance and summarizes recent findings from randomized clinical trials of a new type of nutritional foods, so-called small-quantity lipid-based nutritional supplements.
Key articles reviewed for this chapter

**Long-Chain Polyunsaturated Fatty Acids, Pregnancy, and Lactation**

Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children


*Science* 2016;351 pii: aad3311

Sialylated milk oligosaccharides promote microbiota-dependent growth in models of infant undernutrition


*Cell* 2016;164:859–871

Childhood undernutrition, the gut microbiota, and microbiota-directed therapeutics

Blanton LV, Barratt MJ, Charbonneau MR, Ahmed T, Gordon JI

*Science* 2016;352:1533

Effect of ready-to-use foods for preventing child undernutrition in Niger: analysis of a prospective intervention study over 15 months of follow-up

Prudhon C, Langendorf C, Roederer T, Doyon S, Mamaty AA, Woi-Messe L, Manzo ML, de Pee S, Grais RF

*Matern Child Nutr* 2016, DOI: 10.1111/mcn.12236

Provision of 10–40 g/day lipid-based nutrient supplements from 6 to 18 months of age does not prevent linear growth faltering in Malawi


Provision of lipid-based nutrient supplements from age 6 to 18 months does not affect infant development scores in a randomized trial in Malawi


*Matern Child Health J* 2016;20:2199–2208

Supplementation of maternal diets during pregnancy and for 6 months postpartum and infant diets thereafter with small-quantity lipid-based nutrient supplements does not promote child growth by 18 months of age in rural Malawi: a randomized controlled trial


*J Nutr* 2015;145:1345–1353
Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial in Malawi
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Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh
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Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children
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Note: This manuscript is discussed also in the chapter by Grimberg et al. [this vol., pp. 1–15] and in the chapter by Yackobovitch-Gavan and Bhutta [this vol., pp. 134–151].
Summary: Undernourished children have previously been shown to exhibit impaired development of their gut microbiota. Transplanting such microbiota from healthy or undernourished Malawian donors into young germ-free mice that were fed a Malawian diet revealed that the immature microbiota from the undernourished children led to impaired growth. In the recipient animals, several of the age-discriminatory bacterial taxa correlated with lean body mass gain; liver, muscle, and brain metabolism; and bone morphology. In further experiments, mice were cohoused shortly after
receiving microbiota from healthy or severely malnourished infants. It was found that the age- and growth-discriminatory bacteria from the microbiota of the healthy microbiota were able to invade the microbiota of mice receiving the microbiota from malnourished children and that this prevented growth impairment in recipient animals. Adding 2 invasive species, *Ruminococcus gnavus* and *Clostridium symbiosum*, to the microbiota from undernourished donors also ameliorated growth and metabolic abnormalities in recipient mice. These results provide evidence that microbiota immaturity is causally related to undernutrition and reveal potential therapeutic targets.

**Summary:** In the quest for interventions to effectively promote healthy growth in undernourished children, the investigators analyzed human milk oligosaccharides (HMOs) at 6 months postpartum in 2 cohorts of Malawian mothers. They reported that sialylated HMOs were significantly less abundant in mothers of severely stunted infants. They then colonized young germ-free mice with a consortium of bacterial strains cultured from the fecal microbiota of a 6-month-old stunted Malawian infant and fed the recipient animals a typical Malawian diet with or without purified sialylated bovine milk oligosaccharides (S-BMO). Addition of S-BMO improved lean body mass gain, changed bone morphology, and altered liver, muscle, and brain metabolism in ways indicative of a greater ability to utilize nutrients for anabolism. These microbiome-dependent effects were replicated in gnotobiotic piglets using the same bacterial consortium and Malawian diet. The investigators posit that these preclinical models indicate a causal, microbiota-dependent relationship between S-BMO and growth promotion.
Childhood undernutrition, the gut microbiota, and microbiota-directed therapeutics

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Science 2016;352:1533

Summary: Current therapeutic approaches have reduced mortality in individuals with severe disease, but have had limited efficacy in ameliorating long-term sequelae, notably stunting, immune dysfunction, and neurocognitive deficits. The authors review recent work that has provided insights about the role of impaired development of the human gut microbiota in disease pathogenesis that have led to new concepts for treatment and prevention. The findings raise intriguing basic questions about the mechanisms that direct normal gut microbial community assembly and functional maturation. Designing and implementing new microbiota-directed therapeutics for undernutrition highlights the need to simultaneously consider a variety of features of human biology as well as broader societal issues.

Comments

Jeff Gordon and his team at the University of Washington in St. Louis have been prolific in uncovering mechanisms by which differences in the gut microbiota seem to lie on the causal pathway leading to stunting and malnutrition. They previously demonstrated that the malnourished phenotype of Malawian infants could be faithfully transmitted to germ-free mice via a microbiome “transplant”. The effect was especially marked when the mice were fed a typical Malawian diet with low nutrient density. They later showed that undernourished Bangladeshi infants and children had a delay in the normal maturation of the microbiota that occurs in healthy children as infancy progresses. They made the innovative suggestion that a child’s microbiome maturity could be expressed as a $z$ score relative to the expected distribution based on a healthy population.

The latest studies in Science abstracted above advance the story by showing that the growth impairment caused in mice by the transplantation of a “malnourished” human microbiota affects lean body mass, organ metabolism, and bone morphology. They also show that the microbiota of mice that had initially received a healthy microbial transplantation outcompetes the microbiota from malnourished children, thus giving optimism that children harboring a microbiome that is harming their growth could be cured. Specifically, they showed that addition of just 2 invasive species, R. gnavus and C. symbiosum, to the microbiota from undernourished donors also ameliorated growth and metabolic abnormalities in recipient mice.

Their study in Cell advances the story further. They start with the observation in Malawian infants that HMOs were significantly less abundant in the milk of mothers with severely stunted children than in their better-nourished peers. This was followed by 2 innovations. First they showed that they could mimic the growth-depleting effects in mice of a microbiome transplant from severely stunted Malawian infants by colonizing them with a selected consortium of bacteria from malnourished children’s microbiome. They then showed that the growth-depleting effects were significantly ameliorated by feeding the mice purified S-BMO.
Effect of ready-to-use foods for preventing child undernutrition in Niger: analysis of a prospective intervention study over 15 months of follow-up

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Matern Child Nutr 2016, DOI: 10.1111/mcn.12236

Summary: In this study the investigators compared monthly distributions of 2 different lipid-based nutrient supplements (LNS), large-quantity LNS (LNS-LQ), and medium-quantity LNS (LNS-MQ) for 15 months on prevention of undernutrition among 2,586 children 6–23 months of age and measuring 60–80 cm in Maradi, Niger. Six and 11 villages were randomly allocated to LNS-LQ/cash transfer and LNS-MQ/cash transfer, respectively. This study showed that provision of LNS-LQ (reference) or LNS-MQ did not change the incidence of severe acute malnutrition, moderate acute malnutrition, severe stunting, moderate stunting, or mortality. Compared with LNS-LQ, LNS-MQ showed a greater protective effect on moderate acute malnutrition among children with good dietary adequacy: RR: 0.72; 95% CI: 0.56–0.94; p = 0.01. These results highlight the need to design context-specific programs. Provision of LNS-LQ might be more appropriate when food insecurity is high, while when food security is better, distribution of LNS-MQ might be more appropriate.

Provision of 10–40 g/day lipid-based nutrient supplements from 6 to 18 months of age does not prevent linear growth faltering in Malawi

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Summary: Complementing infant diets with lipid-based nutrient supplements (LNS) has been suggested to improve growth and reduce morbidity, but the cost of such programs is affected by the daily quantity and the milk content of LNS. The investigators studied the change in mean length-for-age z score (LAZ) for infants provided with 10–40 g LNS/day from ages 6 to 18 months compared to those receiving no dietary intervention. They also compared milk-containing LNS against...
non-milk LNS. In a randomized single-blind trial, 1,932 six-month-old infants were allocated to 1 of 6 groups to receive 10, 20, or 40 g LNS/day containing milk powder; 20 or 40 g milk-free LNS/day; or no supplement until 18 months of age. The primary outcome was change in LAZ. Overall reported supplement consumption was 71.6% of days, with no difference between the groups. The overall mean ± SD length and LAZ changes were 13.0 ± 2.1 cm and −0.45 ± 0.77 z score units, respectively, which did not differ between the groups (p = 0.66 for length and p = 0.74 for LAZ). The difference in mean LAZ change in the non-milk LNS group compared with the milk LNS group was −0.02 (95% CI: −0.10, 0.06; p = 0.72). The authors concluded that the results do not support the hypothesis that LNS supplementation during infancy and childhood promotes length gain or prevents stunting between 6 and 18 months of age in Malawi.

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**Provision of lipid-based nutrient supplements from age 6 to 18 months does not affect infant development scores in a randomized trial in Malawi**

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*Matern Child Health J* 2016;20:2199–2208

**Summary:** The objective of this study was to determine whether dietary supplementation with several formulations of lipid-based nutrient supplements (LNS), which differed in dose per day and milk content (see the summary for Maleta et al. above), positively affected infant development in Malawi. The investigators assessed motor, language, socioemotional, and executive function at age 18 months. Primary analysis was by intention-to-treat and they also examined 13 potential effect modifiers, including the child’s initial nutritional status and level of developmental stimulation. There were no significant differences between intervention groups in any scores. Initial nutritional status, developmental stimulation, or other factors did not modify the effect in the LNS versus control groups. The investigators concluded that in a population such as this one in Malawi, provision of LNS from the ages of 6 to 18 months would not affect motor, language, socioemotional, or executive function skills at age 18 months.
Supplementation of maternal diets during pregnancy and for 6 months postpartum and infant diets thereafter with small-quantity lipid-based nutrient supplements does not promote child growth by 18 months of age in rural Malawi: a randomized controlled trial

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Summary: The investigators tested whether provision of small-quantity lipid-based nutrient supplements (SQ-LNS) to mothers in pregnancy and for 6 months postpartum and to their infants from 6–18 months of age would promote infant and child growth in rural Malawi. They enrolled 869 pregnant women in a randomized trial in Malawi. Each day the women received 1 capsule of iron-folic acid (IFA), 1 capsule containing 18 micronutrients (MMN), or one 20-g sachet of SQ-LNS (containing 21 MMN, protein, carbohydrates, essential fatty acids, and 118 kcal). Children in the IFA and MMN groups received no supplementation, while children in the LNS group received SQ-LNS from 6 to 18 months. The primary outcome was child length at 18 months. The mean length in the IFA, MMN, and LNS groups was 77.0, 76.9, and 76.8 cm (ns), respectively, and the prevalence of stunting was 32.7, 35.6, and 37.9% (ns), respectively. No intergroup differences were found in the mean weight, head circumference, or mid-upper arm circumference or the proportions with low z scores for these variables. Covariate adjustment did not change any of the analysis results. The authors concluded that provision of SQ-LNS to women in pregnancy and postpartum, and to children from 6 to 18 months, does promote child growth in this Malawian study area.

Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial in Malawi

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Am J Clin Nutr 2016;103:784–793

Summary: The investigators set out to determine whether provision of small-quantity lipid-based nutrient supplements (SQ-LNS) to mothers during pregnancy and the first 6 months postpartum, and to children aged 6–18 months, improves infant development in Malawi. This is the same study as summarized by Ashborn et al. above. The study recorded the acquisition of 11 developmental
milestones monthly by maternal report; observed the attainment of 7 motor milestones at 6, 12, and 18 months of age; and conducted a comprehensive assessment of motor, language, and socioemotional development and executive function at 18 months of age. By maternal report, children in the LNS group achieved walking alone (B = 0.53; 95% CI: 0.11, 0.94; \( p = 0.034 \)) and waving goodbye (B = 0.60; 95% CI: 0.12, 1.08; \( p = 0.040 \)) earlier than the IFA group, and standing with assistance earlier than the MMN group (B = 0.51; 95% CI: 0.12, 0.89; \( p = 0.029 \)). By researcher observation, there was a trend (\( p = 0.052 \)) for a greater percentage of children in the LNS group (58%) to walk alone at age 12 months than in the IFA (49%) and MMN (49%) groups. At age 18 months, there were no significant differences between groups in any scores. The investigators concluded that although provision of SQ-LNS to pregnant women and infants in Malawi may affect the age of acquisition of certain developmental milestones, it did not affect the assessments of motor, language, socioemotional, or executive function skills at 18 months of age.

**Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh**

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**Note:** This article is discussed also in the chapter by Hiersch and Yogev [this vol., pp. 152–164].

**Summary:** The objective of this study was to evaluate the effect of lipid-based nutrient supplements for pregnant and lactating women (LNS-PL) on birth outcomes in Bangladesh. A cluster-randomized effectiveness trial (the Rang-Din Nutrition Study) was conducted within a community health program in rural Bangladesh. The study enrolled 4,011 pregnant women at \( \leq 20 \) gestational weeks; 48 clusters received iron and folic acid (IFA; 60 mg Fe + 400 μg folic acid) and 16 clusters received LNS-PLs (20 g/day, 118 kcal) containing essential fatty acids and 22 vitamins and minerals. Both of the supplements were intended for daily consumption until delivery. The primary outcomes were birth weight and length. Infants in the LNS-PL group had higher birth weights (2,629 ± 408 compared with 2,588 ± 413 g; \( p = 0.007 \)), weight-for-age \( z \) scores (\( -1.48 \pm 1.01 \) compared with \( -1.59 \pm 1.02; p = 0.006 \)), head-circumference-for-age \( z \) scores (HCZ; \( -1.26 \pm 1.08 \) compared with \( -1.34 \pm 1.12; p = 0.028 \)), and BMI \( z \) scores (\( -1.57 \pm 1.05 \) compared with \( -1.66 \pm 1.03; p = 0.005 \)) than those in the IFA group; in adjusted models, the differences in length (47.6 ± 0.07 compared with 47.4 ± 0.04 cm; \( p = 0.043 \)) and LAZ (\( -1.15 \pm 0.04 \) compared with \( -1.24 \pm 0.02; p = 0.035 \)) were also significant. LNS-PL reduced the risk of newborn stunting (18.7% compared with 22.6%; RR: 0.83; 95% CI: 0.71, 0.97) and small head size (HCZ less than –2) (20.7% compared with 24.9%; RR: 0.85; 95% CI: 0.73, 0.98). The effects of LNS-PL on newborn stunting were greatest in infants born before a 10-week interruption in LNS-PL distribution (\( n = 1,301; 15.7\% \) compared with 23.6%; adjusted RR: 0.69; 95% CI: 0.53, 0.89) and in infants born to women \( \leq 24 \) years of age or with household food insecurity. The investigators concluded that prenatal lipid-based nutrient supplements can improve birth outcomes in Bangladeshi women, especially those at higher risk of fetal growth restriction.
The above series of manuscripts describe some of the emerging results on the efficacy of lipid-based nutrient supplements in childhood, including some of the first outcomes from the International Lipid-Based Nutrient Supplements (iLiNS) Project (see www.ilins.org) funded by the Bill & Melinda Gates Foundation. These latest results regarding the potential efficacy of LNS provided to mothers and/or young children in Niger, Burkina Faso, Malawi, and Bangladesh reveal mixed, but generally disappointing, outcomes.

A cluster-randomized trial in 6 and 11 villages in Niger used large-quantity and medium-quantity LNS. Overall there was no protective effect against the development of malnutrition, though there was slight evidence that medium-quantity LNS was effective in children with good dietary adequacy.

The paper in *Journal of Nutrition* by Maleta et al. was a carefully controlled and implemented randomized controlled trial in children 6–18 months of different quantities of LNS in 2 forms: either containing milk protein or non-milk protein. Disappointingly, there was no evidence that any of the formulations benefitted linear growth and protected from stunting.

In the same trial, Prado et al. reported that provision of LNS from age 6 to 18 months did not affect any of their measures of motor, language, socioemotional, or executive function skills at age 18 months.

In a related trial in which LNS was first provided to pregnant Malawian mothers and then to their children (see Ashorn et al., *J Nutr.* above), there was similarly no detectable benefit on child growth. In the same trial, Prado et al. reported that provision of small-quantity lipid-based nutrient supplements to pregnant women and infants may affect the age of acquisition of certain developmental milestones, but did not affect assessments of motor, language, socioemotional, or executive function skills at 18 months of age.

Better news emerged from the large cluster-randomized trial of prenatal LNS provided to Bangladeshi women by Mridha et al. This showed clear evidence of increased size at birth (and hence a reduction in stunting and risk of small head circumference). The effect was most pronounced among mothers with a higher background risk of having a growth-restricted baby.

In summary, the rather disappointing results from these diligently conducted randomized trials underscores the fact that nutrition does not act alone. Mothers and children will not be able to benefit properly from nutritional inputs while still under the threat of constant infectious assaults that drive persistent gut damage and subclinical inflammation that impairs nutrient utilization. So-called nutrition-sensitive interventions to improve the environment must accompany nutrient-specific interventions.
Author Index

Aburto, T.C. 24
Acerini, C. 124
Adriaanse, M.P.M. 107
Afxentiou, T. 57
Agostoni, C. 63, 80
Ahmed, S.F. 1
Ahmed, T. 169
Akrout, M. 127
Albrecht, P. 99
Alderete, T.L. 22, 121
Alexandre-Gouabau, M.C. 131
Alho, L. 170, 172
Alibrandi, A. 87
Almstrup, K. 6
Altman, D.G. 139
Ambalavanan, N. 69
Ambrosini, G.L. 41, 130
Amezcua-Prieto, C. 157
Andersen, R. 45, 92
Anderson, P.J. 75, 85
Anderson-Berry, A. 70
Andrade, A.C. 13
Angood, C. 136
Ansari, I.U. 4
Appannah, G. 41
Ariceta, G. 111
Armas, L. 70
Ashby, D. 67
Ashley Luciano, A. 65
Ashorn, P. 11, 149, 167, 168, 170, 171, 172
Ashorn, U. 170, 171, 172
Astrup, A. 45, 92
Autran, C. 22, 121
Babalis, D. 67
Baiko, S. 111
Bailey, M.E. 35
Bain, J.R. 168
Baird, D.D. 58

Bakker, E.C. 86
Balan, A. 143
Balan, I. 143
Banaszkiewicz, A. 99
Bao, W. 12
Barberger-Gateau, P. 40
Barclay, A. 100
Barclay, A.W. 42
Barile, D. 168
Baron, J. 13
Barr, S.I. 154
Barratt, M.J. 11, 149, 167, 168, 169
Barros, F.C. 139
Barton, S.J. 35
Batra, P. 143
Battelino, T. 16
Bauer, C.P. 37, 56
Beilin, L.J. 41
Belfort, M.B. 14
Bell, J. 67
Bellinger, D.C. 88
Bendabenda, J. 170
Berdel, D. 37, 56
Berglund, S.K. 140
Berkley, J.A. 136
Bertino, E. 139
Berto, M. 100
Bettocchi, S. 80
Bever Babendure, J. 120
Bhutta, Z.A. 134, 139
Bjerre, A. 111
Björn, M. 140
Blanton, L.V. 11, 149, 167, 168, 169
Blaut, M. 100
Bode, L. 22, 121
Bodewes, F. 108
Böhm, M. 111
Bolca, S. 31
Bonfill Cosp, X. 84
Bonthuis, M. 111
Boquien, C.Y. 131
Boraska, V. 35
Borowitz, D. 108
Bortolotti, M. 145
Bosch, R.J. 88
Bottai, M. 89
Bowers, K. 12
Boyle, E.M. 76
Boyle, R.J. 57
Brabin, B.J. 158
Bradley, E.W. 7
Brady, S. 9
Braet, C. 25
Brand-Miller, J.C. 42
Braun, K.V.E. 129
Braunstein, P. 10
Brekke, B.E. 22, 121
Brennan, P.A. 91
Briend, A. 141
British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study 114
Brosh, T. 144
Brown, C. 143
Brüske, I. 37, 56
Bryan, M. 61
Bryk, G. 148
Bueno-Cavanillas, A. 157
Busch, A.S. 6
Buurman, W.A. 107
Buyken, A. 37

Caldas-Afonso, A. 111
Callaghan, M. 141
Calus, S.T. 100
Calvache, J.A. 84
Camhi, S.M. 43
Camilleri, E.T. 7
Candia Longo, A. 87
Cantoral, A. 24
Cao, Y. 103
Carlo, W.A. 69
Carlsen, E.M. 160
Carnielli, V. 73
Carriere, C. 40
Carriquiry, A.L. 24
Casper, C. 73
Cassidy, O.L. 9
Casteillejo, G. 64
Catassi, C. 64
Chalkiadaki, G. 89
Chaparro, C.M. 156, 173
Chaput, J.-P. 47
Charbonneau, M.R. 11, 149, 167, 168, 169
Chatzi, L. 89

Chavarro, J.E. 12
Che, L. 161, 162
Chen, K.Y. 9
Chen, N.N. 154
Cheng, J. 168
Cheung, Y.B. 170, 172
Chivinge, J. 57
Choisy, C. 145
Christensen, H.T. 3
Christmann, V. 72
Clokie, S.J. 13
Closa-Monasterolo, R. 132
Collins, C.T. 75
Coronel, M.Z. 148
Corpeleijn, W.E. 72
Cortes, D. 160
Corwin, E.J. 91
Couce, M.L. 73
Courville, A.B. 9
Craig, C.M. 69
Crocker, A.H. 142
Cuenca-Garcia, M. 31
Cummins, J.R. 156, 173
Cunha, S. 57
Cynober, L. 145

Dalmeijer, G.W. 83
Dalskov, S.M. 92
Dalskov, S.-M. 45
Damm, P. 12
Dansgaard, C.T. 45, 92
Daniels, L.A. 34
Darmaun, D. 131
Dash, H.S. 125
Davidson, K. 97
Davies, R. 114
Davila, Y.R. 120
Davis, J.C. 168
Day, L.T. 156, 173
Daymont, C. 61
De Bandt, J.P. 145
De Bourdeaudhuij, I. 27
De Decker, A. 25
De Groot, R.H. 86
De Henauw, S. 25, 31
De Luca, A. 131
De Oliveira, L.D. 23
De Pee, S. 170
De Portella, M.L. 148
De Sa, A.B. 143
De Waard, M. 72
Deoudiss, G.Y. 35
Delgado-Noguería, M.F. 84
Denison, F.C. 158
Déti, E.K. 40
<table>
<thead>
<tr>
<th>Author Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dewey, K.G.</td>
<td>11, 149, 156, 167, 168, 170, 171, 172, 173</td>
</tr>
<tr>
<td>Deyle, D.R.</td>
<td>7</td>
</tr>
<tr>
<td>Diaz Heijtz, R.</td>
<td>91</td>
</tr>
<tr>
<td>Dietz, A.B.</td>
<td>7</td>
</tr>
<tr>
<td>Dillon, S.</td>
<td>93</td>
</tr>
<tr>
<td>Dinh, D.M.</td>
<td>10</td>
</tr>
<tr>
<td>Dolan, C.</td>
<td>136</td>
</tr>
<tr>
<td>Dolan, L.M.</td>
<td>44</td>
</tr>
<tr>
<td>Dolkart, O.</td>
<td>144</td>
</tr>
<tr>
<td>Domellöf, M.</td>
<td>64, 68, 140</td>
</tr>
<tr>
<td>Dompeling, E.</td>
<td>107</td>
</tr>
<tr>
<td>Dong, Y.</td>
<td>20</td>
</tr>
<tr>
<td>Doré, C.J.</td>
<td>67</td>
</tr>
<tr>
<td>Douglas, S.M.</td>
<td>28</td>
</tr>
<tr>
<td>Downer, M.K.</td>
<td>35</td>
</tr>
<tr>
<td>Doyle, L.W.</td>
<td>75</td>
</tr>
<tr>
<td>Doyon, S.</td>
<td>170</td>
</tr>
<tr>
<td>Draper, E.S.</td>
<td>76</td>
</tr>
<tr>
<td>Dudakovic, A.</td>
<td>7</td>
</tr>
<tr>
<td>Duggan, C.</td>
<td>88</td>
</tr>
<tr>
<td>Dunger, D.</td>
<td>124</td>
</tr>
<tr>
<td>Dunlop, A.</td>
<td>91</td>
</tr>
<tr>
<td>Durighel, G.</td>
<td>67</td>
</tr>
<tr>
<td>Dyssegaard, C.B.</td>
<td>92</td>
</tr>
<tr>
<td>Dziekiewicz, M.</td>
<td>99</td>
</tr>
<tr>
<td>Ederies, A.</td>
<td>67</td>
</tr>
<tr>
<td>Edwards, C.A.</td>
<td>100</td>
</tr>
<tr>
<td>Egelund, N.</td>
<td>92</td>
</tr>
<tr>
<td>Emmett, P.M.</td>
<td>21</td>
</tr>
<tr>
<td>Eren, A.M.</td>
<td>100</td>
</tr>
<tr>
<td>Ertl, T.</td>
<td>73</td>
</tr>
<tr>
<td>ESCAPE Trial Group</td>
<td>110</td>
</tr>
<tr>
<td>Escribano, J.</td>
<td>132</td>
</tr>
<tr>
<td>Fall, C.H.</td>
<td>14</td>
</tr>
<tr>
<td>Fan, Y.</td>
<td>167</td>
</tr>
<tr>
<td>Fan, Y.M.</td>
<td>149, 168</td>
</tr>
<tr>
<td>Fang, Z.</td>
<td>161, 162</td>
</tr>
<tr>
<td>Fangupo, L.J.</td>
<td>33, 65</td>
</tr>
<tr>
<td>Feng, B.</td>
<td>161, 162</td>
</tr>
<tr>
<td>Ferchaud-Roucher, V.</td>
<td>131</td>
</tr>
<tr>
<td>Ferré, N.</td>
<td>132</td>
</tr>
<tr>
<td>Ferrucci, L.</td>
<td>8, 146</td>
</tr>
<tr>
<td>Feskens, E.J.</td>
<td>125</td>
</tr>
<tr>
<td>Fewtrell, M.S.</td>
<td>64</td>
</tr>
<tr>
<td>Field, D.J.</td>
<td>76</td>
</tr>
<tr>
<td>Fields, D.A.</td>
<td>22, 121</td>
</tr>
<tr>
<td>Filipiak-Pittroff, B.</td>
<td>56</td>
</tr>
<tr>
<td>Fink, A.</td>
<td>104</td>
</tr>
<tr>
<td>Fleming, E.A.</td>
<td>65</td>
</tr>
<tr>
<td>Flexeder, C.</td>
<td>37</td>
</tr>
<tr>
<td>Flume, P.A.</td>
<td>104</td>
</tr>
<tr>
<td>Forman, M.R.</td>
<td>20</td>
</tr>
<tr>
<td>Fort, P.</td>
<td>69</td>
</tr>
<tr>
<td>Franco, O.H.</td>
<td>125, 129</td>
</tr>
<tr>
<td>Frongillo, E.W.</td>
<td>138</td>
</tr>
<tr>
<td>Fthenou, E.</td>
<td>89</td>
</tr>
<tr>
<td>Fulford, A.J.</td>
<td>158</td>
</tr>
<tr>
<td>Gabet, Y.</td>
<td>144</td>
</tr>
<tr>
<td>Gadzinowski, J.S.</td>
<td>73</td>
</tr>
<tr>
<td>Galescu, O.A.</td>
<td>9</td>
</tr>
<tr>
<td>Galland, B.C.</td>
<td>33</td>
</tr>
<tr>
<td>Galli-Tsinopoulou, A.</td>
<td>84</td>
</tr>
<tr>
<td>Gamache, M.G.</td>
<td>143</td>
</tr>
<tr>
<td>Garcia, S.</td>
<td>159</td>
</tr>
<tr>
<td>Garcia-Larsen, V.</td>
<td>57</td>
</tr>
<tr>
<td>Gat-Yablonski, G.</td>
<td>144</td>
</tr>
<tr>
<td>Gawronska, A.</td>
<td>99</td>
</tr>
<tr>
<td>Gehring, U.</td>
<td>83</td>
</tr>
<tr>
<td>Gelfond, D.</td>
<td>108</td>
</tr>
<tr>
<td>Geoghegan, N.</td>
<td>57</td>
</tr>
<tr>
<td>Georgiou, V.</td>
<td>89</td>
</tr>
<tr>
<td>Gerasimidis, K.</td>
<td>100</td>
</tr>
<tr>
<td>Gerber, J.S.</td>
<td>61</td>
</tr>
<tr>
<td>German KIGS Board</td>
<td>110</td>
</tr>
<tr>
<td>Ghassabian, A.</td>
<td>125</td>
</tr>
<tr>
<td>Ghosh, S.</td>
<td>141</td>
</tr>
<tr>
<td>Gibson, R.A.</td>
<td>85</td>
</tr>
<tr>
<td>Gielen, M.</td>
<td>86</td>
</tr>
<tr>
<td>Gillman, M.W.</td>
<td>14</td>
</tr>
<tr>
<td>GINIplus Study Group</td>
<td>37, 56</td>
</tr>
<tr>
<td>Giorgianni, G.</td>
<td>87</td>
</tr>
<tr>
<td>Giuliani, F.</td>
<td>139</td>
</tr>
<tr>
<td>Goday, P.S.</td>
<td>103</td>
</tr>
<tr>
<td>Godschalk, R.W.</td>
<td>86</td>
</tr>
<tr>
<td>Gomes, F.</td>
<td>70</td>
</tr>
<tr>
<td>Gomez-Martinez, S.</td>
<td>31</td>
</tr>
<tr>
<td>Gondwe, A.</td>
<td>172</td>
</tr>
<tr>
<td>Gonzalez-Freire, M.</td>
<td>8</td>
</tr>
<tr>
<td>González-Gross, M.</td>
<td>31</td>
</tr>
<tr>
<td>Goran, M.I.</td>
<td>22, 121</td>
</tr>
<tr>
<td>Gordon, J.I.</td>
<td>11, 90, 149, 167, 168, 169</td>
</tr>
<tr>
<td>Gottrand, F.</td>
<td>31</td>
</tr>
<tr>
<td>Gould, J.F.</td>
<td>85</td>
</tr>
<tr>
<td>Goyal, M.S.</td>
<td>90</td>
</tr>
<tr>
<td>Grais, R.F.</td>
<td>170</td>
</tr>
<tr>
<td>Grammatikakis, E.</td>
<td>31</td>
</tr>
<tr>
<td>Granstrom, C.</td>
<td>12</td>
</tr>
<tr>
<td>Grathwohl, D.</td>
<td>59</td>
</tr>
<tr>
<td>Gravett, M.G.</td>
<td>139</td>
</tr>
<tr>
<td>Gray, A.R.</td>
<td>33</td>
</tr>
<tr>
<td>Green, T.J.</td>
<td>154</td>
</tr>
<tr>
<td>Grimberg, A.</td>
<td>1</td>
</tr>
<tr>
<td>Grise, J.B.</td>
<td>142</td>
</tr>
<tr>
<td>Groothoff, W.J.</td>
<td>111</td>
</tr>
<tr>
<td>Grundmeier, R.W.</td>
<td>61</td>
</tr>
<tr>
<td>Grunnet, L.G.</td>
<td>12</td>
</tr>
</tbody>
</table>
Grzybowska-Chlebowczyk, U. 99
Gualtieri, A.F. 148
Guandalini, S. 63
Gulati, R. 158
Guruge, J. 168
Habicht, J.P. 138
Haffner, D. 110
Hagen, C.P. 6
Haig, S.J. 100
Hallodorsson, T.I. 160
Hamilton, H.A. 47
Hankard, R. 131
Hanna, M.B. 33
Hansen, R. 100
Hansen, S. 12
Hanson, C. 70
Harding, K.L. 156, 173
Harjunmaa, U. 172
Harmon, Q.E. 58
Harris, C. 37
Hartman, C. 95, 97
Hasan, N.M. 4
Hascoet, J.M. 73
Hassoun, S. 10
Haszard, J.J. 65
Haugard, L.K. 14
Hayman, L.L. 43
He, F.J. 29
Heath, A.L. 33
Heath, A.L.M. 65
Heinrich, J. 35, 56
Hellström, A. 68
Henrisat, B. 11, 149, 167
Hernandez, L.M. 20
Hernández-Barrera, L. 24
Hernell, O. 73
Hewavitharana, A. 70
Hiersch, L. 152
Higgins, K.A. 28
Himes, J.H. 20
Hirschfeld, S. 20
Hjorth, M.F. 45
Hoertel, H.A. 28
Hoffmann, B. 56
Hoffmann, U. 56
Hokken-Koelega, A.C. 123
Holloway, J.W. 35
Holmström, G. 68
Hopkins, D. 21
Hornstra, G. 86
Hoyo, C. 155
Hu, F.B. 12, 35
Hu, L. 161
Huang, R.C. 41
Hughes, I. 124
Huikari, V. 35
Husby, S. 64
Hussain, S. 156, 173
Huybrechts, I. 31
Hyrich, K.L. 114
Ierodiakonou, D. 57
Ijaz, U.Z. 100
Ilkayeva, O. 11, 149, 167
Ilkayeva, O. 168
Innis, S.M. 154
Inskip, H. 35
International Fetal and Newborn Growth Consortium for the 21st Century
Jaddoe, V.W. 35, 125
Jaddoe, V.W.V. 129
Jaffer, Y.A. 139
Jager, K.J. 111
Jalal, C.S. 147
Jansen-van der Weide, M.C. 72
Jarrold, K. 57
Jebb, S. 130
Jebb, S.A. 41
Jegatheesan, P. 145
Jensen, J.E. 160
Jha, P. 44
Jiménez-Moleón, J.J. 157
Johnson, L. 130
Johnson, S. 76
Jolly, S.P. 147
Jones, G. 70
Jones, M. 42
Jordan, S. 91
Jorgensen, J. 168
Jorgensen, J.M. 11, 149, 167
Jüliusson, P.B. 3
Justo Giugliani, E.R. 23
Juul, A. 6
Kafatos, A. 31
Kampouri, M. 89
Kamran, F. 13
Kane, A.V. 10
Kang, G. 10
Kapanee, A.R.M. 88
Kaplan, R.C. 35
Karakochuk, C.D. 154
Karaš, J. 127
Katulla, D. 10
Kaufmann, M. 70
Kearsley-Fleet, L. 114
Kelly, N.R. 9
Kendrick, M.A. 4
Kennedy, J.A. 142
Kennedy, S.H. 139
Kersting, M. 31
Khadeer, M.A. 146
Khan, T. 57
Khara, T. 136
Khoury, P.R. 44
Kiefte-de Jong, J.C. 35, 129
Kilpeläinen, T.O. 35
Kimball, T.R. 44
Kippler, M. 89
Kirschner, P.A. 86
Klincewicz, B. 99
Knight, R. 22, 121
Kocevska, D. 125
Kogevinas, M. 89
Kolacek, S. 64
Koletzko, B. 37, 127
Koletzko, S. 37, 56, 64
Kolvek, G. 111
Kooi, E.M. 72
Koorts, P. 70
Kopelman, G.H. 83
Körner, A. 35
Korponay-Szabo, I.R. 64
Kotanidou, E.P. 84
Koutra, K. 89
Kouwenhoven, S.M. 72, 127
Kowalska-Duplaga, K. 99
Kraemer, K. 146
Kramer, M.S. 14
Krämer, U. 56
Krarup, H. 45
Kremer, S. 86
Krishnaveni, G.V. 14
Kriström, B. 140
Krochick, G.A. 159
Kumwenda, C. 170
Kurpad, A.V. 88
Kyriklaki, A. 89

Labaune, J.M. 59
Labayen, I. 31
Lafeber, H.N. 72
Lai, H.J. 102
Laitinen, J. 35
Lakka, T.A. 35
Lambert, A. 139
Langendorf, C. 170
Langevin, C. 40
Langhoff-Roos, J. 12
Lapillonne, A. 73
Larikjær, A. 118
Larson, A.N. 7
Lartey, A. 172
Lauritzen, L. 92
Lawrence, J.A. 33
Lazarte, F. 93
Łazowska-Przeorek, I. 99
Leathwood, P. 66
Lebrilla, C. 168
Leidy, H.J. 28
Leonardi-Bee, J. 57
Leroy, J.L. 138
Levy, H. 103
Lewallen, D.G. 7
Lewallen, E.A. 7
Lewis-Mikhael, A.M. 157
Leyn, S.A. 11, 149, 167
Li, J. 161, 162
Li, S. 12
Lichtenstein, A.H. 43
Lin, Y. 31, 161, 162
Lind, M.V. 118
Lindberg, A. 110
Lindberg, J. 140
Lindhardt Johansen, M. 6
Lindi, V. 35
Link, E. 56
Lionetti, E. 64
Litkowskii, P.E. 142
Liu, A. 12
Liu, G. 35
Liu, P. 161, 162
Liu, X. 67
Livingstone, M.B. 39
Localio, A.R. 61
Loman, N. 100
Longacre, M.J. 4
Loos, R.J.F. 35
Lopez, A.P. 159
Lou, W. 147
Louie, J.C. 42
Lowe, N.M. 93
Lubarsky, B. 108
Lugones, C. 148
Lui, J.C. 13
Luna-Del-Castillo, J.d.D. 157
Lundgren, P. 68
Lunt, M. 114
Luque, V. 132
Lyden, E. 70
Lyon, M.R. 154
<table>
<thead>
<tr>
<th>Author</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma, Y.</td>
<td>29</td>
</tr>
<tr>
<td>MacDonald, M.J.</td>
<td>4</td>
</tr>
<tr>
<td>Mace, K.</td>
<td>59</td>
</tr>
<tr>
<td>MacGregor, G.A.</td>
<td>29</td>
</tr>
<tr>
<td>Machogu, E.</td>
<td>103</td>
</tr>
<tr>
<td>Madsen, C.</td>
<td>12</td>
</tr>
<tr>
<td>Magarey, A.</td>
<td>34</td>
</tr>
<tr>
<td>Magnussson, J.</td>
<td>35</td>
</tr>
<tr>
<td>Maier-Nöth, A.</td>
<td>66</td>
</tr>
<tr>
<td>Makrides, M.</td>
<td>75, 85</td>
</tr>
<tr>
<td>Maleta, K.</td>
<td>168, 171, 172</td>
</tr>
<tr>
<td>Maleta, K.M.</td>
<td>8, 11, 142, 146, 149, 167, 170</td>
</tr>
<tr>
<td>Mallan, K.M.</td>
<td>34</td>
</tr>
<tr>
<td>Mamaty, A.A.</td>
<td>170</td>
</tr>
<tr>
<td>Manary, M.</td>
<td>141</td>
</tr>
<tr>
<td>Manary, M.J.</td>
<td>8, 11, 142, 146, 149, 167</td>
</tr>
<tr>
<td>Mandalunis, P.</td>
<td>148</td>
</tr>
<tr>
<td>Mangani, C.</td>
<td>168</td>
</tr>
<tr>
<td>Manios, Y.</td>
<td>31</td>
</tr>
<tr>
<td>Mank, E.</td>
<td>72</td>
</tr>
<tr>
<td>Manktelow, B.N.</td>
<td>76</td>
</tr>
<tr>
<td>Manzo, M.L.</td>
<td>170</td>
</tr>
<tr>
<td>March, K.M.</td>
<td>154</td>
</tr>
<tr>
<td>Marderfeld, L.</td>
<td>97</td>
</tr>
<tr>
<td>Mårlid, S.</td>
<td>27</td>
</tr>
<tr>
<td>Marlow, N.</td>
<td>76</td>
</tr>
<tr>
<td>Martin, K.</td>
<td>12</td>
</tr>
<tr>
<td>Masarwi, M.</td>
<td>144</td>
</tr>
<tr>
<td>Mattias, S.L.</td>
<td>156, 173</td>
</tr>
<tr>
<td>Matthews, R.</td>
<td>76</td>
</tr>
<tr>
<td>Mauch, C.E.</td>
<td>34</td>
</tr>
<tr>
<td>Maurice, S.</td>
<td>40</td>
</tr>
<tr>
<td>Mayer-Hamblett, N.</td>
<td>104</td>
</tr>
<tr>
<td>Mazza, C.S.</td>
<td>159</td>
</tr>
<tr>
<td>McConachy, H.</td>
<td>70</td>
</tr>
<tr>
<td>McCullough, L.E.</td>
<td>155</td>
</tr>
<tr>
<td>McGee-Lawrence, M.E.</td>
<td>7</td>
</tr>
<tr>
<td>McGrohan, P.</td>
<td>100</td>
</tr>
<tr>
<td>McPhee, A.J.</td>
<td>85</td>
</tr>
<tr>
<td>Mearin, L.</td>
<td>64</td>
</tr>
<tr>
<td>Mehari, R.</td>
<td>9</td>
</tr>
<tr>
<td>Mehis, O.</td>
<td>110</td>
</tr>
<tr>
<td>Melén, E.</td>
<td>35</td>
</tr>
<tr>
<td>Mencarelli, F.</td>
<td>111</td>
</tr>
<tr>
<td>Mendez, M.A.</td>
<td>155</td>
</tr>
<tr>
<td>Mendias, E.</td>
<td>120</td>
</tr>
<tr>
<td>Mendola, P.</td>
<td>12</td>
</tr>
<tr>
<td>Menheere, P.P.C.A.</td>
<td>107</td>
</tr>
<tr>
<td>Michaelson, K.F.</td>
<td>92, 118</td>
</tr>
<tr>
<td>Michaelson, K.M.</td>
<td>45</td>
</tr>
<tr>
<td>Michels, N.</td>
<td>25</td>
</tr>
<tr>
<td>Milbrandt, J.</td>
<td>90</td>
</tr>
<tr>
<td>Miller, E.E.</td>
<td>155</td>
</tr>
<tr>
<td>Miller, T.</td>
<td>103</td>
</tr>
<tr>
<td>Mills, D.A.</td>
<td>168</td>
</tr>
<tr>
<td>Mills, V.C.</td>
<td>33</td>
</tr>
<tr>
<td>Moaddel, R.</td>
<td>8, 146</td>
</tr>
<tr>
<td>Modi, N.</td>
<td>67</td>
</tr>
<tr>
<td>Molchanova, E.A.</td>
<td>111</td>
</tr>
<tr>
<td>Moleti, M.</td>
<td>87</td>
</tr>
<tr>
<td>Mølgaard, C.</td>
<td>45, 118</td>
</tr>
<tr>
<td>Molloy, C.S.</td>
<td>75</td>
</tr>
<tr>
<td>Molnár, D.</td>
<td>31</td>
</tr>
<tr>
<td>Molnár, D.</td>
<td>27</td>
</tr>
<tr>
<td>Montecino, M.A.</td>
<td>7</td>
</tr>
<tr>
<td>Moramarco, M.W.</td>
<td>120</td>
</tr>
<tr>
<td>Morel, Y.</td>
<td>59</td>
</tr>
<tr>
<td>Moreno, L.A.</td>
<td>16, 27, 31</td>
</tr>
<tr>
<td>Morgan, W.J.</td>
<td>104</td>
</tr>
<tr>
<td>Mori, T.A.</td>
<td>41</td>
</tr>
<tr>
<td>Morison, B.J.</td>
<td>65</td>
</tr>
<tr>
<td>Mossavar-Rahmani, Y.</td>
<td>35</td>
</tr>
<tr>
<td>Mouratidou, T.</td>
<td>27, 31</td>
</tr>
<tr>
<td>Mozas-Moreno, J.</td>
<td>157</td>
</tr>
<tr>
<td>Mozer-Glassberg, Y.</td>
<td>97</td>
</tr>
<tr>
<td>Mridha, M.K.</td>
<td>156, 173</td>
</tr>
<tr>
<td>Muehlbauer, M.J.</td>
<td>168</td>
</tr>
<tr>
<td>Mulder, M.T.</td>
<td>123</td>
</tr>
<tr>
<td>Munck, A.</td>
<td>108</td>
</tr>
<tr>
<td>Murakami, K.</td>
<td>39</td>
</tr>
<tr>
<td>Murphy, J.R.</td>
<td>91</td>
</tr>
<tr>
<td>Murphy, S.K.</td>
<td>155</td>
</tr>
<tr>
<td>Murtha, A.P.</td>
<td>155</td>
</tr>
<tr>
<td>Must, A.</td>
<td>43</td>
</tr>
<tr>
<td>Naumbiar, S.</td>
<td>34</td>
</tr>
<tr>
<td>Naumova, E.N.</td>
<td>10</td>
</tr>
<tr>
<td>Nella, A.A.</td>
<td>13</td>
</tr>
<tr>
<td>Newgard, C.B.</td>
<td>11, 149, 167, 168</td>
</tr>
<tr>
<td>Nicholson, J.M.</td>
<td>34</td>
</tr>
<tr>
<td>Nicola, T.</td>
<td>69</td>
</tr>
<tr>
<td>Nielsen, J.E.</td>
<td>6</td>
</tr>
<tr>
<td>Nilas, L.</td>
<td>160</td>
</tr>
<tr>
<td>Nilsson, O.</td>
<td>13</td>
</tr>
<tr>
<td>Noble, J.A.</td>
<td>139</td>
</tr>
<tr>
<td>Nørgaard, K.</td>
<td>160</td>
</tr>
<tr>
<td>Norman, M.</td>
<td>140</td>
</tr>
<tr>
<td>Northstone, K.</td>
<td>21</td>
</tr>
<tr>
<td>Ntalla, I.</td>
<td>35</td>
</tr>
<tr>
<td>O’Donnell, D.</td>
<td>168</td>
</tr>
<tr>
<td>Ochieng, R.</td>
<td>139</td>
</tr>
<tr>
<td>Oddy, W.H.</td>
<td>41</td>
</tr>
<tr>
<td>Öhlund, I.</td>
<td>68</td>
</tr>
<tr>
<td>Ohuma, E.O.</td>
<td>139</td>
</tr>
<tr>
<td>Oken, E.</td>
<td>14</td>
</tr>
<tr>
<td>Okuda, M.</td>
<td>35</td>
</tr>
<tr>
<td>Olmedo-Requena, R.</td>
<td>157</td>
</tr>
<tr>
<td>Olsen, S.F.</td>
<td>12, 160</td>
</tr>
<tr>
<td>Ong, K.</td>
<td>124</td>
</tr>
<tr>
<td>Author</td>
<td>Pages</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Ordiz, M.I.</td>
<td>8, 146</td>
</tr>
<tr>
<td>Osmond, C.</td>
<td>14</td>
</tr>
<tr>
<td>Osterman, A.L.</td>
<td>11, 149, 167</td>
</tr>
<tr>
<td>Owens, S.</td>
<td>158</td>
</tr>
<tr>
<td>Pacce, S.</td>
<td>159</td>
</tr>
<tr>
<td>Palmgren, I.</td>
<td>73</td>
</tr>
<tr>
<td>Pang, R.</td>
<td>139</td>
</tr>
<tr>
<td>Papadopoulou, A.</td>
<td>64</td>
</tr>
<tr>
<td>Papageorghiou, A.T.</td>
<td>139</td>
</tr>
<tr>
<td>Paradise, C.R.</td>
<td>7</td>
</tr>
<tr>
<td>Parks, E.P.</td>
<td>61</td>
</tr>
<tr>
<td>Patro-Goląb, B.</td>
<td>127</td>
</tr>
<tr>
<td>Patterson, E.</td>
<td>31</td>
</tr>
<tr>
<td>Paul, R.R.</td>
<td>156, 173</td>
</tr>
<tr>
<td>Pedersen, B.T.</td>
<td>3</td>
</tr>
<tr>
<td>Peerson, J.M.</td>
<td>156, 173</td>
</tr>
<tr>
<td>Péneau, S.</td>
<td>127</td>
</tr>
<tr>
<td>Perng, W.</td>
<td>14</td>
</tr>
<tr>
<td>Petersen, J.H.</td>
<td>6</td>
</tr>
<tr>
<td>Petersen, R.A.</td>
<td>45, 92</td>
</tr>
<tr>
<td>Petit, I.O.</td>
<td>3</td>
</tr>
<tr>
<td>Phillip, M.</td>
<td>1, 144</td>
</tr>
<tr>
<td>Phiri, N.</td>
<td>170, 172</td>
</tr>
<tr>
<td>Phiri, T.E.</td>
<td>170, 172</td>
</tr>
<tr>
<td>Phuka, J.</td>
<td>170, 171</td>
</tr>
<tr>
<td>Picaud, J.C.</td>
<td>59</td>
</tr>
<tr>
<td>Pieścik-Lech, M.</td>
<td>62</td>
</tr>
<tr>
<td>Pigeot, I.</td>
<td>27</td>
</tr>
<tr>
<td>Pimpin, L.</td>
<td>130</td>
</tr>
<tr>
<td>Pitkänen, N.</td>
<td>35</td>
</tr>
<tr>
<td>Pitsiladis, Y.</td>
<td>35</td>
</tr>
<tr>
<td>Pituch-Zdanowska, A.</td>
<td>99</td>
</tr>
<tr>
<td>Polanco, I.</td>
<td>64</td>
</tr>
<tr>
<td>Poraz, I.</td>
<td>97</td>
</tr>
<tr>
<td>Pot, G.K.</td>
<td>41</td>
</tr>
<tr>
<td>Pournara, E.</td>
<td>3</td>
</tr>
<tr>
<td>Prado, E.L.</td>
<td>171, 172</td>
</tr>
<tr>
<td>Prentice, A.M.</td>
<td>158, 165</td>
</tr>
<tr>
<td>Prentice, P.</td>
<td>124</td>
</tr>
<tr>
<td>Prudhon, C.</td>
<td>170</td>
</tr>
<tr>
<td>Pruzenisky, W.</td>
<td>143</td>
</tr>
<tr>
<td>Pryds, O.</td>
<td>160</td>
</tr>
<tr>
<td>Pulakka, A.</td>
<td>170</td>
</tr>
<tr>
<td>Purwar, M.</td>
<td>139</td>
</tr>
<tr>
<td>Putet, G.</td>
<td>59</td>
</tr>
<tr>
<td>Qi, L.</td>
<td>35</td>
</tr>
<tr>
<td>Qi, Q.</td>
<td>35</td>
</tr>
<tr>
<td>Qin, L.</td>
<td>161</td>
</tr>
<tr>
<td>Qualter, P.</td>
<td>93</td>
</tr>
<tr>
<td>Quick, J.</td>
<td>100</td>
</tr>
<tr>
<td>Quince, C.</td>
<td>100</td>
</tr>
<tr>
<td>Quintero, D.</td>
<td>103</td>
</tr>
<tr>
<td>Radin, R.M.</td>
<td>9</td>
</tr>
<tr>
<td>Raichle, M.E.</td>
<td>90</td>
</tr>
<tr>
<td>Raitakari, O.</td>
<td>35</td>
</tr>
<tr>
<td>Ramadass, B.</td>
<td>10</td>
</tr>
<tr>
<td>Ramthal, A.</td>
<td>88</td>
</tr>
<tr>
<td>Raverot, V.</td>
<td>59</td>
</tr>
<tr>
<td>Reeves, T.</td>
<td>57</td>
</tr>
<tr>
<td>Reifsnider, E.</td>
<td>120</td>
</tr>
<tr>
<td>Reisch, L.</td>
<td>27</td>
</tr>
<tr>
<td>Renault, K.M.</td>
<td>160</td>
</tr>
<tr>
<td>Renders, C.M.</td>
<td>83</td>
</tr>
<tr>
<td>Reusz, G.</td>
<td>111</td>
</tr>
<tr>
<td>Rezvani, G.</td>
<td>13</td>
</tr>
<tr>
<td>Ribarola, L.</td>
<td>159</td>
</tr>
<tr>
<td>Ribes-Könic, C.</td>
<td>64</td>
</tr>
<tr>
<td>Richmond, R.</td>
<td>35</td>
</tr>
<tr>
<td>Riester, S.M.</td>
<td>7</td>
</tr>
<tr>
<td>Rifas-Shiman, S.L.</td>
<td>14</td>
</tr>
<tr>
<td>Rigo, J.</td>
<td>73</td>
</tr>
<tr>
<td>Rijlaarsdam, J.</td>
<td>125</td>
</tr>
<tr>
<td>Rio, M.E.</td>
<td>148</td>
</tr>
<tr>
<td>Ritz, C.</td>
<td>45</td>
</tr>
<tr>
<td>Rivera, J.A.</td>
<td>24</td>
</tr>
<tr>
<td>Roberts, S.B.</td>
<td>143</td>
</tr>
<tr>
<td>Robinson, Z.</td>
<td>57</td>
</tr>
<tr>
<td>Roccaldo, R.</td>
<td>31</td>
</tr>
<tr>
<td>Rodionov, D.A.</td>
<td>11, 149, 167</td>
</tr>
<tr>
<td>Roederer, T.</td>
<td>170</td>
</tr>
<tr>
<td>Rolland-Cachera, M.F.</td>
<td>127</td>
</tr>
<tr>
<td>Rosenfeld, M.</td>
<td>104</td>
</tr>
<tr>
<td>Ross, R.K.</td>
<td>61</td>
</tr>
<tr>
<td>Ruel, M.</td>
<td>138</td>
</tr>
<tr>
<td>Russell, J.</td>
<td>100</td>
</tr>
<tr>
<td>Russell, R.K.</td>
<td>100</td>
</tr>
<tr>
<td>Ryan, K.N.</td>
<td>142</td>
</tr>
<tr>
<td>Sadalaki, J.</td>
<td>172</td>
</tr>
<tr>
<td>Saha, S.L.</td>
<td>156, 173</td>
</tr>
<tr>
<td>Sahpazova, E.</td>
<td>111</td>
</tr>
<tr>
<td>Sakr Ashour, F.A.</td>
<td>146</td>
</tr>
<tr>
<td>Salas, A.A.</td>
<td>69</td>
</tr>
<tr>
<td>Salih, T.</td>
<td>11, 149, 167</td>
</tr>
<tr>
<td>Saltzman, E.</td>
<td>143</td>
</tr>
<tr>
<td>Sampasa-Kanyinga, H.</td>
<td>47</td>
</tr>
<tr>
<td>Sanders, D.B.</td>
<td>104</td>
</tr>
<tr>
<td>Santaliestra-Pasias, A.M.</td>
<td>27</td>
</tr>
<tr>
<td>Sanz, Y.</td>
<td>63</td>
</tr>
<tr>
<td>Sarkar, R.</td>
<td>10</td>
</tr>
<tr>
<td>Saulnier, D.</td>
<td>100</td>
</tr>
<tr>
<td>Saure, C.</td>
<td>159</td>
</tr>
<tr>
<td>Sawicki, G.S.</td>
<td>104</td>
</tr>
<tr>
<td>Sayers, R.M.</td>
<td>33</td>
</tr>
<tr>
<td>Schaal, B.</td>
<td>66</td>
</tr>
<tr>
<td>Schaefer, F.</td>
<td>110, 111</td>
</tr>
<tr>
<td>Schechter, M.S.</td>
<td>104</td>
</tr>
</tbody>
</table>

Author Index
Scheuermann, K.  35
Schleicher, MM.  143
Schlossman, N.  143
Schnappinger, M.  56
Schneider, N.  125
Schoemaker, M.  124
Schramm, C.J.  65
Schulz, H.  56
Schwarz, R.  23
Schwarzenberg, S.J.  108
Scott, R.A.  35
Secher, N.J.  160
Sellen, D.W.  147
Semba, R.  8
Semba, R.D.  146
Shafer, R.S.  28
Shafique, S.  147
Shah, A.S.  44
Shalitin, S.  16
Shamir, R.  64, 95, 97
Shamir, S.  144
Shand, A.W.  154
Shardell, M.  146
Shaw, N.  70
Shoff, S.M.  102
Shomaker, L.B.  9
Siani, A.  27
Sieri, S.  27
Silano, M.  63
Silbermintz, A.  97
Simpson, P.  103
Singh, L.  141
Sioen, I.  25
Sjöström, M.  31
Skörka, A.  62
Smit, H.A.  83
Smith, L.K.  76
Smithers, L.G.  85
Snieder, H.  35
Somerville, M.R.  33
Sorensen, L.B.  45, 92
Sosseh, F.  158
Southwood, T.R.  114
Spasoveić, B.  111
Srinivasan, K.  14, 88
Stallings, V.A.  61
Standl, M.  35, 37, 56
Stark, K.D.  92
Steenhout, P.  59
Steer, C.D.  21
Stein, G.S.  7
Stobaugh, H.C.  142
Stoker, S.W.  4
Stokes, S.  75
Stoltz Sjöström, E.  68

Struckmeyer, T.  168
Sturniolo, G.  87
Subramanian, S.  11, 149, 167
Sußmann, M.  56
Szajewska, H.  62, 64, 127

Taal, H.R.  35
Tai, A.  10
Talcott, M.  168
Tanofsky-Kraff, M.  9
Taylor, B.J.  33
Taylor, R.W.  33, 65
Tetens, I.  45, 92
Thakwalakwa, C.  142
Thaler, R.  7
Thibault, H.  40
Thiering, E.  37
Thomas, L.  67
Thomas, T.  88
Thompson, K.A.  9
Thorpe, K.  34
Tiemeier, H.  125
Timdahl, K.  73
Timpson, N.J.  35
Tomzig, R.G.  159
Tornatiris, M.  27
Tortorella, G.  87
Toti, E.  31
Totten, S.M.  168
Trehan, I.  8, 11, 142, 146, 149, 167
Treyvaud, K.  85
Trimarchi, F.  87
Trivella, M.  57
Troncone, R.  64
Turck, D.  52

Upson, K.  58
Urbina, E.M.  44
Uthaya, S.  67

Vaag, A.  12
Vafeiadi, M.  89
Vägerö, M.  73
Vahter, M.  89
Valtueña, J.  31
Van Camp, J.  31
van den Hooven, E.H.  125, 129
van den Neucker, A.M.  107
van der Sande, L.J.T.M.  107
van der Wurff, I.S.  86
van Goudoever, J.B.  52, 72, 127
van Huis, M.  111
van Rossem, L.  83
van Stralen, K.J.  111
van Töl, E.  124
<table>
<thead>
<tr>
<th>Author Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Toledo, L.</td>
<td>72</td>
</tr>
<tr>
<td>van Vark-van der Zee, L.C.</td>
<td>123</td>
</tr>
<tr>
<td>van Vliet, I.</td>
<td>72</td>
</tr>
<tr>
<td>van Wijnen, A.J.</td>
<td>7</td>
</tr>
<tr>
<td>van Zoeren-Grobben, D.</td>
<td>72</td>
</tr>
<tr>
<td>Vandenplas, Y.</td>
<td>64</td>
</tr>
<tr>
<td>Vassilaki, M.</td>
<td>89</td>
</tr>
<tr>
<td>Veena, S.R.</td>
<td>14</td>
</tr>
<tr>
<td>Veidebaum, T.</td>
<td>27</td>
</tr>
<tr>
<td>Venkatesh, S.</td>
<td>11, 90, 149, 167</td>
</tr>
<tr>
<td>Ventura, G.</td>
<td>145</td>
</tr>
<tr>
<td>Verbeken, S.</td>
<td>25</td>
</tr>
<tr>
<td>Verbestel, V.</td>
<td>27</td>
</tr>
<tr>
<td>Vereecken, C.</td>
<td>31</td>
</tr>
<tr>
<td>Vermeulen, M.J.</td>
<td>72</td>
</tr>
<tr>
<td>Vermiglio, F.</td>
<td>87</td>
</tr>
<tr>
<td>Vervoort, J.</td>
<td>124</td>
</tr>
<tr>
<td>Victoria, C.</td>
<td>139</td>
</tr>
<tr>
<td>Vigo, Á.</td>
<td>23</td>
</tr>
<tr>
<td>Villar, J.</td>
<td>139</td>
</tr>
<tr>
<td>von Berg, A.</td>
<td>56</td>
</tr>
<tr>
<td>von Dadelszen, P.</td>
<td>154</td>
</tr>
<tr>
<td>Vondrak, K.</td>
<td>111</td>
</tr>
<tr>
<td>Voortman, T.</td>
<td>125, 129</td>
</tr>
<tr>
<td>Vosti, S.A.</td>
<td>156, 170, 171, 172, 173</td>
</tr>
<tr>
<td>Vreugdenhil, A.C.E.</td>
<td>107</td>
</tr>
<tr>
<td>Walkowiak, J.</td>
<td>99</td>
</tr>
<tr>
<td>Wang, R.</td>
<td>161</td>
</tr>
<tr>
<td>Wang, T.</td>
<td>35</td>
</tr>
<tr>
<td>Wanke, C.A.</td>
<td>10</td>
</tr>
<tr>
<td>Ward, H.D.</td>
<td>10</td>
</tr>
<tr>
<td>Wardle, J.</td>
<td>130</td>
</tr>
<tr>
<td>Wärnberg, J.</td>
<td>31</td>
</tr>
<tr>
<td>Warthon-Medina, M.</td>
<td>93</td>
</tr>
<tr>
<td>Warwick, J.</td>
<td>67</td>
</tr>
<tr>
<td>WASt Technical Interest Group</td>
<td>136</td>
</tr>
<tr>
<td>Watson, E.O.</td>
<td>33</td>
</tr>
<tr>
<td>Weiler, H.A.</td>
<td>154</td>
</tr>
<tr>
<td>Westendorf, J.J.</td>
<td>7</td>
</tr>
<tr>
<td>Westrup, B.</td>
<td>140</td>
</tr>
<tr>
<td>Whitfield, K.</td>
<td>70</td>
</tr>
<tr>
<td>Whiting, S.J.</td>
<td>154</td>
</tr>
<tr>
<td>Whitney Evans, E.</td>
<td>43</td>
</tr>
<tr>
<td>Widhalm, K.</td>
<td>31</td>
</tr>
<tr>
<td>Wijga, A.H.</td>
<td>83</td>
</tr>
<tr>
<td>Williams Erickson, L.</td>
<td>65</td>
</tr>
<tr>
<td>Williams, S.M.</td>
<td>33</td>
</tr>
<tr>
<td>Wilschanski, M.</td>
<td>108</td>
</tr>
<tr>
<td>Woi-Messe, L.</td>
<td>170</td>
</tr>
<tr>
<td>Wong, J.</td>
<td>1</td>
</tr>
<tr>
<td>Wood, L.</td>
<td>143</td>
</tr>
<tr>
<td>Wu, C.</td>
<td>168</td>
</tr>
<tr>
<td>Wu, D.</td>
<td>161, 162</td>
</tr>
<tr>
<td>Wühl, E.</td>
<td>110</td>
</tr>
<tr>
<td>Wylie-Rosett, J.</td>
<td>35</td>
</tr>
<tr>
<td>Xu, F.</td>
<td>7</td>
</tr>
<tr>
<td>Xu, S.</td>
<td>161, 162</td>
</tr>
<tr>
<td>Yackobovitch-Gavan, M.</td>
<td>134</td>
</tr>
<tr>
<td>Yanez-Lopez, M.</td>
<td>67</td>
</tr>
<tr>
<td>Yang, I.</td>
<td>91</td>
</tr>
<tr>
<td>Yang, Z.</td>
<td>161, 162</td>
</tr>
<tr>
<td>Yanovskï, J.A.</td>
<td>9</td>
</tr>
<tr>
<td>Yelland, L.N.</td>
<td>85</td>
</tr>
<tr>
<td>Yeung, E.H.</td>
<td>12</td>
</tr>
<tr>
<td>Yoge, Y.</td>
<td>152</td>
</tr>
<tr>
<td>Yuji, H.</td>
<td>35</td>
</tr>
<tr>
<td>Zaikova, N.</td>
<td>111</td>
</tr>
<tr>
<td>Zalewski, B.M.</td>
<td>127</td>
</tr>
<tr>
<td>Zaoutis, T.E.</td>
<td>61</td>
</tr>
<tr>
<td>Zavaleta, N.</td>
<td>93</td>
</tr>
<tr>
<td>Zeegers, M.P.</td>
<td>86</td>
</tr>
<tr>
<td>Zeggini, E.</td>
<td>35</td>
</tr>
<tr>
<td>Zeilani, M.</td>
<td>170, 172</td>
</tr>
<tr>
<td>Zeni, S.N.</td>
<td>148</td>
</tr>
<tr>
<td>Zevit, N.</td>
<td>97</td>
</tr>
<tr>
<td>Zhang, C.</td>
<td>12</td>
</tr>
<tr>
<td>Zhang, P.</td>
<td>8</td>
</tr>
<tr>
<td>Zhang, Z.</td>
<td>102</td>
</tr>
<tr>
<td>Zhu, Y.</td>
<td>12, 20</td>
</tr>
<tr>
<td>Zlotkin, S.H.</td>
<td>147</td>
</tr>
</tbody>
</table>
Subject Index

Allergic rhinitis, hydrolyzed formula, and allergy outcomes in adolescents 56, 57
Antibiotics, infant exposure, and childhood weight gain 61, 62
Arthritis, see Juvenile idiopathic arthritis
Asthma, hydrolyzed formula, and allergy outcomes in adolescents 56, 57

Baby-led weaning (BLW) 65
Bile salt-stimulated lipase, preterm infant feeding 73, 74
BLW, see Baby-led weaning
Body composition
  appetite-regulating hormones and infant body composition 123, 124
  breast milk oligosaccharides and infant body composition 22, 23, 121, 122
  cognitive outcomes in adolescents 14, 15
  IDEFICS study 27, 28
  infant protein intake effects at 6 years of age 129
  pregnancy and neonatal outcomes
  carbohydrate intake in obese mothers and neonatal fat mass 160, 161
  maternal nutritional status and neonatal body composition 159, 160
Breakfast, obesity studies 28, 29
Breastfeeding
  adolescent mother interventions 23, 24
  appetite-regulating hormones and infant body composition 123, 124
  docosahexaenoic acid and cognitive outcomes 83
  donor milk
  pasteurization effects of vitamin D 70–72
  preterm infant infection and mortality outcomes 72, 73
duration and growth outcomes 20, 21
  later infancy versus milk/formula feeding growth patterns 21, 22
  nutrient composition and infant growth 124, 125
  obese mothers
  branched-chain amino acid content of milk 131, 132
  trends 120, 121
  oligosaccharides and infant body composition 22, 23, 121, 122
  vegetable acceptance effects 66

Cadmium, cognition impact in prenatal period 89
Calcium, oligosaccharide supplementation studies absorption in recovery from protein malnutrition 148, 149
Casein, catch-up growth studies in rats 144, 145
Catch-up growth
  casein and whey intake and catch-up growth in rats 144, 145
growth standards for preterm infants 139, 140
  height-for-age difference versus height-for-age z scores for measurement 138
  low birthweight and outcomes at three and a half years of age 140
  nitrogen supply studies in food-deprived refed rats 145, 146
Celiac disease
  gluten introduction studies 64
  infant feeding practices and risks 63
CF, see Cystic fibrosis
Choline, serum status and growth failure 8
Chronic kidney disease (CKD), growth hormone therapy
  European policy and prescription 111–115
  renal function trajectory 110
CKD, see Chronic kidney disease
Cognition
  body composition and linear growth effects on outcomes in adolescents 14, 15
  cadmium impact in prenatal period 89
  gut microbiota in brain development 90–92
  iodine supplementation in pregnancy and cognition outcomes 87
  multiple micronutrient supplementation studies 93, 94
  omega-3 fatty acids
    outcomes from breastfeeding 83, 84
    pregnancy supplementation outcomes 85, 86
    school performance at 7 years 86
  vitamin B₁₂ supplementation in pregnancy and cognition outcomes 88
Complementary feeding
  adolescent mother interventions 23, 24
  baby-led weaning 65
  obesity prevention 34, 35
Crohn’s disease, see Inflammatory bowel disease
Cystic fibrosis (CF)
  enteropathy 107, 108
  growth charts
    children through 2 years of age 102, 103
    pulmonary outcome prediction 103, 104
  growth trajectories and pulmonary function at 6 years of age 104–106
  ivecaster therapy and nutritional outcomes with CFTR G551D mutation 108, 109
DED, see Dietary energy density
DHA, see Docosahexaenoic acid
Diabetes
  type 1 and Mauriac syndrome 4, 5
  type 2
    sleep patterns and eating behaviors in adolescent girls 9
    vitamin D status and arterial stiffness in youth 44, 45
Dietary energy density (DED), obesity studies in children 24, 25
Digestible Indispensable Amino Acid Score (DIAAS) 141, 142
DNA methylation
  peripheral blood patterns and pubertal development 6
  pregnancy, B vitamin supplementation, and offspring weight and DNA methylation patterns 155, 156
Docosahexaenoic acid (DHA), preterm infant supplementation, and vision outcomes 75, 76
cognition outcomes from breastfeeding 83
  supplementation and school performance at 7 years 86
Eczema, hydrolyzed formula and allergy outcomes in adolescents 56, 57
Epigenetics
  pregnancy, B vitamin supplementation, and offspring weight and DNA methylation patterns 155, 156
  puberty and DNA methylation patterns in development 6
  skeletal development 7
ESCAPE trial 110
Etanercept, juvenile idiopathic arthritis treatment and growth in children and adolescents 114–116
Ezh2, skeletal development role 7
Fiber, intake and obesity 31–33
Formula, see Infant formula
FTO, polymorphisms in obesity 35–37
Generation R study 129
Ghrelin, appetite-regulating hormones and infant body composition 123, 124
GINI study 56, 57
GINIplus birth cohort study 37, 38
Gluten, see Celiac disease
Glycemic index, Australian Health Survey of children and adolescents 42, 43
Glycogen phosphorylase kinase, mutation in Mauriac syndrome 4, 5
Growth hormone
deficiency 3, 4
  therapy in chronic kidney disease
    European policy and prescription 111–115
Subject Index

renal function trajectory 110
Growth standards 3, 4
Gut microbiota
brain development studies 90–92
growth impairment prevention in malnutrition 11, 149, 150
sialylated milk oligosaccharide promotion of growth 168
stunted children 10, 167, 168
therapeutics in childhood undernutrition 169, 170
HELENA study 31–33
Hypertension, growth pattern effects in mid-childhood 14
IBD, see Inflammatory bowel disease
IDFICS study 27, 28
IGF-1, see Insulin-like growth factor-1
Infant formula
appetite-regulating hormones and infant body composition 123, 124
breastfeeding in later infancy versus milk/formula feeding growth patterns 21, 22
fermented without live bacteria 62
hydrolyzed formula and allergy outcomes in adolescents 56–58
protein concentration and obesity in later life 127, 128
protein intake and insulin-like growth factor-1 plasma levels 59, 60
soy-based formula and uterine fibroid outcomes in later life 58, 59
Inflammatory bowel disease (IBD)
fecal metagenome in Crohn’s disease children during exclusive enteral nutrition 100–102
food intake adequacy in children and adolescents 97, 98
obesity in newly diagnosed disease 99, 100
Insulin-like growth factor-1 (IGF-1)
infant formula protein intake and plasma levels 59, 60
pregnancy high-energy diet effects on intestinal development and intrauterine growth 162, 163
INTERGROWTH-21st Project 139, 140
Iodine, pregnancy supplementation
cadmium detoxification 89
cognition outcomes 87
Iron, diet-induced changes in status in children 92, 93
Ivecaster, nutritional outcomes with CFTR G551D mutation 108, 109
JIA, see Juvenile idiopathic arthritis
Juvenile idiopathic arthritis (JIA), etanercept therapy and growth in children and adolescents 114–116
LAIF study, see Lipase Added to Infant Feeding study
Leptin, appetite-regulating hormones and infant body composition 123, 124
Lipase Added to Infant Feeding (LAIF) study 74
Malnutrition, see also Stunting
gut microbiota immaturity 149, 150
nitrogen supply studies in food-deprived refed rats 145, 146
oligosaccharide supplementation studies of calcium absorption in recovery from protein malnutrition 148, 149
protein quality and growth 141, 142
second dairy meal and recovery 143, 144
whey protein studies in child recovery 142, 143
Mauriac syndrome, type 1 diabetes 4, 5
Metabolically healthy obesity (MHO) 43, 44
MHO, see Metabolically healthy obesity
MicroRNA, postnatal body growth deceleration role 13
Obesity
adolescent mother interventions 23, 24
antibiotic, infant exposure and childhood weight gain 61, 62
appetite-regulating hormones and infant body composition 123, 124
breakfast studies 28, 29
breastfeeding by obese mothers branched-chain amino acid composition in milk 1131, 132
trends 120, 121
carbohydrate intake in obese mothers and neonatal fat mass 160, 161
cardiometabolic risk factors in adolescence 41, 42
complementary feeding practices 34, 35
dietary energy density in children 24, 25
eyoung nutrition and later obesity 127
eating and snack frequency studies 39, 40
fiber intake studies 31–33
French children trends 40, 41
FTO polymorphisms 35–37
inflammatory bowel disease, newly
diagnosed cases 99, 100
metabolically healthy obesity 43, 44
pregnancy hyperglycemia and growth/
obesity in offspring 12
Prevention of Overweight in Infancy study
33, 34
protein intake in early life
milk protein concentration effects in
later life 127, 128
programming of adiposity and organ
growth/function 132, 133
twin studies of effects up to 5 years of
age 130, 131
reward sensitivity 25, 26
salt intake studies 29–31
social network site use in adolescent 47, 48
Omega-3 fatty acids, see also Docosahexaenoic
acid
cognition outcomes from breastfeeding 83,
84
diet-induced changes in status in children
92, 93
physical development outcomes from
breastfeeding 84
pregnancy supplementation and cognition
outcomes 85, 86

Pancreatic polypeptide (PP), appetite-
regulating hormones and infant body
composition 123, 124
PCAAS, see Protein Digestibility-Corrected
Amino Acid Score
Peptide YY (PYY), appetite-regulating
hormones and infant body composition
123, 124
POI study, see Prevention of Overweight in
Infancy study
PP, see Pancreatic polypeptide
Pregnancy
B vitamin supplementation and offspring
weight and DNA methylation patterns
155, 156
carbohydrate intake in obese mothers and
neonatal fat mass 160, 161
cognition outcomes
cadmium exposure 89
iocline supplementation 87
omega-3 fatty acid supplementation and
cognition outcomes 85, 86
vitamin B12 supplementation 88
dairy intake and birthweight 157, 158
fat intake effects in pig model 161, 162
gestational weight gain and breastfeeding
duration 20, 21
high-energy diet effects on intestinal
development and intrauterine growth
162, 163
hyperglycemia and growth/obesity in
offspring 12
lipid-based nutrient supplementation and
stunting reduction 156, 157, 170–174
nutritional status and neonatal body
composition 159, 160
periconceptional micronutrient
supplementation and placental function
158, 159
vitamin D supplementation studies 154,
155
Preterm infants, see also Catch-up growth
amino acids and lipids in parenteral
nutrition 67, 68
bile salt-stimulated lipase feeding 73, 74
docosahexaenoic acid supplementation and
vision outcomes 75, 76
eating difficulties 76, 77
retinopathy of prematurity and low energy
intake 68, 69
vitamin D
dosing regimens 69
metabolism 70
Prevention of Overweight in Infancy (POI)
study 33, 34
Project Viva 14
Protein Digestibility-Corrected Amino Acid
Score (PCAAS) 141, 142
Puberty
dietary intake changes and determinants
37, 38
DNA methylation patterns in development 6
PYY, see Peptide YY
Subject Index

Ready-to-use supplementary food (RUSF) 143, 144, 170
Renal failure, see Chronic kidney disease
Retinopathy of prematurity, risks with low energy intake 68, 69
Reward sensitivity (RS), obesity studies 25, 26
RS, see Reward sensitivity
RUSF, see Ready-to-use supplementary food

Salt, intake and obesity 29–31
Selenium, cadmium detoxification in prenatal period 89
Short stature
low birthweight and outcomes at three and a half years of age 140
World Health Organization standards 3, 4
Sleep
infant macronutrient intake and toddler sleep duration 125, 126
patterns and eating behaviors in adolescent girls at risk for diabetes 9
Stunting, see also Malnutrition
Bangladesh
lipid-based nutrient supplementation studies in pregnancy 173, 174
micronutrient powder trial 147, 148
choline serum status and growth failure 8
essential amino acid levels in stunted children 146, 147
gut microbes
growth impairment prevention in malnutrition 11
intestinal microbiota in children 10
gut microbiota 10, 167, 168
lipid-based nutrient supplementation studies in Malawi
maternal 172, 173
six to 18 months 170, 171
pregnancy
dairy intake and birthweight 157, 158
lipid-based nutrient supplementation and stunting reduction 156, 157
ready-to-use food study in Niger 170
TMAO, see Trimethylene N-oxide
Trimethylene N-oxide (TMAO), choline metabolism 8
TRIP6, expression in pubertal development 5
Ulcerative colitis, see Inflammatory bowel disease
Uterine fibroids, soy-based formula and outcomes in later life 58, 59
Vegetable acceptance, early food-related variety experience studies 66
Vitamin B12, supplementation in pregnancy and cognition outcomes 88
Vitamin D
breast milk pasteurization effects 70–72
pregnancy/lactation supplementation studies 154, 155
preterm infants
dosing regimens 69
metabolism 70
status
arterial stiffness in diabetic youth 44, 45
cardiometabolic markers in preteens 45–47
Whey protein
catch-up growth studies in rats 144, 145
child malnutrition recovery studies 142, 143
WHO, see World Health Organization
World Health Organization (WHO), growth standards 3, 4, 102–104