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Nutrition and Growth

Yearbook 2024

Editors
Berthold Koletzko
Moshe Phillip
Dominique Turck
Raanan Shamir

Nutrition and Dietetics
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Yearbook 2024

Volume Editors

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2024

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Preface

We all know that appropriate nutrition is important for child growth and development. However, the precise mechanism of the interaction between nutrition and children's growth is still not fully elucidated, neither the "appropriate" nor "ideal" nutrition for growth and development has been well defined. The relation between nutrition and growth still presents a challenge to pediatricians, subspecialists in pediatric nutrition, endocrinologists, gastroenterologists, pediatric dieticians, and other health professionals involved in the care of children.

The growing interest in the relationship between nutrition and growth gave rise to numerous manuscripts. In this book, we summarize selected peer-reviewed manuscripts that were published between July 1, 2022, and June 30, 2023. We aim to provide an overview of the chosen manuscripts for healthcare professionals involved with the care of growing children. The emphasis was made on manuscripts that we believe are important and might shed some light on the mechanisms of the interaction between nutrition and growth and add some insight to the readers. The summary was made by renowned experts in their fields; each selected a few manuscripts, summarized them briefly, and accompanied them with editorial comments, evaluating the clinical importance of each article and discussing its application.

We could not cover all important manuscripts. We hope, however, that our readers of this summary will find it useful and helpful and that it will encourage them to further explore the literature.

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Malnutrition and Catch-Up Growth during Childhood and Puberty

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Introduction

In 2022, approximately 148.1 million children, or 22%, of all children under 5 years of age across the globe were estimated to be to be affected by stunting, and 45 million children under five by wasting, of whom 13.7 million were severely wasted [1].

Although remarkable progress was achieved in the reduction of stunting in the first 15 years of the millennium, since 2015 this progress has begun to slow down. The COVID-19 pandemic further exacerbated the situation, as it overwhelmed healthcare systems and disrupted vital healthcare services. To achieve the targets set forth in the Sustainable Development Goals by 2030, a substantial increase in attention and investment, both in terms of financial resources and political commitment, is imperative.

This chapter reviews the most recent data on childhood malnutrition and catch-up growth, published between July 1, 2022, and June 30, 2023, and addresses several topics:

a. Interventional studies. This section includes various intervention strategies for addressing childhood malnutrition: milk proteins by Mbabazi et al. [2]; eggs by Suta et al. [3], Perez-Plazola et al. [4], and Mi et al. [5]; micronutrients by Khan et al. [6]; vitamin D by Ganmaa et al. [7]; and a comprehensive intervention package by Ara et al. [8].

b. Reviews. This section includes several important reviews related to different aspects of malnutrition, by Simeone et al. [9], Mamun et al. [10], Saavedra and Prentice [11], and Njunge and Walson [12].

c. Large cross-sectional studies. This section includes two studies evaluating the trends on zero vegetables and fruit consumption by Allen et al. [13] and patterns of child stunting by Karlsson et al. [14] across a large number of low- and middle-income countries.
d. Long-term outcomes from cohort studies. This section includes one study by Freer et al. [15], which evaluated the impact of short stature on language development.

Key articles reviewed for this chapter

Interventions to Treat Childhood Malnutrition

Effect of milk protein and whey permeate in large quantity lipid-based nutrient supplement on linear growth and body composition among stunted children: a randomized 2 × 2 factorial trial in Uganda
Mbabazi J, Pesu H, Mutumba R, Filteau S, Lewis JI, Wells JC, Olsen MF, Briend A, Michaelsen KF, Mølgaard C, Ritz C, Nabukeera-Barungi N, Mupere E, Friis H, Grenov B
PLoS Med 2023;20:e1004227

Prolonged egg supplement advances growing child's growth and gut microbiota
Suta S, Surawit A, Mongkolsucharitkul P, Pinsawas B, Manosan T, Ophakas S, Pongkunakorn T, Pumeiam S, Sranacharoenpong K, Sutheeworapong S, Poungsombat P, Khoomrung S, Akarasereenont P, Thaipisuttikul I, Suktitipat B, Mayurasakorn K
Nutrients 2023;15:1143

Plasma mineral status after a six-month intervention providing one egg per day to young Malawian children: a randomized controlled trial
Perez-Plazola M, Diaz J, Stewart CP, Arnold CD, Caswell BL, Lutter CK, Werner ER, Maleta K, Turner J, Prathibha P, Liu X, Gyimah E, Iannotti L
Sci Rep 2023;13:6698

Infant age at egg introduction and malnutrition-related child growth in the United States
Mi B, Liu H, Wang Y, Small H, Surguy-Bowers A, Rideout TC, Cameron CE, Lehman HK, Starke K, Wen X
Matern Child Nutr 2022;18:e13390

Long-term impact of multiple micronutrient supplementation on micronutrient status, hemoglobin level, and growth in children 24 to 59 months of age: a non-randomized community-based trial from Pakistan
Khan A, Ul-Haq Z, Fatima S, Ahmed J, Alobaid HM, Fazid S, Muhammad N, Garzon C, Ihtesham Y, Habib I, Tanimoune M, Iqbal K, Arshad M, Safi SZ
Nutrients 2023;15:1690

Influence of vitamin D supplementation on growth, body composition, and pubertal development among school-aged children in an area with a high prevalence of vitamin D deficiency: a randomized clinical trial
Ganmaa D, Bromage S, Khudyakov P, Erdenenbaatar S, Delgererekh B, Martineau AR
JAMA Pediatr 2023;177:32–41

A comprehensive intervention package improves the linear growth of children under 2-years-old in rural Bangladesh: a community-based cluster randomized controlled trial
Ara G, Sanin KI, Khanam M, Sarker MSA, Tofail F, Nahar B, Chowdhury IA, Boitchi AB, Gibson S, Afsana K, Askari S, Ahmed T
Sci Rep 2022;12:21962

Reviews

Do vegetarian diets provide adequate nutrient intake during complementary feeding? A systematic review
Simeone G, Bergamini M, Verga MC, Cuomo B, D'Antonio G, Iacono ID, Mauro DD, Mauro FD, Mauro GD, Leonardi L, Miniello VL, Palma F, Scotese I, Tezza G, Vania A, Caroli M
Nutrients 2022;14:3591

Effectiveness of food-based intervention to improve the linear growth of children under five: a systematic review and meta-analysis
Mamun AA, Mahmudiono T, Yudhastuti R, Triatmaja NT, Chen HL
Nutrients 2023;15:2430

Nutrition in school-age children: a rationale for revisiting priorities
Saavedra JM, Prentice AM
Nutr Rev 2023;81:823–843

Microbiota and growth among infants and children in low-income and middle-income settings
Njunge JM, Walson JL
Curr Opin Clin Nutr Metab Care 2023;26:245–252

Large Cross-Sectional Studies

Estimates and trends of zero vegetable or fruit consumption among children aged 6–23 months in 64 countries
Allen CK, Assaf S, Namaste S, Benedict RK
PLoS Glob Public Health 2023;3:e0001662

Patterns in child stunting by age: a cross-sectional study of 94 low- and middle-income countries
Karlsson O, Kim R, Moloney GM, Hasman A, Subramanian SV
Matern Child Nutr 2023;e13537

Long-Term Outcomes from Cohort Studies

Short stature and language development in the United Kingdom: a longitudinal analysis of children from the Millennium Cohort Study
Freer J, Orr J, Morris JK, Walton R, Dunkel L, Storr HL, Prendergast AJ
BMC Med 2022;20:468

Effect of milk protein and whey permeate in large quantity lipid-based nutrient supplement on linear growth and body composition among stunted children: a randomized 2 × 2 factorial trial in Uganda

Mbabazi J[1,2], Pesu H[1], Mutumba R[1,2], Filteau S[3], Lewis JI[1], Wells JC[4], Olsen MF[1,5], Briend A[1,6], Michaelsen KF[1], Mølgaard C[1], Ritz C[7], Nabukeera-Barungi N[2], Mupere E[2], Friis H[1], Grenov B[1]

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PLoS Med 2023;20:e1004227

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https://pubmed.ncbi.nlm.nih.gov/37220111/

Comments: Milk proteins (MPs) are believed to stimulate growth factors due to their complete amino acid profile, and their consumption has been linked to promoting linear growth and lean mass development. However, MPs are relatively expensive, and their inclusion in food supplements increases costs. Whey permeate (WP), a residual by-product from whey processing containing lactose and bioavailable minerals, is considered to have potential prebiotic effects and to positively influence lean mass gain and bone mineralization.

Mbabazi et al. [2] conducted an elegant randomized, double-blind trial among 12- to 59-month-old stunted children (height *Z*-score < −2) in Uganda. The study aimed to compare the effects of four large quantity lipid-based nutrient supplement (LNS) formulations on linear growth and body composition.

The study randomized 750 children to a 12-week intervention with one of the four formulations based on MPs, soy protein, WP, or maltodextrin ($n = 600$). Children in the control group ($n = 150$) were randomized to receiving no supplement.

Key findings of this study showed that neither MPs nor WP in LNS formulations significantly affected the height increment, although MPs exhibited a trend toward enhancing fat-free mass index. Nevertheless, compared to the unsupplemented group, the LNS supplementation had clear positive effects on growth and changes in body composition. Children in the unsupplemented group showed a decline in height *Z*-score and an increase in fat mass index, whereas those receiving any LNS demonstrated an increase in height *Z*-score and fat-free mass. The main limitations of this study include the lack of blinding of caregivers regarding LNS supplementation versus no supplementation, and the short duration of the intervention (12 weeks).

Several previous studies suggest that consumption of MPs may improve linear growth [16, 17]. Other studies, however, did not find an effect of MPs on linear growth, but did observe an impact on weight gain and lean mass gain [18, 19]. The inconsistent findings across studies can be attributed to multiple factors. These factors include differences in the dietary composition of the supplementation (such as differences in protein quantity and quality, as well as the amount and composition of other macro- and micronutrients), characteristics of the study population (such as the age range of participants and the degree of malnutrition), and the study design (including the length of the intervention, the control intervention or lack thereof, and compliance with the intervention).

Interestingly, this study's results revealed an interaction between consumption of WP and breastfeeding. WP positively affected linear growth in breastfed children but negatively affected non-breastfed children. The authors suggest that the high lactose content of WP may explain this difference. Breastfed children, who possess significantly more lactobacilli and bifidobacteria, capable of fermenting lactose to short-chain fatty acids, may benefit from the high lactose content of WP, enhancing linear growth. However, in non-breastfed children with different microbiota, the high lactose content of WP might lead to energy loss or osmotic diarrhea, thus hampering growth.

Prolonged egg supplement advances growing child's growth and gut microbiota

Suta S[1], Surawit A[1], Mongkolsucharitkul P[1], Pinsawas B[1], Manosan T[1], Ophakas S[1], Pongkunakorn T[1], Pumeiam S[1], Sranacharoenpong K[2], Sutheeworapong S[3], Poungsombat P[4], Khoomrung S[4,5], Akarasereenont P[6], Thaipisuttikul I[7], Suktitipat B[8], Mayurasakorn K[1]

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Plasma mineral status after a six-month intervention providing one egg per day to young Malawian children: a randomized controlled trial

Perez-Plazola M[1], Diaz J[2], Stewart CP[3], Arnold CD[3], Caswell BL[3,4], Lutter CK[5], Werner ER[3], Maleta K[6], Turner J[7], Prathibha P[7], Liu X[7], Gyimah E[8], Iannotti L[8]

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Infant age at egg introduction and malnutrition-related child growth in the United States

Mi B[1,2], Liu H[1,2], Wang Y[1,2], Small H[3], Surguy-Bowers A[3], Rideout TC[4], Cameron CE[5], Lehman HK[6], Starke K[5], Wen X[3]

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Comments:

Eggs are a common and affordable food consumed worldwide, serving as a natural source of numerous nutrients. Each egg provides approximately 60–90 kcal and about 6–8 g of high-quality protein. Eggs are also naturally abundant in B vitamins, vitamin A, vitamin D, folate, biotin, pantothenic acid, selenium, iodine, phosphorus, choline, and other essential minerals and trace elements.

Recently, three studies conducted by Suta et al. [3], Perez-Plazola et al. [4], and Mi et al. [5] have explored the effects of egg consumption on various pediatric populations.

Suta et al. [3] investigated the impacts of an 8-month egg supplementation on growth and microbiota among 8- to 14-year-old children ($n = 635$) attending six rural schools in Thailand. The participants were randomly divided into three groups:

1. The whole egg group, who consumed an additional 10 eggs per week
2. The protein substitute group, who consumed yolk-free egg substitutes equivalent to the nutritional content of 10 eggs per week
3. The control group, who received standard school lunches according to the Thai school lunch program

The findings revealed that whole egg supplementation yielded a more effective intervention compared to protein substitutes and standard school lunches. It led to improvements in weight, height, and gut microbiota, without adverse effects on blood lipoproteins. One limitation of this study was the omission of an evaluation of pubertal status, which could potentially impact the study outcomes.

Perez-Plazola et al. [4] conducted a randomized controlled trial nested within the Mazira study [20], with the aim of evaluating the effects of egg consumption on plasma mineral status in infants aged 6–9 months from rural Malawi, a population characterized by high rates of stunting and underweight. Participants were randomly assigned to either receive one egg per day for 6 months or undergo no intervention. The analysis encompassed 187 children in the intervention group and 200 children in the control group. Anthropometric data, 24-h dietary recalls, and venous blood to evaluate plasma minerals (magnesium, copper, iron, selenium, and zinc) were collected at baseline and 6-month follow-up.

The results showed a high prevalence of mineral deficiencies at baseline and after the intervention, especially zinc deficiency (~60%) in the study cohort. Both at baseline and at the end of the study, there were no differences between the groups in plasma magnesium, selenium, copper, and zinc levels. However, iron levels, which were comparable at baseline, were significantly lower in the egg intervention group compared to the control group at the end of the study. The authors proposed a potential explanation for this finding, attributing it to the presence of egg proteins like phosvitin, ovalbumin, and ovotransferrin, which can reduce iron bioavailability through chelation, thereby decreasing its absorption in processes intended to prevent microbial growth in eggs. Notably, the egg intervention did not lead to improvements in any of the evaluated minerals.

It should be noted that the researchers were unable to determine total calcium levels or the intervention’s impact on calcium levels due to technical issues. An additional limitation was the inability to measure mineral concentrations within protein carriers like lipoproteins (for selenium) or body stores. It is possible that there was an increase in total body mineral content that wasn’t accounted for in the study analysis.

This study’s findings suggest that egg intervention alone did not suffice to address the micronutrient deficits in this nutritionally vulnerable population.

Mi et al. [5] conducted a prospective cohort study based on a US national cohort known as the Infant Feeding Practices Study II, along with its Year 6 Follow-Up Study. The study aimed to investigate the potential associations between the age at which infants were introduced to eggs and later malnutrition-related growth outcomes at 12 months and 6 years. The analysis included data from 1,716 mother-child dyads. The authors also explored interactions involving child sex, maternal race, ethnicity, maternal educational level, history of breastfeeding, and formula feeding.

Within the study cohort, it was observed that 75.52% of infants were introduced to eggs at 12 months or earlier, while the remaining 24.48% were not yet introduced by 12 months. Mothers of infants not yet introduced to eggs by 12 months tended to have an older age at pregnancy, possess higher educational levels, and enjoy higher family incomes. These mothers were also more likely to be married, were nonsmokers, and had a lower preconception body mass index.

The study results demonstrated that delaying the introduction of eggs to infants was associated with a lower height *Z*-score and a higher risk of stunting at 6 years of age. The relationship between the age of egg introduction and growth outcomes at 12 months was different among boys and girls: later introduction of eggs was associated with a lower mean weight for height *Z*-score at 12 months in girls, but not in boys. This suggests that delaying egg introduction during infancy might be related to a reduced risk of obesity at 12 months in female infants.

The main limitation of this study was the relatively high attrition rates – 40% at 12 months and 49% at 6 years. Such attrition rates are typical in long-term prospective cohort studies and could potentially introduce a significant selection bias.

This study suggests a beneficial effect of early egg introduction on long-term linear growth in children living in medium- to high-income developed countries, such as the United States. Interestingly, mothers with higher educational levels and higher family incomes tended to introduce their children to eggs at a later age.

The results of these three extensive studies, conducted among diverse sociodemographic pediatric populations, hold significant importance. Notably, two of these studies [3, 5] suggest the positive effects of early egg consumption on growth indicators. These effects are observed both in children at high risk of malnutrition and in developed nations such as the United States.

However, child growth is influenced by a multitude of factors. Apart from egg consumption, aspects like complementary foods, overall dietary quality, and living conditions play crucial roles in determining child growth trajectories. This could potentially explain the lack of significant findings in the study by Perez-Plazola et al. [8] that focused on infants with elevated malnutrition rates from rural Malawi.

More research is needed to determine other nutritionally relevant ways and additional strategies, together with egg consumption, to improve nutritional status and growth parameters, especially in nutritionally at-risk pediatric populations.

Long-term impact of multiple micronutrient supplementation on micronutrient status, hemoglobin level, and growth in children 24 to 59 months of age: a non-randomized community-based trial from Pakistan

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Comments: Deficiencies in essential micronutrients are widespread among children under five worldwide and particularly in low- and middle-income countries. A community-centered, nonrandomized clinical study by Khan et al. [6] was conducted in children aged 24–59 months from a food-insecure area in Pakistan from January 2018 to June 2019. The study aimed to assess the impact of a micronutrient supplementation on plasma micronutrient levels, hemoglobin concentration, and anthropometric measurements.

The children in the intervention arm ($n = 58$) received a multimicronutrient powder (one sachet per day) for 1 year, and children in the control group ($n = 53$) received no supplementation. The results of this study showed that a 1-year micronutrient supplementation improved plasma micronutrient status (specifically vitamin A, vitamin D, and zinc), hemoglobin levels, and weight status parameters, including weight *Z*-score and weight-for-height *Z*-score, compared to the control group. However, there was no effect of the intervention on the height *Z*-score and stunting rate.

This study suggests that micronutrient supplementation is a cost-effective way to address undernutrition in vulnerable areas. The main strength of this study, compared to other similar intervention studies, is the very high compliance rate, and zero loss of follow-up over the study course. However, a major limitation of this study is the absence of random allocation.

Influence of vitamin D supplementation on growth, body composition, and pubertal development among school-aged children in an area with a high prevalence of vitamin D deficiency: a randomized clinical trial

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Comments: Vitamin D plays a crucial role in bone health and other physiological processes related to growth and metabolism. Vitamin D deficiency is prevalent among children living in temperate climates and has been associated with stunting, obesity, and early activation of the hypothalamic-pituitary-gonadal axis.

This randomized, double-blind, placebo-controlled study by Ganmaa et al. [7] aimed to determine whether providing weekly doses of vitamin D could influence linear growth, body composition, and pubertal development of 6- to 13-year-old children ($n = 8{,}851$) living in Ulaanbaatar, Mongolia, where vitamin D deficiency is highly prevalent. The intervention included weekly oral doses of vitamin D3, 14,000 IU, or placebo for 3 years.

The outcomes of the study indicated that vitamin D supplementation successfully raised the levels of 25(OH)D into the desired physiological range. However, the intervention did not result in any significant changes in terms of height Z-score, body mass index Z-score, waist-to-height ratio, percentage of body fat, fat mass, fat-free mass, or pubertal development. These findings held true for the entire study population, and also when analyzing different subgroups based on factors such as sex, age at baseline, estimated calcium intake, baseline 25(OH)D concentration, or presence vs absence of stunting at baseline.

The main strengths of this study include a large sample size, its long duration, and the very low attrition rate (~8% over 3 years). In addition, the supplementation regimen was highly effective in correcting vitamin D deficiency in the intervention arm of the trial. However, this study does come with certain limitations. The limitations include the wide age range of the children at baseline, which posed challenges due to variations in growth trajectories resulting from the large interpersonal heterogeneity in pubertal timing and tempo. Another limitation is the use of self-assessed pubertal status. Furthermore, the study only measured 25(OH)D concentrations at baseline and at the end of the study (3 years from baseline), without considering potential seasonal fluctuations.

It is worth noting that the results of this study differed from those of two other randomized clinical trials conducted earlier by the same researchers in Mongolia [21]. In these trials, there was an improvement in growth among children receiving vitamin D compared to those receiving placebo. This discrepancy might be due to variations in participant age, study outcome measures, and the different dosage and duration of vitamin D supplementation used. Additional randomized controlled trials, comparing the effects of different vitamin D supplementation regimens in different pediatric populations on anthropometric outcomes, are needed to resolve this discrepancy.

A comprehensive intervention package improves the linear growth of children under 2-years-old in rural Bangladesh: a community-based cluster randomized controlled trial

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Comments: This important pragmatic trial by Ara et al. [8] included a package of direct and indirect nutrition interventions on linear growth and dietary diversity among 6- to 12-month-old children in rural Bangladesh. In this 1-year community-based cluster randomized controlled trial, 412 mother-infant pairs in 12 clusters (representing sub-district units with ultrapoor households with children under 24 months of age) were randomly assigned to receive monthly food vouchers (for eggs, milk, semolina, sugar, and oil) to prepare egg and milk-based snacks for their children, along with multiple micronutrient powder, counseling on child feeding and handwashing, or regular government health communication alone (control, $n = 206$; treatment, $n = 206$). The primary and secondary outcomes were differences in children's length gain and dietary diversity. The effect of intervention on child growth (linear growth primarily) was examined using a mixed effect linear regression model. Mean weight and length of the children were comparable between groups at baseline. Around 90% of the children in both groups were breastfed. After receiving intervention for 12 months, length-for-age Z-score increased by 0.37 (confidence interval: 0.24, 0.51; $p < 0.001$) and risk of stunting reduced by 73% (odds ratio: 0.27; confidence interval: 0.13, 0.58; $p = 0.001$). This comprehensive intervention package improved the growth and dietary diversity of predominantly breastfed children in extremely poor Bangladeshi households and provided important evidence for policy.

This trial is one of several studies employing packages of interventions using community-based platforms for delivery. In a similar study in rural Pakistan, Soofi et al. [22] used a combination of prenatal and postnatal interventions and demonstrated a major impact on stunting. A similar study deploying home visits in Yogyakarta, Indonesia, also led to significant increase in maternal knowledge, growth parameters, and developmental outcomes [23]. These studies deploying low-cost strategies have comparable benefits to those observed after large-scale evaluation of commodities such as lipid supplements [24] or a much more ambitious package of interventions in India with health, nutrition, psychosocial support, and water, sanitation, and hygiene interventions delivered during preconception, pregnancy, and early childhood periods on birth outcomes and on linear growth at 24 months [25]. The benefit of delivering indirect and nutrition interventions is consonant with the observations from several real-life exemplar countries where improved linear growth in children is associated with investments that address social determinants of health such as poverty, women empowerment, environmental health, and direct nutrition interventions in programs [26], all important for global policy.

Do vegetarian diets provide adequate nutrient intake during complementary feeding? A systematic review

Simeone G[1], Bergamini M[2], Verga MC[3], Cuomo B[4], D'Antonio G[5], Iacono ID[6], Mauro DD[7], Mauro FD[8], Mauro GD[9], Leonardi L[10], Miniello VL[11], Palma F[12], Scotese I[13], Tezza G[14], Vania A[15], Caroli M[16]

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This article is also reviewed in the chapter by Larnkjær et al. [this vol., pp. 144–158].

The period of complementary feeding (CF, age 6–24 months) is characterized by rapid growth, during which infants are susceptible to both nutrient deficiencies and excesses. Accordingly, the World Health Organization (WHO) advises that infants should be provided with a well-balanced diet containing all essential nutrients to support their growth and proper psychomotor development.

The rising popularity of vegetarianism among young people in developed countries has led to a growing number of parents introducing a CF diet that either partially or completely excludes animal foods for their infants. Consequently, there is considerable interest in understanding the potential effects of early introduction of vegetarian or vegan diets on various health outcomes. In adults, some benefits of vegetarian and vegan diets have been described, but there remains lack of data regarding their effects in children. The aim of this systematic review by Simeone et al. [9] was to evaluate the existing data on the impact of various vegetarian CF diets on growth, psychomotor development, vitamin deficiencies, and communicable and noncommunicable diseases.

The study focused on healthy infants, born at term with normal birth weight, residing in Western developed countries. The defined exposure was a CF diet with limited or eliminated animal products (following a vegetarian or vegan diet), while the comparator was a CF diet that included animal-sourced foods.

Overall, the quality of the studies reviewed was low, and there was a limited number of interventional studies due to ethical constraints (i.e., deliberately exposing infants to elimination diets). The analyses revealed a higher percentage of infants with stunted growth and wasting in the group exposed to little or no animal-sourced foods during CF, compared to the omnivorous group (with a moderate level of certainty). In terms of neurodevelopmental outcomes, there was very limited evidence available. It appears that the risk of adverse outcomes was not higher in the exposure group compared to the control group, but the grade of evidence was low. A large number of case reports described nutritional deficiencies in infants following various vegetarian diets, which resulted in severe neurologic consequences. No long-term data were available. The authors did not find sufficient evidence regarding the relative risk of developing vitamin deficiencies or communicable or noncommunicable diseases when exposed to vegetarian or vegan diets.

This study highlights important evidence, and also the lack of such evidence, regarding various elimination diets before the age of 2 years and concludes that there is insufficient data to support recommendation of vegetarian or vegan diets during CF.

Effectiveness of food-based intervention to improve the linear growth of children under five: a systematic review and meta-analysis

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Comments: Various food intervention strategies have been developed over the years and across the globe, each aiming to address different variables such as locally available family foods, energy and micronutrient priorities, obtainable resources, and food sources. Numerous original studies have investigated the effects of food interventions on stunting and other malnutrition-related outcomes; however, not all studies and interventions yield equal impacts on stunting. Effectiveness may vary according to the baseline characteristics of the intervention group, the nutritional content of the food-based intervention, and the duration of intervention, among other factors.

This systematic review and meta-analysis by Mamun et al. [10] were conducted to merge findings from existing studies on the effectiveness of food-based interventions in the reduction of stunting, in children under the age of 5 years. The search for relevant studies encompassed databases such as Scopus, Web of Science, PubMed, ScienceDirect, and ProQuest from 2000 to 2022. Only randomized controlled studies meeting specific inclusion and exclusion criteria were included in the systematic review and meta-analysis. Out of the 1,125 studies initially identified, only 15 studies involving 15,909 participants met the criteria and were included. All 15 studies were randomized controlled trials.

The analyses revealed that food-based interventions led to an improvement in linear growth (mean difference: 0.20, 95% confidence interval: 0.04–0.35, $p = 0.01$). However, no significant difference was found in the change in underweight status between the intervention and control groups (mean difference: 0.25; confidence interval: −0.15 to 0.64; $p = 0.22$). Similarly, no significant improvement in child wasting was found between the intervention and control groups (mean difference: 0.09; confidence interval: −0.02 to 0.20; $p = 0.12$). Additionally, the study findings support a greater impact of animal protein compared to plant-based sources on linear growth. The findings of this study can provide a valuable resource both for those designing future research in this field and for policymakers aiming to reduce stunting by effective interventions.

Nutrition in school-age children: a rationale for revisiting priorities

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Comments: Nutrition and growth during the first 1,000 days of life, and during early childhood up to 5 years of age, have rightfully gained significant attention in recent decades. However, the school-age years (age 5–15 years) also represent a crucial and final window of opportunity to exert a meaningful influence on growth, development, and the resulting health outcomes in adulthood. Unfortunately, this period has not been studied as extensively as the earlier years of life in this context. Insufficient research in this age group can be attributed, in part, to the lack of clarity and consistency in terminology. Terms such as “early childhood,” “middle childhood,” “late childhood,” “school age,” “adolescence,” and “young adulthood” often overlap and merge.

This review by Saavedra and Prentice [11] aims to underscore the pivotal aspects of growth, development, and nutrition during these transformative school-age years, while also highlighting the existing challenges and knowledge gaps. It advocates for increased and more targeted attention to nutrition during this important phase to optimize this final opportunity for investment in influencing growth, nutrition, and ultimately, overall health and cognitive outcomes.

Microbiota and growth among infants and children in low-income and middle-income settings

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Comments: This review by Njunge and Walson [12] evaluated the role of intestinal microbiota in relation to childhood growth and also assessed interventions targeting the gut microbiota to impact growth in children in low- and middle-income countries. Evidence suggests that the diversity and maturation of the infant microbiota is linked with the development of the immune system and host-microbe symbiosis. Infants lacking Bifidobacterium longum subsp. Infantes, which predominates the breastfed microbiome, demonstrate immune activation with potential adverse effects on the gut. Conversely, supplementation with B longum subsp. Infantes is linked to increased immune tolerance and improved growth among undernourished children. Dietary patterns during pregnancy may also influence the selection of gut microbial species that impact infant health and growth.

These interesting findings have generated a lot of interest in understanding the relationship between environmental factors and the role of age in maturation and diversification of microbiome among children living in rural and urban settings in low- and middle-income countries [27], and the relationship between diets and gut microbiome [28]. Others have evaluated the potential impact of nutritional supplements in the growth and suppression of healthy microbiome [29]. However, the most promising studies appear to be microbiome-directed complimentary foods containing local ingredients as a novel strategy to reduce dysbiosis, promote gut microbiota development, especially among undernourished children, and improve growth [30, 31]. Several studies are underway to evaluate how these strategies, using scalable nutritional commodities, could impact linear growth and development in low- and middle-income countries [32].

Estimates and trends of zero vegetable or fruit consumption among children aged 6–23 months in 64 countries

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Comments: The role of fruits and vegetables (FV) in a balanced diet for children is well recognized, and while dietary diversity is often measured, it does not fully capture the relative intake of FV. The WHO and UNICEF established a new infant and young child feeding indicator: zero vegetable or fruit (ZVF) consumption among children aged 6–23 months. Allen et al. [13] estimated the prevalence, trends, and factors associated with ZVF consumption using nationally representative, cross-sectional data on child health and nutrition from 125 Demographic and Health Surveys. Prevalence of ZVF consumption was calculated by country, region, and globally. Using a pooled estimate of the most recent survey available in each country, the authors estimated the global prevalence of ZVF consumption as 45.7%, with the highest prevalence in West and Central Africa (56.1%) and the lowest in Latin America and the Caribbean (34.5%). Recent trends in ZVF consumption also varied across countries (16 decreasing, eight increasing, and 14 no change). Country trends in ZVF consumption represented diverse patterns of food consumption over time and may be affected by the timing of surveys. The authors noted that children from wealthier households and children of mothers who were employed, more educated, and had access to media were less likely to consume ZVF.

These findings underscore the scale and importance of balanced diets across countries among young children. These have important implications for policy given the importance of dietary diversification and school feeding programs globally addressing optimal nutrition and obesity prevention across the continuum from under five to school-age children and adolescents, and nutrition recommendations across childhood.

Other systematic reviews have also highlighted suboptimal dietary patterns and low intake of FV among adolescent girls globally [33]. The analysis of the global school health survey data also underscored the wide prevalence of poor dietary habits among adolescents in Southeast Asia [34]. It must also be recognized that while generally considered low cost, FV are often expensive and often beyond the reach of poor families, especially those not engaged in subsistence farming [35]. In such circumstances, poverty alleviation strategies and conditional cash transfers can improve food security and dietary diversity related to FV intake [36]. Such benefits have also been demonstrated from trials of parenting interventions in adolescents and can also be integrated with additional interventions [37].

Patterns in child stunting by age: a cross-sectional study of 94 low- and middle-income countries

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Comments: Karlsson et al. [14] estimated the relationship between stunting prevalence and age for children 0–59 months old in 94 low- and middle-income countries. While the overall stunting prevalence was 32%, they found higher stunting prevalence among older children until around 28 months of age, presumably from longer exposure times and accumulation of adverse exposures to undernutrition and infections. Stunting prevalence and gradient of the rise in stunting prevalence by age varied across world regions, countries, living standards, and sex. Poorer countries and households had a higher prevalence at all ages and a sharper positive age gradient before age 2. Boys had higher stunting prevalence, but had peak stunting prevalence at lower ages than girls. Stunting prevalence was similar for boys and girls after around age 45 months.

The age for which stunting prevalence was the highest was fairly consistent across countries. In most countries, the stunting prevalence was lower for older children after around 28 months, presumably mostly due to further adverse exposures being less detrimental for older children, and catch-up growth. These results suggest that programs to prevent undernutrition and infections should focus on younger children to optimize impact in reducing stunting prevalence. Importantly, however, since some catch-up growth may be achieved after age 2, screening around this time can be beneficial.

As other studies have repeatedly underscored as well, child stunting prevalence is primarily used as an indicator of impeded physical growth due to undernutrition, often starting with the mother and affecting fetal growth and a consequence of repeated early exposure to infections in the wake of poor diets and infant feeding [38]. Regardless of pathways, stunting significantly increases the risk of mortality, morbidity, and cognitive problems, particularly when occurring during the first 1,000 days of life, encompassing conception to age 2 years. As a risk factor for adverse outcomes, early childhood stunting has well-recognized consequences for human capital [39]. Close attention to maternal health, nutrition, and environmental factors is key to addressing the problem at scale, and, as several countries have shown, can be achieved within a few decades [40].

Short stature and language development in the United Kingdom: a longitudinal analysis of children from the Millennium Cohort Study

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Comments: Many studies conducted in low- and middle-income countries have established significant links between linear growth in the initial 6 months of life and cognitive outcomes during adolescence and adulthood. While stunting is predominantly observed in low- and middle-income countries, there is growing evidence that poor linear growth also serves as an indicator of socioeconomic disadvantage in high-income countries [41]. Limited information exists concerning the long-term consequences of poor early-life linear growth in high-income countries.

This present study by Freer et al. [15] utilized longitudinal data from the UK Millennium Cohort Study, which comprises children born in the United Kingdom between 2000 and 2002. The authors examined verbal and language development from age 3 to age 11 to investigate whether diminished stature is correlated with impaired language development within a contemporary, high-income society.

The study gathered information on 15,406 children who met the criteria for analysis. In the final sample, 514 (4.1%) children were classified as having short stature (height *Z*-score ≤ −2). Children with short stature exhibited lower birth weights, younger maternal ages, lower income quintiles, residence in areas with lower Index of Multiple Deprivation scores, a decreased likelihood of maternal education at a higher level, lower chances of having been breastfed, and increased exposure to secondhand smoke.

Within the study cohort, an association was observed between short stature and poorer performance in language testing between ages 3 and 11 years. Children with short stature exhibited language scores approximately one-quarter of a standard deviation lower than those with normal height. Although the association between short stature and language development weakened after accounting for maternal, child, and deprivation factors, it remained a significant predictor of diminished language development.

Among children with short stature at age 3 years who experienced height catch-up by age 5 years, better language test scores were observed compared to those who still had short stature at age 5 years. However, there was still a discernible lag in language attainment when compared to children who had never experienced short stature. Academic performance was also assessed at age 14 and at age 17 years, and again, associations between short stature and language development as well as mathematical proficiency were found. The precise mechanisms underlying the link between early-life linear growth and subsequent cognitive outcomes remain incompletely understood.

This large, longitudinal study is based on a national cohort of children born in the twenty-first century in the United Kingdom, and its data are robust. The follow-up period is longer than in most other similar studies [41]. Underlying mechanisms for the associations between poor growth and cognitive development have yet to be discovered in future studies. In the meantime, this study suggests that early-life stunting may help to identify children who can benefit from intervention to support cognitive development.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Stunting in Developing Countries

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Introduction

Globally, over 148 million children under five are stunted (i.e., weight-for-age *Z*-score 2 standard deviations below the WHO growth reference standard) [1, 2]. Although 30 million fewer children are stunted compared to a decade ago, the progress is insufficient. The majority of stunted children live in Asia (52%) and Africa (43%), and these two regions are predicted to have the bulk of the ~40 million “missed” children under five in 2030, as they are unlikely to meet the global target of reducing the global prevalence of stunting to 13.5% by 2030 [1, 2].

Since the onset of the Sustainable Development Goals (SDGs) in 2012, all countries committed to reducing stunting by 2024 as part of their efforts to achieve SDG 2, aimed at ending all forms of hunger [3]. However, the 2023 Joint Child Malnutrition Estimates showed that only about a third of countries are making progress toward this target [2]. Focusing solely on stunting targets overlooks and diminishes the complexity of interaction between the different forms of malnutrition that often coexist among children in impoverished communities in low- and middle-income countries. This has direct implications for the design of interventions, policy, and implementation strategies that focus on individual forms of malnutrition, instead of using an integrated approach to address them all. As stunting often stems from inadequate antenatal nutrition and infant feeding practices, poor access to clean water and sanitation, and recurrent childhood illnesses [3], efforts toward addressing the gaps in antenatal and early childhood nutrition and health for mothers and their infants using an integrated approach are crucial.

In the recently launched *Lancet* series for the small vulnerable newborns (SVNs), paper 4 summarizes evidence-based antenatal and intrapartum interventions to prevent SVN births and/or improve maternal and infant outcomes when SVNs are born [4]. By increasing coverage of the eight proven preventative interventions (including multiple micronutrient supplements, balanced protein and energy supplements, aspirin, treatment of syphilis, education for smoking cessation, prevention of malaria in pregnancy, treatment of asymptomatic bacteriuria, and progesterone provided vaginally) in all 81 low- and middle-income countries, we could prevent stunting in 4.5 million children (2.9%) by 2030 [4]. In addition, by combining these preventative interventions with childhood nutritional supplements (omega-3 fatty acid supplements, zinc supplements, and calcium supplements), stunting could be averted in 8.5 million stunted children (5.4%) [4] by 2030. The authors reported that this would lead to an additional 0.529 million extra years of schooling and ~USD 7.269 billion more in lifetime earnings [4]. The potential impact is significant, yet challenges persist in increasing the coverage and ensuring the implementation fidelity of these interventions [5].

Finally, "big data" (e.g., satellite-derived data) is increasingly being used to inform healthcare strategies. Village-level data, with the most detailed administrative perspective, provide valuable insights into the socioeconomic and environmental determinants influencing the achievement of the SDGs [6]. Analyzing the spatial patterns of environmental variables at this level and their links to child malnutrition provides a more in-depth exploration of key factors in the causal pathway that could lead to more targeted policies for the most vulnerable communities within a region or country [6].

Key articles reviewed for this chapter

Planetary Health Insights into Childhood Stunting

Impact of floods on undernutrition among children under five years of age in low- and middle-income countries: a systematic review
Agabiirwe CN, Dambach P, Methula TC, Phalkey RK
Environ Health 2022;21:98

Is stunting in children under five associated with the state of vegetation in the Democratic Republic of the Congo? Secondary analysis of Demographic Health Survey data and the satellite-derived leaf area index
Bangelesa F, Hatløy A, Mbunga BK, Mutombo PB, Matina MK, Akilimali PZ, Paeth H, Mapatano MA
Heliyon 2023;9:e13453

Climate change and food systems: linking adaptive capacity and nutritional needs of low-income households in Ghana
Issahaku D, Manteaw BO, Wrigley-Asante C
PLoS Clim 2023;2:e0000154

Projecting the impact of air pollution on child stunting in India – synergies and trade-offs between climate change mitigation, ambient air quality control, and clean cooking access (air pollution)
Dimitrova A, Marois G, Kiesewetter G, Rafaj P, Pachauri S, Samir KC, Olmos S, Rasella D, Tonne C
Environ Res Lett 2022;*17:104004*

Spatial variations of village-level environmental variables from satellite big data and implications for public health-related sustainable development goals
Liu X, Kim R, Zhang W, Guan WW, Subramanian SV
Sustainability 2022;14:10450

Impact of Maternal Nutrition and Health on Stunting and Subsequent Implications

Maternal height-standardised prevalence of stunting in 67 low- and middle-income countries
Karlsson O, Kim R, Bogin B, Subramanian SV
J Epidemiol 2022;32:337–344

Stunting at birth: linear growth failure at an early age among newborns in Hawassa city public health hospitals, Sidama region, Ethiopia: a facility-based cross-sectional study
Ejigu H, Tafese Z
J Nutr Sci 2023;12:e63

The Concurrent Presence of Stunting with Other Forms of Malnutrition

How can nutrition research better reflect the relationship between wasting and stunting in children? Learnings from the wasting and stunting project
Sadler K. James PT, Bhutta ZA, Briend A, Isanaka S, Mertens A, Myatt M, O'Brien KS, Webb P, Khara T, Wells JC
J Nutr 2023;152:2645–2651

Associations between stunting, wasting and body composition: a longitudinal study in 6- to 15-month-old Kenyan children
Konyole SO, Omollo SA, Kinyuru JN, Owuor BO, Estambale BB, Ritz C, Michaelsen KF, Filteau SM, Wells JC, Roos N, Friis H, Owino VO, Grenov B
J Nutr 2023;153:970–978

The coexistence of stunting and overweight or obesity in Ethiopian children: prevalence, trends and associated factors
Sahiledengle B, Mwanri L, Kumie A, Beressa G, Atlaw D, Tekalegn Y, Zenbaba D, Desta F, Kene C, Seyoum K, Gomora D, Woldeyohannes D, Agho KE
BMC Pediatr 202;23:218

The effect of wasting and stunting during severe acute malnutrition in infancy on insulin sensitivity and insulin clearance in adult life
Thompson DS, Francis-Emmanuel PM, Barnett AT, Osmond C, Hanson MA, Byrne CD, Gluckman PD, Forrester TE, Boyne M
J Dev Orig Health Dis 2022;13:750–756

Linear Growth Trajectories in LMICS and Their Impact on Stunting

Linear growth spurts are preceded by higher weight gain velocity and followed by weight slowdowns among rural children in Burkina Faso: a longitudinal study
Cliffer IR, Perumal N, Masters WA, Naumova EN, Ouedraogo LN, Garanet F, Rogers BL
J Nutr 2022;152:1963–1973

Interventions for Stunted Children

Postnatal Interventions

Preventive small-quantity lipid-based nutrient supplements reduce severe wasting and severe stunting among young children: an individual participant data meta-analysis of randomised controlled trials
Dewey KG, Arnold CD, Wessells KR, Prado EL, Abbeddou S, Adu-Afarwuah S, Ali H, Arnold BF, Ashorn P, Ashorn U, Ashraf S, Becquey E, Brown KH, Christian P, Colford JM Jr, Dulience SJ, Fernald LC, Galasso E', Hallamaa L, Hess SY, Humphrey JH, Huybregts L, Iannotti LL, Jannat K, Lartey A, Le Port A, Leroy JL, Luby SP, Maleta K, Matias SL, Mbuya MN, Mridha MK, Nkhoma M, Null C, Paul RR, Okronipa H, Ouédraogo JB, Pickering AJ, Prendergast AJ, Ruel M, Shaikh S, Weber AM, Wolff P, Zongrone A, Stewart CP
Am J Clin Nutr 2022;116:1314–1333

Effect of milk protein and whey permeate in large-quantity lipid-based nutrient supplements on early child development among children with stunting: a randomised 2 × 2 factorial trial in Uganda
Mbabazi J, Pesu H, Mutumba R, McCray G, Michaelsen KF, Ritz C, Filteau S, Briend A, Mupere E, Grenov B, Friis H, Olsen MF
Nutrients 2023;15:2659

Antenatal Interventions

Fortified balanced energy–protein supplementation during pregnancy, lactation, and infant growth in rural Burkina Faso: a 2× 2 factorial individually randomised controlled trial
Argaw A, de Kok B, Toe LC, Hanley-Cook G, Dailey-Chwalibóg T, Ouédraogo M, Compaoré A, Vanslambrouck K, Ganaba R, Kolsteren P, Lachat C, Huybregts L
PLoS Med 2023;20:e1004186

Planetary Health Insights into Childhood Stunting

Impact of floods on undernutrition among children under five years of age in low- and middle-income countries: a systematic review

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Comments: Agabiirwe et al. conducted a systematic review to map out existing evidence of the impact of floods on undernutrition in children under 5 years of age in low- and middle-income countries. All the studies were from South Asia (Bangladesh, India, Nepal, and Pakistan). Stunting was the most frequently reported form of undernutrition in flood-affected regions, with severe and recurrent floods showing the most significant impacts on stunting. In India, a community-based survey (rated as fair; lack of sufficient time between exposure and outcome) conducted 1 month after the floods reported that children living in repeatedly flooded communities were more likely to be underweight (adjusted prevalence rate [APR] = 1.86, 95% confidence interval [CI]: 1.04–3.30) and stunted (APR = 1.60, 95% CI: 1.05–2.44) but not wasted (APR = 1.2, 95% CI: 0.61–2.42) relative to those in the nonflooded villages. In the 1-year follow-up study (study rated as “Good”), a significant increase in the prevalence of underweight (APR = 1.48, 95% CI: 1.21–1.81) and wasting (APR = 2.30, 95% CI: 1.86–2.85) was reported but not stunting, for communities that were flooded twice (2006 and 2008) relative to the nonflooded communities. A more recent study (rated as “Good”) reported an increased risk of stunting (odds ratio [OR] = 1.04, 95% CI: 1.01–1.07) for children exposed to seasonal (monsoon) floods in infancy. In Bangladesh, a study conducted 2 months after the floods (rated as “Fair”) observed a 2-fold (OR = 2.18) increase in stunting for children living in villages very severely exposed. In another follow-up study conducted 15 months after the floods (a year after a baseline of 2 months after floods), severe and moderate levels of flood exposure were observed as predictors of stunting (OR = 8.210, 95% CI: 1.194–56.464) and wasting (OR = 25.06, 95% CI: 1.81–347.45), respectively. The only study conducted 6 months after floods reported a significant increase in underweight prevalence compared to before ($p < 0.001$). Factors associated with child undernutrition in the flood-affected areas included age, gender, diarrhea, maternal and paternal education, maternal age, household size, land ownership, and socioeconomic status. Stunting was the most frequently reported form of undernutrition over the long term following floods. The quality of the evidence was fairly weak, with the main challenge lying in the inability of the studies to establish causal pathways for the observed effects, lack of sufficient time between exposure and outcome, use of unreliable outcome assessment tools (e.g., the National Center for Health Statistics median reference standard), and use of unreliable outcome data and selection bias.

Is stunting in children under five associated with the state of vegetation in the Democratic Republic of the Congo? Secondary analysis of Demographic Health Survey data and the satellite-derived leaf area index

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Comments: This was a secondary data analysis of 5,241 children from the Democratic Republic of the Congo Demographic Health Survey 2013–2014 to measure the association between forest cover (here, leaf area index [LAI]) and under five childhood stunting, focusing on the differences between children living in rural versus urban environments. The LAI is a biophysical variable that measures the total green leaf area per unit of horizontal ground surface area. The median LAI value was 4.21 m^2/m^2. Children living in an area with a higher LAI (4.21 m^2/m^2 and above) were compared with those living in an area with a lower LAI (<4.21 m^2/m^2), that is, the reference group. The key findings showed that children in communities surrounded by high LAI values have lower odds of being stunted (OR = 0.63; 95% CI: 0.47–0.86) than those exposed to low LAI values. The association still held when the exposure was analyzed as a continuous variable (OR = 0.84; 95% CI: 0.74–0.95). When stratified in rural and urban areas, a significant association was only observed in rural areas (OR = 0.6; 95% CI: 0.39–0.81) but not in urban areas (OR = 0.9; 95% CI: 0.5–0.5). Children from wealthier households were less likely to be stunted by a factor of 0.22 (95% CI: 0.14–0.34), 0.57 (95% CI: 0.42–0.78), and 0.76 (95% CI: 0.59–0.98) for wealthiest, wealthy, and middle-class households, respectively. The child's age, mother's previous birth interval, and work status were not associated with stunting. The association between LAI and childhood stunting is statistically significant and negative in rural areas (OR = 0.6; 95% CI: 0.39–0.81); however, this association does not hold in urban areas (OR = 0.9; 95% CI: 0.5–1.5), where the mother's work status and previous birth interval are not associated with stunting. In urban areas, children whose mothers had secondary-level education had lower odds of being stunted compared to those whose mothers only had primary-level education. Previous birth intervals of 24–35 months and >35 months are associated with lower odds of being stunted in a rural area, OR 0.7 (95% CI: 0.52–0.96) and 0.7 (95% CI: 0.56–0.97), respectively. In a rural area, being from the wealthiest and wealthier households reduced the odds of being stunted by a factor of 0.2 (95% CI: 0.06–0.82) and 0.5 (95% CI: 0.36–0.78), respectively, while in an urban area, only the wealthiest households are associated with lower stunting (OR = 0.3; 95% CI: 0.2–0.6). In conclusion, the association observed between LAI and stunting was attributed to the fact that forest vegetation is the primary source of local and affordable foods, especially in rural areas. The lack of association between childhood stunting and the LAI in urban areas is probably due to the low prevalence of stunting there compared to rural areas and the high deforestation in urban areas, reducing LAI value below 4.21 m^2/m^2. Despite controlling for many possible confounders, the main limitation of this study is its inability to inform the temporality of the cause and effect or its susceptibility to retaining a residual confounding. Though the study findings are limited to children under 5 years living in the Democratic Republic of the Congo, they can be used to inform policies on integrating forest conservation to improve nutritional status and combat stunting in children in rural areas.

Climate change and food systems: linking adaptive capacity and nutritional needs of low-income households in Ghana

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Comments: In this quantitative cross-sectional study conducted in northern Ghana, Issahaku et al. utilized the sustainable livelihoods framework to investigate the connection between household adaptive capacity – assessed through human, physical, financial, and social capital – and climate change as well as its impact on nutritional requirements of low-income households. It explores how the poor adaptive capacity of low-income households acts as a barrier to meeting nutritional requirements. The study focused on 288 households with at least one child under five. The overall prevalence of stunting among children was 39.2%. Findings showed a negative correlation between household adaptive capacity and stunting in children (β −1.125; OR 0.263; $p < 0.01$). This means that a child from a household with a high adaptive capacity was about four times (3.8, $p < 0.01$) more likely to be nonstunted than a child from a low adaptive capacity household. Of significant note, the study population's biggest driver of low adaptive capacity was low financial capital (37.9%). Regarding human capital, remittances and livestock ownership were the two most significant drivers of variation in adaptive capacity. Children from households that adopted new crop varieties were more than two times (2.3; $p < 0.05$) more likely to be normal (nonstunted) than children from households that did not. Children from households that adapted dry season farming via irrigation technology were six times (6.1; $p < 0.05$) less likely to be stunted than children from households that did not. Furthermore, children from households that adopted mulching were found to be seven times (7.4) less likely to be stunted than those from households that did not. These adaptive practices increased household income and food availability, impacting food security and nutrition. However, children from households involved in hairdressing, fitting mechanics, and building masonry were 2.6 times more likely to be stunted than their counterparts. While adaptive capacity is essential for predicting nutritional needs and improving food and nutrition security, it interacts with other factors. Therefore, it should be considered part of a spectrum of determinants influencing malnutrition.

Projecting the impact of air pollution on child stunting in India – synergies and trade-offs between climate change mitigation, ambient air quality control, and clean cooking access (air pollution)

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Comments: Dimitrova et al. investigated the correlations between early-life exposure to ambient particulate matter ($PM_{2.5}$) and the use of polluting cooking fuels, as well as stunting among 203,870 children under the age of 5 years in India. In the subsequent phase of the study, the researchers developed a static microsimulation model to analyze childhood stunting, utilizing data from the National Family Health Survey, multidimensional population projections, and projections of ambient $PM_{2.5}$ concentrations, clean fuel usage, and per capita income levels derived from an integrated assessment model. After adjusting for confounding factors, they showed that in utero exposure to ambient $PM_{2.5}$ was significantly associated with increased odds of childhood stunting (OR: 1.04, 95% CI: 1.03–1.05 per 10 µg/m^3 increase in $PM_{2.5}$). Conversely, using clean cooking fuel, compared to polluting fuels, was linked to reduced odds of stunting (OR: 0.81, 95% CI: 0.79–0.84). Female children, those residing in urban areas, born to less educated mothers, belonging to socially disadvantaged castes, and living in lower-income households exhibited greater susceptibility to the detrimental effects of $PM_{2.5}$ on linear growth ($p < 0.05$). Adjusting for additional covariates, such as the month of birth to account for seasonal variations in exposures, had minimal impact on the estimated effects of exposure. Projected data indicated a decrease in maternal $PM_{2.5}$ exposure and an increase in clean cooking over time reduced the risk of childhood stunting.

Spatial variations of village-level environmental variables from satellite big data and implications for public health-related sustainable development goals

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Comments: Liu et al. [6] aimed to demonstrate the potential of high-resolution satellite data to provide valuable insights into different socioeconomic and environmental factors relevant to achieving the Sustainable Development Goals. The primary focus was child malnutrition indicators – stunting, underweight, and wasting – and the authors demonstrated the utilization of a cloud platform for deriving village-level environmental variables from big satellite datasets. Spatial data analysis revealed distinct patterns of environmental variables across the study area, with each village group showing different statistics. The study also explored the correlations between these environmental variables – normalized difference vegetation index (NDVI), rainfall (RF), elevation, slope, and land surface temperature (LST) – and child malnutrition indicators. All three malnutrition indicators showed negative correlations with NDVI, RF, elevation, and slope. This indicates that higher levels of NDVI (β −0.269; −0.382; −0.468), RF (β −0.365; −0.370; −0.431), elevation (β −0.639; −0.654; −0.387), and slope (β −0.725; −0.782; −0.568) were associated with lower prevalences of child stunting, underweight, and wasting, respectively. On the other hand, there was a positive correlation between malnutrition indicators and LST (stunting β 0.627; underweight β 0.792; and wasting β 0.822), suggesting that higher LST was associated with higher rates of child malnutrition. Additionally, the study found that stunting and underweight showed stronger correlations with slope, elevation, and LST, while wasting exhibited stronger correlations with LST and slope compared to NDVI and RF. Furthermore, NDVI, LST, and rainfall showed stronger correlations with wasting compared to underweight and stunting. In contrast, elevation and slope were more strongly correlated with stunting and underweight than wasting. Overall, the findings suggest that environmental factors, such as vegetation, rainfall, elevation, slope, and LST, significantly influence child malnutrition at the village level in India.

Impact of Maternal Nutrition and Health on Stunting and Subsequent Implications

Maternal height-standardised prevalence of stunting in 67 low- and middle-income countries

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Comments: Karlsson et al. argued that, as parental height is a major determinant of stunting, the variation in adult height may, therefore, account for the variation in the prevalence of stunting across low- and middle-income countries (LMICs). Karlsson et al. estimated the maternal height standardized prevalence of stunting (SPS) in 67 LMICs and the parental height SPS in 20 LMICs to understand this from a policy perspective. SPS is the standardized prevalence of stunting and is calculated by rescaling the sampling weights, to sum up the probability density within each stratum of maternal height in the Multicentre Growth Reference Study reference population. These estimates were compared with the crude prevalence of stunting (CPS) using data from 575,767 children under five from 67 demographic and health surveys. On average, the mothers in the sample were 157.4 cm tall, with variations observed across regions. The shortest maternal heights were observed in Guatemala (148.5 cm), whereas the tallest were in

West Africa, particularly Senegal (163.6 cm). When comparing maternal heights between the study sample and the Multicentre Growth Reference Study, mothers in the study sample were generally shorter, except for seven countries, predominantly in sub-Saharan Africa. The findings revealed that the average CPS across the LMICs was 27.8% (95% CI 27.5–28.1), with the highest prevalence in Burundi (51%) and the lowest in the Dominican Republic (7.1%). After standardizing maternal height, SPS was 23.3% (95% CI 23.0–23.6) in the pooled sample. Burundi had the highest SPS (41.3%), along with Niger (41.9%) and Chad (41.3%). Peru had the lowest SPS (5.8%), followed by the Dominican Republic (6.4%). The most considerable deterioration in the ranking of countries according to the prevalence of stunting after standardizing maternal height was for West African countries, such as Mali, Gambia, and Senegal. Countries in South Asia, such as Nepal, Bangladesh, India, and Pakistan, improved their rankings. In terms of correlation, maternal height SPS demonstrated better associations than CPS with various child health indicators, including diarrhea, anemia, under five, and child mortality rates. In conclusion, SPS is a more sensitive indicator of health outcomes. The findings also underscore the role of maternal height in understanding child malnutrition.

Stunting at birth: linear growth failure at an early age among newborns in Hawassa city public health hospitals, Sidama region, Ethiopia: a facility-based cross-sectional study

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Comments: Ejigu et al. conducted a facility-based cross-sectional study to investigate the prevalence of stunting at birth, low birth weight (<2,500 g), and their coexistence among newborns delivered across the public hospitals of Hawassa city, Ethiopia (*n* = 371). Ejigu et al. found that 35.6% of newborns were stunted, and 24.6% were having low birth weight. Among the newborns, 5.8% had only low birth weight, 16.9% had only stunting, and 18.8% had both stunting and low birth weight. The study also evaluated antenatal and postnatal factors associated with stunting at birth. Maternal adverse antenatal exposures, including living in food-insecure households (adjusted odds ratio [AOR] 2.56; 95% CI 1.46, 4.49) and accessing inadequate dietary diversity (AOR 4.03; 95% CI 2.18, 7.48), were predictors of stunting at birth. Newborns of mothers with a mid-upper arm circumference of less than 23 cm had a 2-fold increased risk of being stunted at birth compared to those born to mothers with mid-upper arm circumference ≥23 cm (AOR 2.13; 95% CI 1.13, 4.01). Similarly, newborns of mothers with a birthing interval of less than 24 months had more than double the risk of being stunted at birth compared to those born to mothers with a birth interval of ≥24 months (AOR 2.55; 95% CI 1.39, 4.69). Infants with low birth weight were 11 times more likely to be stunted at birth compared to normal-weight babies (AOR 10.9; 95% CI 5.85, 20.30). The findings underscore the importance of addressing maternal health, nutrition, and household factors to improve newborns' nutritional status and overall health in Ethiopia and similar settings. Existing community-based interventions to improve maternal nutrition, household food security, and birth spacing should be strengthened to help reduce the burden of stunting at birth and its associated complications.

The Concurrent Presence of Stunting with Other Forms of Malnutrition

How can nutrition research better reflect the relationship between wasting and stunting in children? Learnings from the wasting and stunting project

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Comments: The Emergency Nutrition Network (ENN) has conducted extensive research on the relationship between wasting and stunting, two forms of malnutrition in children often treated separately despite sharing common risk factors and frequently occurring in the same child. The ENN initiated the Wasting and Stunting project to understand better these conditions and their implications for policies and programs. Lessons learned from the project included identifying and targeting high-risk individuals, such as those with concurrent wasting and stunting, who face a significant mortality risk. Anthropometric measures like weight-for-age and mid-upper arm circumference have shown promise in identifying high-risk children. Longitudinal data analysis has shown that episodes of wasting can contribute to later episodes of stunting, emphasizing the importance of preventing wasting to prevent stunting. Additionally, Sadler et al. suggested that it was crucial to report the combined extent of wasting and stunting and measure the incidence of wasting to understand their burden better. The project stated that diverse pathways and factors drive different forms of undernutrition, including maternal factors, early markers, seasonality, age, and sex. Overall, future research should focus on the processes of wasting and stunting, explore risk factors in different contexts, use diagnostic criteria to identify high-risk children, prioritize seasonality, utilize longitudinal data, and develop innovative markers for early identification and monitoring of undernutrition risks. Collaboration and coherent research investments were also discussed as crucial to addressing wasting and stunting effectively.

Associations between stunting, wasting and body composition: a longitudinal study in 6- to 15-month-old Kenyan children

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Comments: Konyole et al. aimed to investigate the association between undernutrition (stunting and wasting) and body composition in early life. This longitudinal study was nested in a randomized controlled nutrition trial. Konyole et al. used deuterium dilution to assess fat mass (FM) and fat-free mass (FFM) among children between ages 6 and 15 months. Findings showed that out of 499 children enrolled in the study between 6 and 15 months, breastfeeding rates declined from 99 to 87%, while stunting rates increased from 13 to 32%. However, wasting remained stable at 2–3%. A comparison made with the length-for-age *Z*-score (LAZ) showed that stunted children exhibited a 1.12 kg (95% CI: 0.88, 1.36; $p < 0.001$) lower FFM at 6 months, which increased to 1.59 kg (95% CI: 1.25, 1.94; $p < 0.001$) at 15 months. Further analysis of the fat-free mass index showed that the deficit in FFM was less than proportional to children's height at 6 months ($p < 0.060$) though not significant at 15 months ($p < 0.40$). Although stunting was associated with 0.28 kg lower FM at 6 months (95% CI: 0.09, 0.47; $p = 0.004$), neither of these negative associations was observed at 15 months, nor was it associated with stunting at any time point. Overall, differences in FFM were observed, while no differences were detected for FM and FFM index. The author concluded that children with a low length-for-age *Z*-score and a weight-for-length *Z*-score may have long-term health consequences because of reduced lean tissue suffered due to undernutrition.

The coexistence of stunting and overweight or obesity in Ethiopian children: prevalence, trends and associated factors

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Comments: Sahiledengle et al. conducted a cross-sectional study in Ethiopia to examine the prevalence, trends, and factors associated with the coexistence of stunting and overweight or obesity (CSO) among children aged 0–59 months. The study included a total of 23,756 children in the analysis. CSO was defined as a child being stunted (height-for-age *Z*-score below −2 standard deviation) and overweight or obese (weight-for-height *Z*-score above 2 standard deviation). The prevalence of stunting, overweight or obesity, and CSO among children under five was 43.12% (95% CI: 42.50, 43.75%), 2.62% (95% CI: 2.42, 2.83%), and 1.33% (95% CI: 1.18, 1.48%), respectively. The percentage of CSO children was reported to have declined from 2.36% (95% CI: 1.94–2.85) in 2005 to 0.87% (95% CI: 0.07–1.07) in 2011, and the same appeared to have increased slightly to 1.34% (95% CI: 1.13–1.59) in 2016. Children who were currently breastfeeding (AOR: 1.64, 95% CI: 1.01–2.72), born to an overweight mother (AOR: 2.65, 95% CI: 1.19–5.88), and lived in families with 1–4 household members (AOR: 1.52, 95% CI: 1.02–2.26) were significantly positively associated with CSO. At the community level, the odds of having CSO were higher among children included in the Ethiopia Mini Demographic and Health Survey 2005 (AOR: 4.38, 95% CI: 2.42–7.95). Overall, the study findings indicate that the double burden of malnutrition must be addressed concurrently through targeted interventions. Early identification of at-risk children, including those born to overweight women and those living with multiple household members, is essential to combating the double burden of malnutrition.

The effect of wasting and stunting during severe acute malnutrition in infancy on insulin sensitivity and insulin clearance in adult life

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Comments: In this retrospective cohort study of 40 Afro-Caribbean survivors of severe acute malnutrition nondiabetic adults, Thompson et al. aimed to investigate the association between wasting and/or stunting in adults and glucose disposal rate (*M*) and insulin clearance (MCR) in adulthood. The 20 marasmus survivors (MS) and 20 kwashiorkor survivors (KS) had been admitted with severe malnutrition between ages 6 and 18 months. It was hypothesized that wasting and stunting were associated with lower glucose rate disposal and insulin clearance in adulthood. At admission, findings showed that children with marasmus had significantly lower weight-for-height *Z*-scores (-3.8 ± 0.9 vs. -2.2 ± 1.4; $p < 0.001$) and height-for-age *Z*-scores (-4.6 ± 1.1 vs. -3.4 ± 1.5; $p = 0.0092$) than those with Kwashiorkor. MS had higher fasting glucose concentrations in adulthood than KS, even after adjusting for age and sex ($p \leq 0.001$). However, there was no difference in *M* and MCR among the adult MS, KS, and controls ($p > 0.3$). Neither the weight-for-height *Z*-score nor the height-for-age *Z*-score was associated with insulin sensitivity, MCR, or fasting adiponectin ($p > 0.35$), even in overweight or obese adults ($p > 0.34$). Even after adjusting for fat mass, the weight-for-height *Z*-score was not associated with *M* ($r = 0.12$, $p = 0.54$) and MCR ($r = -0.08$, $p = 0.66$). Similarly, the height-for-age *Z*-score was not associated with *M* ($r = 0.16$, $P = 0.35$) and MCR ($r = -0.08$, $p = 0.65$) after adjustment of fat mass. Developmental factors like intrauterine growth restriction may influence beta cell mass and function. The study limitations were the small sample size, lack of data regarding beta cell function, and the absence of C-peptide data to support the claim that basal insulin secretion was unaffected by the insulin infusion during the clamp. The authors concluded that wasting and stunting in early childhood are not associated with differences in insulin sensitivity and insulin clearance in lean young adult severe acute malnutrition survivors, possibly due to adequate nutritional recovery. Instead, the glucose intolerance in MS is mainly attributed to beta cell dysfunction. Finally, there is a need to estimate hepatic insulin clearance and pancreatic islet function in this cohort and carry out follow-up studies in obese survivors of malnutrition.

Linear growth spurts are preceded by higher weight gain velocity and followed by weight slowdowns among rural children in Burkina Faso: a longitudinal study

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Comments: Cliffer et al. conducted a clustered trial in Burkina Faso using monthly anthropometric measurements of 5,039 children aged 6–28 months who were followed up for 18 months between August 2014 and December 2016 as part of a geographically clustered trial comparing the cost of effectiveness of 4 supplementary food in preventing stunting and wasting in children aged 6–23 months in Sanmatenga Province. Cliffer et al. aimed to evaluate how changes in one growth parameter impact others and identify critical age ranges when growth rates influence each other. Monthly anthropometric assessments were conducted, including recumbent length, weight, and mid-upper arm circumference. Overall, the findings showed that boys exhibited poorer growth and morbidity parameters than girls, yet linear growth seasonality did not differ by gender. Faster ponderal growth occurred when average linear growth increased within the same month (0.07–0.13 increase in weight velocity *Z*-score [WVZ] per unit increase in concurrent length velocity *Z*-score [LVZ]). Notably, faster linear growth (0.21–0.72 increase in LVZ per unit increase in WVZ) was associated with faster ponderal growth, either preceding or happening concurrently. However, faster linear growth in children 9–14 months old was associated with slower future ponderal growth (0.009–0.02 decrease in WVZ per unit increase in lagged LVZ). Girls aged 6–8 months exhibited the highest linear growth with increased weight gain. There was a strong association between linear and ponderal growth velocity, with conditions affecting one parameter and the other roughly simultaneously. Due to the slower linear growth process, the effects in weight are seen first. Furthermore, the slowest ponderal growth velocity coincided with peak morbidity, subsequently followed by the slowest linear growth velocity. The main limitation is the lack of longitudinal data on food security and diet diversity, key exposures that influence growth velocity and morbidity. Cliffer et al. concluded that a systems approach to improve living conditions (sanitation, hygiene infrastructure, access to nutritious foods) and address community-level deficiencies that constrain growth would help address growth faltering. Moreover, the best way to understand the temporal dependencies between linear and ponderal growth is by assessing growth velocity and changes in growth drivers. They also did not assess the associated neurodevelopmental outcomes of these children at any point during the 18 months of follow-up.

Postnatal Interventions

Preventive small-quantity lipid-based nutrient supplements reduce severe wasting and severe stunting among young children: an individual participant data meta-analysis of randomised controlled trials

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Comments: This meta-analysis by Dewey et al. included data from 14 randomized controlled trials to investigate the impact of small-quantity lipid-based nutrient supplements (SQ-LNSs) on the prevalence of severe wasting (weight-for-length Z-score < −3) and severe stunting (length-for-age Z-score < −3) in children aged 6–24 months. The analysis, which involved 34,373 participants for severe wasting and 36,795 participants for severe stunting, showed consistent positive effects of SQ-LNSs across the studies. The findings demonstrated that the provision of SQ-LNSs resulted in a relative reduction of 31% in severe wasting (prevalence ratio [PR]: 0.69; 95% CI: 0.55–0.86) and 17% in severe stunting (PR: 0.83; 95% CI: 0.78–0.90) at the end of the study. The study-level characteristics did not significantly modify the effects of SQ-LNSs. However, there were indications that the supplements had greater effects in locations with higher burdens of wasting or stunting or where water quality and sanitation were poorer. The authors concluded that incorporating SQ-LNSs into preventive interventions to promote healthy child growth and development will likely reduce the rates of severe wasting and stunting.

Effect of milk protein and whey permeate in large-quantity lipid-based nutrient supplements on early child development among children with stunting: a randomised 2 × 2 factorial trial in Uganda

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Comments: This randomized, double-blind, 2 × 2 controlled trial by Mbabazi et al. assessed the effects of milk protein (MP) and whey permeate (WP) and lipid-based nutrient supplement (LNS) on linear growth and body composition among 750 stunted children. Findings showed that unsupplemented children had a 0.06 (95% CI [0.02, 0.10]; p = 0.015) decline in height-for-age Z-score, accompanied by 0.29 (95% CI [0.20, 0.39]; p < 0.001) kg/m^2 increase in fat mass index, but 0.06 (95% CI [−0.002; 0.12]; p = 0.057) kg/m^2 decline in fat-free mass index. There were no interactions between MP and WP. The main effects of MP were 0.03 cm (95% CI [−0.10, 0.16]; p = 0.662) in height and 0.2 mm (95% CI [−0.3, 0.7]; p = 0.389) in knee-heel length. The main effects of WP were −0.08 cm (95% CI [−0.21, 0.05]; p = 220) and −0.2 mm (95% CI [−0.7; 0.3]; p = 403), respectively. Interactions were found between WP and breastfeeding with respect to linear growth (p < 0.02) due to positive effects among breastfed and negative effects among non-breastfed children. Overall, LNS resulted in 0.56 cm (95% CI [0.42, 0.70]; p

< 0.001) height increase, corresponding to 0.17 (95% CI [0.13, 0.21]; $p < 0.001$) height-for-age Z-score increase and 0.21 kg (95% CI [0.14, 0.28]; $p < 0.001$) weight increase, of which 76.5% (95% CI [61.9; 91.1]) was fat-free mass. Using height-adjusted indicators, LNS increased fat-free mass index (0.07 kg/m^2, 95% CI [0.0001; 0.13]; $p = 0.049$) but not fat mass index (0.01 kg/m^2, 95% CI [−0.10, 0.12]; $p = 0.800$). The main limitations were the lack of blinding of caregivers and the short study duration. The authors concluded that adding dairy to LNS has no additional effects on linear growth or body composition in stunted children aged 12–59 months. However, regardless of milk, LNS supplementation promotes linear catch-up growth and fat-free mass accretion, but not fat mass.

Antenatal Interventions

Fortified balanced energy-protein supplementation during pregnancy, lactation, and infant growth in rural Burkina Faso: a 2 × 2 factorial individually randomised controlled trial

Argaw A[1,2], de Kok B[1], Toe LC[1,3], Hanley-Cook G[1], Dailey-Chwalibóg T[1], Ouédraogo M[4], Compaoré A[4], Vanslambrouck K[1], Ganaba R[4], Kolsteren P[1], Lachat C[1], Huybregts L[1,5]

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Comments: In this 2 × 2 factorial individually randomized controlled trial (MISAME-III) by Argaw et al. conducted in rural Burkina Faso, the efficacy of daily fortified balanced energy-protein (BEP) supplementation during pregnancy and lactation on infant growth was evaluated. The study recruited 1,897 pregnant women aged 15–40 with a gestational age of less than 21 weeks. The women were randomly assigned to one of the two prenatal interventions: (i) fortified BEP supplements and iron-folic acid (IFA) tablets (intervention group) or (ii) IFA alone, which is the standard care during pregnancy (control group). Concurrently, the same women were randomized to receive either postnatal fortified BEP supplementation during the first 6 months postpartum along with IFA for the first 6 weeks (intervention group) or postnatal IFA alone for 6 weeks postpartum (control group). The primary postnatal study outcome was the length-for-age Z-score (LAZ) at 6 months. The results showed that prenatal BEP supplementation led to a significantly higher LAZ (0.11 standard deviation, 95% CI [0.01–0.21], $p = 0.032$) and lower stunting prevalence (3.18 percentage points, 95% CI [−5.86– −0.51], $p = 0.020$) at 6 months of age. However, postnatal BEP supplementation did not significantly affect LAZ or stunting at 6 months. Nevertheless, postnatal BEP supplementa-

tion did result in a modest improvement in the rate of monthly LAZ increment during the first 12 months postpartum (0.01 Z-score/month, 95% CI [0.00–0.02], $p = 0.030$). At 6 months, no significant effects were observed on secondary outcomes related to stunting, wasting, being underweight, anemia, or hemoglobin concentration. In conclusion, this study demonstrated that prenatal BEP supplementation positively impacted infant linear growth and stunting. However, postnatal BEP supplementation did not significantly impact these outcomes at 6 months postpartum. The findings contribute to the growing evidence that nutrition interventions targeting women in the prenatal period are likely to be more impactful in improving linear growth among infants than those delivered during the postnatal period in resource-limited settings like rural Burkina Faso.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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The Physiology and Mechanisms of Growth

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Introduction

A selection of articles published in the period from July 1, 2022, to June 30, 2023, addressing physiology and mechanisms of growth is presented in this chapter. We acknowledge that the selection is subjective, and some essential articles may have not been included, due to shortage of space.

The following themes were addressed in this year's chapter: Management of growth disorders during puberty is complex. Puberty is the final period where gains in linear growth can be made. However, it should be emphasized that other physiological processes during puberty are also important and should not be disregarded when planning growth-promoting interventions. Physical and/or psychological stress can affect growth and could, if chronic, result in suboptimal final height. Interventions regulating stress in growing children and adolescents should be either prevented, recognized, or managed early. More insights into mechanisms involved in growth failure related to attention deficit medications and inflammation were published. It was determined that proper nutrition could alter the outcome regarding growth during acute or chronic inflammation. Several manuscripts are presented on the management of comorbidities of skeletal dysplasia, with an emphasis on nutritional management. Interesting data on the mechanisms of growth in premature infants are discussed. Nutrition and gut microbiota were further acknowledged as essential players in these subjects. Finally, more data on the role of protein-fortified nutrition in linear growth are presented.

Key articles reviewed for this chapter

Management of growth disorders in puberty: GH, GnRHa, and aromatase inhibitors: a clinical review
Mauras N, Ross J, Mericq V
Endocr Rev 2023;12;44:1–13

Methylphenidate promotes premature growth plate closure: in vitro evidence
Pazos-Pérez A, Piñeiro-Ramil M, Franco-Trepat E, Guillán-Fresco M, López-López V, Jorge-Mora A, Alonso-Pérez A, Gómez R
Int J Mol Sci 2023;24:4175

Stress and growth in children and adolescents
Mousikou M, Kyriakou A, Skordis N
Horm Res Paediatr 2023;96:25–33

A whey-based diet can ameliorate the effects of LPS-induced growth attenuation in young rats
Menahem C, Foist M, Mansour Y, Shtaif B, Bar-Maisels M, Phillip M, Gat-Yablonski G
Nutrients 2023;15:1823

TNF overexpression and dexamethasone treatment impair chondrogenesis and bone growth in an additive manner
Zhao Y, Celvin B, Denis MC, Karagianni N, Aulin C, Zaman F, Sävendahl L
Sci Rep 2022;12:18189

Osteolectin increases bone elongation and body length by promoting growth plate chondrocyte proliferation
Zhang J, Du L, Davis B, Gu Z, Lyu J, Zhao Z, Xu J, Morrison SJ
Proc Natl Acad Sci U S A 2023;120:e2220159120

Hepatic steatosis assessment as a new strategy for the metabolic and nutritional management of Duchenne muscular dystrophy
Tang YC, Tsui PH, Wang CY, Chien YH, Weng HL, Yang CY, Weng W
Nutrients 2022;14:727

Metabolic assessment in children with neuromuscular disorders shows risk of liver enlargement, steatosis and fibrosis
Naume MM, Jørgensen MH, Høi-Hansen CE, Born AP, Vissing J, Borgwardt L, Staerk DMR, Ørngreen MC
Acta Paediatr 2023;112:846–853

Assessment of body fat mass, anthropometric measurement and cardiometabolic risk in children and adolescents with achondroplasia and hypochondroplasia
Nakano Y, Kubota T, Ohata Y, Takeyari S, Kitaoka T, Miyoshi Y, Ozono K
Endocr J 2023;70:435–443

A scoping review of nutrition issues and management strategies in individuals with skeletal dysplasia
Billich N, O'Brien K, Fredwall SO, Lee M, Savarirayan R, Davidson ZE
Genet Med 2023;25:100920

The crosstalk between FGF21 and GH leads to weakened GH receptor signalling and IGF1 expression and is associated with growth failure in very preterm infants
Mistry JN, Silvennoinen S, Zaman F, Sävendahl L, Mariniello K, Hall C, Howard SR, Dunkel L, Sankilampi U, Guasti L
Front Endocrinol (Lausanne) 2023;14:1105602

The gut microbiome and early-life growth in a population with high prevalence of stunting
Robertson RC, Edens TJ, Carr L, Mutasa K, Gough EK, Evans C, Geum HM, Baharmand I, Gill SK, Ntozini R, Smith LE, Chasekwa B, Majo FD, Tavengwa NV, Mutasa B, Francis F, Tome J, Stoltzfus RJ, Humphrey JH, Prendergast AJ, Manges AR
Nat Commun 2023;14:654

The effect of a nutritional supplement on growth and body composition in short and lean preadolescent boys following one-year of intervention
Yackobovitch-Gavan M, Lazar L, Demol S, Mouler M, Rachmiel M, Hershkovitz E, Shamir R, Phillip M, Shvalb NF
Horm Res Paediatr 2023;96:278–288

Management of growth disorders in puberty: GH, GnRHa, and aromatase inhibitors: a clinical review

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Endocr Rev 2023;12;44:1–13

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Comments: The magnitude of the growth spurt during puberty is the result of the race between the stimulatory effect of the sex hormones on the growth hormone–insulin-like growth factor 1 axis and directly on the epiphyseal growth plate and its senescence effect on the growth plate which occurs simultaneously. In the present excellent review manuscript, the authors discuss ways to extend the growth of the long bones during puberty of children with short stature. The authors discuss the physiology of the growth during puberty and review the possible ways to influence the process with gonadotropin-releasing hormone analogues and aromatase inhibitors. This review is one of the most important manuscripts that addresses the topic in the literature and helps to bring the reader to the edge of the knowledge available today on the topic.

Methylphenidate promotes premature growth plate closure: in vitro evidence

Pazos-Pérez A, Piñeiro-Ramil M, Franco-Trepat E, Guillán-Fresco M, López-López V, Jorge-Mora A, Alonso-Pérez A, Gómez R

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Comments: Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by difficulties in maintaining attention, hyperactivity, excessive movement, and impulsiveness. It is the most diagnosed neuropsychiatric disorder, with a prevalence of 5–10% in children and young people. Multidisciplinary treatment that includes parental training, behavior therapy, and pharmacotherapy is the accepted mode of treatment. Methylphenidate (MPH) is among the most frequently used medication. It increases the availability of dopamine and norepinephrine in the synaptic space by inhibiting their presynaptic transporters in central adrenergic neurons, thus leading to stimulation of their receptors [1].

Patients with ADHD have relatively reduced final height and weight [2, 3]. Anorexigenic effect of the medication, with reduced caloric intake, is the suspected mechanism. However, in this study, the authors, for the first time, describe a possible direct effect of MPH on the bone plate, influencing endochondral ossification and senescence. To this effect, it was determined that in the in vitro model, MPH did not influence the viability, proliferation, and differentiation of the prechondrogenic cells in the growth plate. However, it reduced the expression of cartilage extracellular matrix–related genes and increased the expression of genes involved in growth plate calcification.

These data suggest that MPH directly influences the mechanisms of growth in the growth plate, possibly leading to premature closure of the growth plate. This would contribute to the growth retardation that has been described to be induced by this drug. These data need to be further verified in the humans; however, they could potentially have an important influence for many patients with ADHD treated with MPH.

Stress and growth in children and adolescents

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Horm Res Paediatr 2023;96:25–33

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https://pubmed.ncbi.nlm.nih.gov/34814153/

Comments: Stress is defined as a state of threatened or perceived threatened homeostasis in the system (e.g., human organism). Impulses leading to stress in humans can be either physical or psychological and are called stressors. They can be isolated or multiple, internal or external. The human organism reacts to stress by activating adaptive hormonal and neural responses. They are protective for human health; however, if they are too extensive or persist longer, they may be maladaptive [4].

From the point of view of linear growth, stress can lead to suboptimal height velocity and reduced final height. It can impact linear growth in all phases of growth (prenatal/fetal, infancy, childhood, or adolescence) by acting through different physiological mechanisms, either by directly modulating the growth hormone axis or indirectly through other factors. The adaptive response to stressors culminates in behavioral, physiological, and biochemical responses, which together support survival and conservation of energy [4].

The acute and time-limited response to stress does not result in long-lasting consequences for growth. Actually, growth and other processes, such as reproduction, can however be halted, the potential for both is not lost. Chronic activation of the stress system and especially hypercortisolism however do have a negative impact on growth, thyroid function, reproduction, puberty, and metabolism.

Mechanisms involved in how stress influences linear growth are discussed in this interesting review. In addition, targeted interventions to reduce stress during infancy, childhood, and adolescence, with the goal of maintaining long-term health and normal growth and pubertal development, are suggested.

Altogether, for those interested in growth and development of children, this is a must-read review article.

A whey-based diet can ameliorate the effects of LPS-induced growth attenuation in young rats

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https://pubmed.ncbi.nlm.nih.gov/37111042/

Comments: Children with chronic inflammatory diseases are at an increased risk for decreased growth velocity, and if inflammation persists over the long term, for decreased final height. It is imperative that inflammatory disease is diagnosed early in childhood and is well managed, possibly without measures that influence growth (e.g., glucocorticoids). Mechanisms linked to impaired growth in inflammatory diseases are linked to direct actions of cytokines on the growth plate, decreased energy intake, and long-term use of medications as are glucocorticoids. It has recently been shown that inflammatory cytokines (e.g., tumor necrosis factor) and therapy (e.g., dexamethasone) separately suppress chondrogenesis and bone growth [5].

Nutrition influences linear growth through different mechanisms linked to sufficient caloric intake and/or beneficial nutrition composition (protein source and ratio) [6]. In the present study, the effect of whey-based nutrition in comparison to soy-based diet on linear growth in the lipopolysaccharide animal model was studied. Humerus length and epiphyseal growth plate height were used as a proxy for determination of linear growth. Whey, but not soy, protected the growing animals from the effects of the inflammation. Those rats that were fed isoenergetic whey-based diet had longer humerus and higher epiphyseal growth plate. Therefore, nutrition with whey protein appeared to protect the experimental animals from the LPS-induced growth attenuation.

Although these findings need to be further validated and studies need to be performed in humans, they are exciting and again show the importance of proper composition of nutrition in children with chronic diseases.

TNF overexpression and dexamethasone treatment impair chondrogenesis and bone growth in an additive manner

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Comments: In this manuscript, the authors describe a set of studies they have done in order to better understand the mechanism of stunted growth during chronic inflammation and to explore the role of glucocorticoids in such cases. In the experiments, they have used a model of transgenic mouse where human tumor necrosis factor (TNF) is overexpressed (huTNFTg). In that animal model, a chronic polyarthritis is developed early in life. The authors have studied the effect of the TNF-induced chronic inflammation on linear growth and the morphology of the growth plate with and without dexamethasone treatment. The authors discovered that the TNF overexpression reduced the length of the bones and the growth plate height, increased apoptosis, suppressed Indian hedgehog, decreased hypertrophy, and disorganized chondrocytes columns. Dexamethasone treatment reduced the inflammatory score; however, it further impaired bone growth, accelerated chondrocyte apoptosis, and reduced the number of chondrocyte columns in huTNFTg mice.

It is an important basic research study that tries to explain the mechanism of a very well-known clinical observation of the effect of chronic inflammation on linear growth of children. We are also all aware of the effect of glucocorticoid on linear growth despite the positive effect it has on inflammation. The present manuscript emphasizes the need to develop a better tool to cope with chronic inflammations in children than the use of glucocorticoids.

Osteolectin increases bone elongation and body length by promoting growth plate chondrocyte proliferation

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Comments: Osteolectin is a recently identified osteogenic growth factor. By binding to integrin α11 and activation of the Wnt signaling pathway, it promotes osteogenic differentiation in the bone marrow stromal cells. It is not required for the formation of the skeleton during fetal development, but for the maintenance of adult bone mass [7]. Osteolectin was not previously known to play any role in the regulation of bone elongation or height.

In this study, the authors however show that osteolectin promotes chondrocyte proliferation and bone elongation, by activating integrin α11 and Wnt pathway. In addition, it was shown that recombinant osteolectin promotes bone elongation in experimental animals by activating the Wnt pathway in the chondrocytes of the growth plate. The importance of osteolectin in bone elongation and height is corroborated by data in humans. A single nucleotide variant associated with reduced height in humans was determined [8]. In addition, the role of this variant was tested in human bone marrow stromal cells. In these cells, osteolectin production was diminished and osteogenic differentiation decreased.

Osteolectin seems to be another important mediator of endochondral ossification and a possible target for measures addressing growth also in humans.

Hepatic steatosis assessment as a new strategy for the metabolic and nutritional management of Duchenne muscular dystrophy

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https://pubmed.ncbi.nlm.nih.gov/35215377/

Metabolic assessment in children with neuromuscular disorders shows risk of liver enlargement, steatosis and fibrosis

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Comments: Pediatric neuromuscular conditions encompass a spectrum of rare hereditary disorders characterized by anomalous muscle structure and function, resulting in varying degrees of muscular weakness. Among these infrequent neuromuscular disorders, the most prevalent are Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA). Predictably, as these conditions progress throughout childhood, throughout adolescence, and into adulthood, suboptimal nutritional status becomes commonplace. However, as the care of these young individuals advances, leading to improved survival rates, particularly with the implementation of disease-modifying therapies such as oral glucocorticoid treatment for DMD, a new set of nutritional challenges emerges. Within the context of DMD and SMA, emerging evidence highlights a notable concern: substantial weight gain leading to obesity, accompanied by components of the metabolic syndrome. Although limited literature exists on metabolic outcomes among young people with DMD, even scarcer data pertain to those with other rare neuromuscular conditions. Understanding these outcomes is essential for informing the development of condition-specific nutritional care standards for young individuals with neuromuscular disorders.

A study conducted by Tang et al. employed a cross-sectional design to explore metabolic syndrome occurrences in young individuals with DMD. The study encompassed anthropometric assessments, biochemical analyses, and hepatic steatosis imaging using ultrasound, with a specific focus on the Nakagami parametric index (NPI) as an indicator of hepatic steatosis severity (NPI >0.73 indicating moderate to severe steatosis). In a cohort of 42 DMD patients, 79% of whom were receiving glucocorticoid therapy, no differences in fasting glucose levels were observed across the ambulatory, early nonambulatory, and late ambulatory phases. Notably, the early nonambulatory phase exhibited the highest absolute body mass index in kg/m2. In the overall cohort, 38% exhibited a body mass index above the 85th percentile, and 41% displayed evidence of moderate to severe hepatic steatosis. Conversely, abnormal triglyceride levels were detected in only 14% of cases, whereas abnormal high-density lipoprotein levels, biochemical indications of insulin resistance based on the homeostatic model assessment for insulin resistance index, and abnormal fasting glucose were observed in 5, 5, and 0% of cases, respectively. No significant differences in metabolic parameters were discerned between those undergoing glucocorticoid treatment and those who were not, except for higher NPI values in ambulatory glucocor-

ticoid-treated patients compared to nonambulatory patients without glucocorticoid therapy. More recently, Naume et al. reported the outcomes of their cross-sectional study, which evaluated hepatic steatosis and fibrosis in a cohort of children encompassing 44 distinct neuromuscular conditions, including DMD (23 cases), SMA (11 cases), and various other conditions (merosin-deficient congenital muscular dystrophy, Charcot-Marie-Tooth neuropathy, Bethlem myopathy, giant axonal neuropathy, and GRIN2A mutation neuropathy). This investigation employed ultrasound for hepatic abnormality assessment and vibration-controlled transient elastography (FibroScan) to evaluate fibrosis. Among the entire cohort, hepatic involvement was noted in 31%, with DMD and SMA cases exhibiting hepatic involvement rates of 41 and 50%, respectively. Notably, no hepatic involvement was observed in the remaining neuromuscular conditions. Hepatic steatosis was identified in 5% of the overall cohort, with DMD and SMA cases accounting for 5 and 13%, respectively.
Both of these studies provide preliminary evidence of hepatic level metabolic irregularities in young individuals with neuromuscular conditions, particularly DMD and SMA. The authors propose the routine assessment of hepatic metabolic abnormalities as a component of the standard nutritional monitoring and management protocol. However, it is the opinion of the reviewer that further research is required before this recommendation can be integrated into clinical care standards. This necessitates large-scale studies, longitudinal investigations utilizing standardized outcome metrics, and an exploration of the clinical significance of these findings, including the impact of disease-modifying therapies and nutritional interventions. Nevertheless, these recent studies collectively contribute evidence supporting the presence of metabolic anomalies in the context of these conditions.

Assessment of body fat mass, anthropometric measurement and cardiometabolic risk in children and adolescents with achondroplasia and hypochondroplasia

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A scoping review of nutrition issues and management strategies in individuals with skeletal dysplasia

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Comments: Skeletal dysplasia encompasses a range of hereditary conditions that impede proper skeletal growth, development, and structural integrity, leading to abnormal long bone growth, stature, and skeletal fragility. This diverse group comprises nearly 800 distinct diagnoses. While the primary issues manifest as increased fracture risk, notably in association with short stature, particularly disproportionate short stature, bone pain, and other skeletal complications, secondary nutritional concerns, particularly obesity, are common and can further exacerbate some skeletal complications. Among this heterogeneous and rare spectrum of disorders, the most prevalent entities are osteogenesis imperfecta (OI), achondroplasia, and hypochondroplasia. OI, colloquially known as brittle bone disease, constitutes a collection of genetic disorders heightening susceptibility to bone fractures. This spectrum of conditions extends beyond skeletal manifestations, affecting various bodily systems with varying severity. The genetic foundation of OI lies in mutations within genes like COL1A1 and COL1A2, accounting for approximately 90% of cases. These genes direct the synthesis of critical proteins for type I collagen assembly, vital to the structural integrity of bone, skin, and connective tissues. Achondroplasia, an autosomal dominant genetic disorder, is hallmarked by dwarfism, characterized by shortened limbs in conjunction with a relatively normal length torso. The average adult stature in individuals with achondroplasia approximates 131 cm (4 ft 4 in) for males and 123 cm (4 ft) for females. This condition is attributed to mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, which disrupts the corresponding fibroblast growth factor receptor 3 protein's role in collagen synthesis and other critical structural components. These mutations hinder the interaction between the protein and growth factors, thereby hampering proper bone formation and culminating in a stature discrepancy due to incomplete cartilage-to-bone development.

Nakano et al. conducted a cross-sectional study involving 32 participants with achondroplasia and 10 with hypochondroplasia, aged 1.9–18.7 years. Nearly half of the subjects exhibited at least one cardiometabolic abnormality, with elevated systolic blood pressure being predominant. Notably, around 70% of patients received recombinant human growth hormone, which might influence metabolic profiles. Nevertheless, metabolic syndrome or type 2 diabetes mellitus did not develop in any participants. Significant associations were noted between body mass index and standard deviation scores and hip:height ratio, correlated with body fat percentage measured by dual-energy X-ray absorptiometry. However, no statistically significant connections emerged between anthropometric measurements, body fat mass, and various cardiometabolic risk factors. Distinctive contrasts in these parameters were absent between groups with normal versus abnormal cardiometabolic profiles. Notably, body mass index Z-scores remained comparable between females with achondroplasia and hypochondroplasia, while in males, hypochondroplasia was associated with lower BMI Z-scores, albeit not statistically significant. The findings underscore the necessity of vigilant monitoring not only for weight gain and hip/height alterations but also encompassing a comprehensive evaluation of individual cardiometabolic risk factors. These considerations are pivotal in the healthcare management of pediatric patients afflicted with achondroplasia and hypochondroplasia, aiming to preempt potential cardiometabolic events. Furthermore, future research should explore suitable nutritional outcome measures, particularly those associated with or predictive of clinically significant metabolic outcomes in these young individuals.

Billich et al. conducted a scoping review on nutritional outcomes and intervention in young people with skeletal dysplasia. A comprehensive search was conducted across multiple databases, including Ovid MEDLINE, Ovid EMBASE, Ebsco CINAHL, Scopus, and the Cochrane Central Register of Controlled Trials and Database of Systematic Reviews. Supplementary searches encompassed perusal of reference lists and citations within the included studies. The inclusion criteria involved studies featuring participants with skeletal dysplasia, focusing on elucidating aspects such as anthropometry, body composition, nutrition-related biochemistry, clinical manifestations, dietary intake, quantified energy or nutrition requisites, and nutritional interventions. A detailed exploration of the literature yielded a total of 8,509 references, subsequently leading to the inclusion of 138 studies in the analysis. The compiled dataset comprised 130 observational studies, 3 intervention studies, 2 systematic reviews, and 3 clinical guidelines. Spanning across a spectrum of 17 distinct diagnoses, the studies predominantly revolved around OI (n = 50) and achondroplasia or hypochondroplasia (n = 47). Prevailing subjects of investigation included nutrition-linked clinical concerns, biochemical aspects, obesity, and metabolic intricacies. Remarkably, a limited number of studies (n = 5) broached the assessment of energy requirements. Specifically, none of the studies in achondroplasia and/or hypochondroplasia or OI have conducted research into total energy expenditure, which is key to developing evidence-based guidelines for nutritional intake. This comprehensive scoping review into the area of nutrition in people with skeletal dysplasia underscored the documented presence of nutrition-related comorbidities. Nevertheless, the dearth of substantial evidence for guiding effective management strategies remains conspicuous. Notably, a discernible gap exists in the literature concerning the nutritional facets of less common skeletal dysplasia conditions. Thus, the imperative to propel advances in our understanding of skeletal dysplasia nutrition cannot be overstated, as it stands to optimize broader health outcomes within this population. A key area of research of priority is on the nutritional outcome measure to be used to delineate increased fat mass in children and adolescents with significant short stature given potential limitations of BMI. In particular, research into energy expenditure, especially total energy expenditure, is much needed to develop nutritional guidelines that are catered to this population.

The crosstalk between FGF21 and GH leads to weakened GH receptor signalling and IGF1 expression and is associated with growth failure in very preterm infants

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Comments: Fibroblast growth factor 21 (*FGF21*), a liver-secreted peptide hormone encoded by the *FGF21* gene in humans, constitutes a member of the endocrine subgroup within the fibroblast growth factor (FGF) family, accompanied by *FGF19* (*FGF15* in rodents) and *FGF23*. *FGF21* functions as a potent extracellular metabolic regulator, its significance having been initially unveiled through in vitro phenotypic screening and rodent-based diet manipulation studies. Its beneficial impact extends to the orchestration of lipid, glucose, and energy metabolism. While the peptide finds synthesis across various organs and tissues, its primary production site is the liver, with secretion responsive to stress or dietary cues, encompassing caloric or protein intake. The modality of *FGF21's* function hinges upon the context of its production and target sites, encompassing autocrine, paracrine, or endocrine modes. Recent investigations highlight *FGF21's* pivotal role in mediating growth impairment in chronic conditions, particularly its involvement in growth plate growth hormone (GH) resistance. In infants born very preterm (<32 weeks gestation), an initial growth deceleration phase after birth is succeeded by a period of catch-up growth. However, the precise mechanistic underpinnings of this growth pattern, especially the interplay of *FGF21* with the GH receptor and downstream GH signaling pathways, remain incompletely elucidated.

Mistry et al. developed an in vitro model employing GH and *FGF21*-responsive HEK-293 cells, revealing that *FGF21* intensified GH-induced GH receptor turnover and augmented SOCS2 expression, consequently inhibiting STAT5 phosphorylation. This observation was validated in a clinical study where circulating *FGF21* surged during the growth deceleration phase in infants born very preterm, subsequently receding during the catch-up growth period. Notably, in this clinical context, circulating *FGF21* levels exhibited an inverse correlation with length velocity and circulating IGF1 levels. The intricate interplay between factors such as nutrition, inflammation, infection, and *FGF21* may offer avenues for interventions aimed at enhancing growth and nutritional status in the highly vulnerable population of infants born very preterm.

The gut microbiome and early-life growth in a population with high prevalence of stunting

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Comments: Globally, stunting stands as a consequential clinical challenge marked by significant impacts on critical outcomes such as infectious disease–related morbidity, diminished childhood survival rates, and impaired cognitive function. While nutritional deficiencies contribute to stunting, research into nutritional interventions has yielded only modest improvements, with rates of stunting barely surpassing a 10% reduction. This implies the involvement of other mechanisms underlying this condition. Recent focus has shifted toward investigating the influence of gut microbiota on outcomes like stunting; however, studies assessing the composition and functional maturation of gut microbiota in relation to stunting remain scarce.

In a study employing comprehensive metagenomic sequencing, Robertson et al. meticulously elucidated the developmental trajectory of the gut microbiome in a cohort of 335 children aged 1–18 months from rural Zimbabwe. This study unfolded within the framework of the Sanitation, Hygiene, Infant Nutrition Efficacy Trial (SHINE; NCT01824940), a randomized trial scrutinizing augmented water, sanitation, and hygiene practices, alongside infant and young child feeding interventions. The study's findings underscore that the early-life gut microbiome follows a programmed assembly pattern, resilient to alterations through the randomized interventions targeting linear growth enhancement. Intriguingly, maternal HIV infection emerges as a factor associated with heightened diversification and early maturation of the early-life gut microbiome in their noninfected offspring, alongside a depletion of Bifidobacterium species. Employing machine learning models, specifically XGBoost, the authors establish that taxonomic microbiome attributes exhibit limited predictive capability for child growth. However, the predictive potential of functional metagenomic attributes, particularly pathways linked to B vitamin and nucleotide biosynthesis, emerge as a moderate predictor of both linear and ponderal growth, as well as growth velocity. These findings suggest that innovative strategies targeting the gut microbiome during early childhood could serve as a promising complement to ongoing initiatives addressing child undernutrition globally. Importantly, the impact of HIV exposure on infant gut microbiota remains a significant and enigmatic aspect, warranting further dedicated investigation and exploration of potential effective intervention.

The effect of a nutritional supplement on growth and body composition in short and lean preadolescent boys following one-year of intervention

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Comments: The present study again stresses the point of the importance of adequate nutrition to linear growth even where food shortage does not exist. It is important to remember that even in privileged areas where shortrange of food is not an issue, there are children and adolescents who might benefit from more attention to their diet requirements. It is important to emphasize that prospective randomized double-blind studies in preadolescents children are scarce and of significance.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Obesity, Metabolic Syndrome, and Nutrition

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Introduction

Obesity is a major public health problem that affects more than 300 million children worldwide. Childhood obesity has negative effects on physical and mental health and tends to persist in adulthood, carrying an increased risk of morbidity and mortality. The development of obesity relates to the combined influence of genetic susceptibility and environmental factors, such as sedentary lifestyle and high caloric diet.

Early life environment can have lasting effects on the physiology and metabolism of the fetus. In utero exposure to maternal adverse conditions is associated with the early metabolic programming of human health. Both small and large for gestational age infants have been linked to an increased risk of later cardiometabolic diseases. Maternal obesity during pregnancy is associated with an increased risk of obesity and metabolic disease in the offspring. Also, maternal diet during pregnancy might influence offspring's predisposition to obesity and diet choice. Some studies reviewed in this chapter evaluate several in utero exposures such as maternal weight, maternal diet and maternal intake of ultra-processed food during pregnancy, and their association with the subsequent development of childhood obesity and metabolic risk of the offspring. Another study assessed the impact of fish oil supplementation of mothers with overweight or obesity during pregnancy on infant body composition and metabolic effects on the offspring.

Nutrition during the first years of life also has a significant impact on lifelong health. Exclusive breastfeeding is recommended for the first 6 months of life to promote adequate infant growth and development. Breastfeeding has been suggested as a preventive measure against obesity. One of the reviewed studies found that exclusive breastfeeding for at least

4 months has a protective role both for postpartum maternal weight gain and against childhood overweight and obesity. Another study evaluated the "early protein hypothesis," suggesting that higher protein intake in the first year(s) of life enhances adipogenic activity. In addition, a randomized controlled trial reported the results of using a novel starting infant formula with reduced protein content and lower casein to whey protein ratio compared to a standard formula on weight gain and body composition of infants up to 6 and 12 months.

Other studies tried to evaluate the impact of the diet composition during later childhood on adiposity. A healthy diet during childhood is fundamental for healthy growth and for the prevention of developing diseases later in life. As the association between dietary diversity and childhood obesity remains unclear, one of the studies was conducted to analyze the effects of dietary diversity on childhood obesity.

Sugar-containing ultra-processed food and beverage consumption has increased globally in recent years and contributes to the rising global trends of obesity. One of the reviewed studies reported that changes in diet from low to higher dairy consumption and from sugar-sweetened beverages to noncaloric beverages or flavored milk resulted in favorable changes in body composition among children and adolescents.

Children with obesity are prone to develop obesity-related comorbidities including metabolic syndrome. The association between oral intake of omega-3 fatty acids and metabolic syndrome in adolescents is reported in one of the studies.

Finally, considering the deleterious consequences of obesity in childhood, public health interventions are urgently called to take nutritional measures with policies that encourage healthy eating among infants and children.

In this year's edition of the yearbook chapter focused on the relation between nutrition, obesity, and metabolic comorbidities from infancy to childhood and young adulthood, we selected 12 notable articles from many meritorious manuscripts published in the past year between July 2022 and June 2023.

Key articles reviewed for this chapter

Maternal Diet during Pregnancy and Risk of Childhood Obesity

Maternal consumption of ultra-processed foods and subsequent risk of offspring overweight or obesity: results from three prospective cohort studies
Wang Y, Wang K, Du M, Khandpur N, Rossato SL, Lo CH, VanEvery H, Kim DY, Zhang FF, Chavarro JE, Sun Q, Huttenhower C, Song M, Nguyen LH, Chan AT
BMJ 2022;379:e071767

Fish oil supplementation during pregnancy and postpartum in mothers with overweight and obesity to improve body composition and metabolic health during infancy: a double-blind randomized controlled trial
Satokar VV, Derraik JGB, Harwood M, Okesene-Gafa K, Beck K, Cameron-Smith D, Garg ML, O'Sullivan JM, Sundborn G, Pundir S, Mason RP, Cutfield WS, Albert BB
Am J Clin Nutr 2023;117:883–895

Maternal pre-pregnancy nutritional status and infant birth weight in relation to 0–2 year-growth trajectory and adiposity in term Chinese newborns with appropriate birth weight-for-gestational age
Ouyang F, Wang X, Wells JC, Wang X, Shen L, Zhang J
Nutrients 2023;15:1125

Nutrition during Infancy and Risk of Childhood Obesity

Exclusive breastfeeding for at least four months is associated with a lower prevalence of overweight and obesity in mothers and their children after 2–5 years from delivery
Mantzorou M, Papandreou D, Vasios GK, Pavlidou E, Antasouras G, Psara E, Taha Z, Poulios E, Giaginis C
Nutrients 2022;14:3599

Effects of a novel infant formula on weight gain, body composition, safety and tolerability to infants: the INNOVA 2020 study
Plaza-Diaz J, Ruiz-Ojeda FJ, Morales J, de la Torre AIC, García-García A, de Prado CN, Coronel-Rodríguez C, Crespo C, Ortega E, Martín-Pérez E, Ferreira F, García-Ron G, Galicia I, Santos-García-Cuéllar MT, Maroto M, Ruiz P, Martín-Molina R, Viver-Gómez S, Gil A
Nutrients 2022;15:147

Different protein intake in the first year and its effects on adiposity rebound and obesity throughout childhood: 11 years follow-up of a randomized controlled trial
Totzauer M, Escribano J, Closa-Monasterolo R, Luque V, Verduci E, ReDionigi A, Langhendries JP, Martin F, Xhonneux A, Gruszfeld D, Socha P, Grote V, Koletzko B
Pediatr Obes 2022;17:e12961

The effectiveness of interventions during the first 1,000 days to improve energy balance-related behaviors or prevent overweight/obesity in children from socio-economically disadvantaged families of high-income countries: a systematic review
Lioret S, Harrar F, Boccia D, Hesketh KD, Kuswara K, Van Baaren C, Maritano S, Charles MA, Heude B, Laws R
Obes Rev 2023;24:e13524

Nutrition during Childhood and Risk of Childhood Obesity

Metabolic profiles of ultra-processed food consumption and their role in obesity risk in British children
Handakas E, Chang K, Khandpur N, Vamos EP, Millett C, Sassi F, Vineis P, Robinson O
Clin Nutr 2022;41:2537–2548

Effects of foods, beverages and macronutrients on BMI z-score and body composition in children and adolescents: a systematic review and meta-analysis of randomized controlled trials
Jakobsen DD, Brader L, Bruun JM
Eur J Nutr 2023;62:1–15

Low dietary diversity for recommended food groups increases the risk of obesity among children: evidence from a Chinese longitudinal study
Xu H, Du S, Liu A, Zhang Q, Ma G
Nutrients 2022;14:4068

Combined intake of sugar-sweetened beverages and sugar-containing ultra-processed foods is associated with an increase in body mass index during early childhood
Pereyra-González I, Mattei J
Pediatr Obes 2023;18:e13025

Nutrition and Risk of Obesity-Related Comorbidities

Scientific evidence of the association between oral intake of OMEGA-3 and OMEGA-6 fatty acids and the metabolic syndrome in adolescents: a systematic review
Tureck C, Barboza BP, Bricarello LP, Retondario A, Alves MA, de Moura Souza A, Fernandes R, de Vasconcelos FAG
Nutr Metab Cardiovasc Dis 2022;32:2689–2704

Maternal Diet during Pregnancy and Risk of Childhood Obesity

Maternal consumption of ultra-processed foods and subsequent risk of offspring overweight or obesity: results from three prospective cohort studies

Wang Y[1,2], Wang K[3], Du M[4], Khandpur N[5,6,7], Rossato SL[7,8], Lo CH[1,2,3], VanEvery H[1,2], Kim DY[1,2], Zhang FF[4,9], Chavarro JE[3,7,10], Sun Q[3,7,10], Huttenhower C[11,12], Song M[1,2,3,7], Nguyen LH[1,2,11], Chan AT[1,2,7,10]

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Comments: One of the potential contributors to the obesity epidemic among children and young people is the unhealthy Western diet characterized by increased consumption of ultra-processed foods. These foods generally have higher sugar, sodium, and saturated fat content compared with less processed foods.

Previous data reported the link between ultra-processed food intake and excess body fat and obesity in adults and children [1, 2]. Mounting evidence suggests that maternal diet influences pregnancy and birth outcomes, but its contribution to childhood obesity has not yet been definitively characterized. Chen et al. [3] reported that low-quality maternal antenatal diet may adversely influence offspring body composition and obesity risk. The current study assessed whether maternal ultra-processed food intake during peripregnancy and during the child-rearing period is associated with offspring risk of overweight or obesity during childhood and adolescence. A potential mechanism by which peripregnancy ultra-processed food intake could affect offspring adiposity includes epigenetic modification of offspring's susceptibility to obesity. The findings of the study were that peripregnancy consumption of ultra-processed foods was not significantly associated with an increased risk of overweight or obesity in offspring when comparing the group with the highest ultra-processed food intake with the group with the lowest intake. However, maternal consumption of ultra-processed food during the child-rearing period was associated with an increased risk of overweight or obesity in offspring, independent of maternal and offspring lifestyle risk factors. This observation suggests that maternal ultra-processed food consumption during child rearing might have a stronger association with offspring obesity than peripregnancy ultra-processed food consumption.

The study strengths include the data that were based on three prospective cohort studies including a large number of participants with long-term follow-up from preconception among mothers and through childhood and adolescence of offspring, and also the use of standardized questionnaires covering a wide range of socioeconomic, lifestyle, and other health risk factors, and the use of detailed dietary assessments using validated food frequency questionnaires. The study used the NOVA classification system (based on the nature, purpose, and extent of food processing: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and ultra-processed foods) [4] to distinguish ultra-processed foods from other foods, which provides robust epidemiological evidence for the role of maternal ultra-processed food consumption in the development of childhood obesity.

The study limitations include the self-reported diet and weight measurements that might be subject to misreporting. Mothers included were predominantly white and were of comparable socioeconomic backgrounds, which could restrict study generalizability.

In conclusion, the data of the study support the importance of addressing and improving dietary recommendations for women of reproductive age with the aim to improve the health of the offspring.

Fish oil supplementation during pregnancy and postpartum in mothers with overweight and obesity to improve body composition and metabolic health during infancy: a double-blind randomized controlled trial

Satokar VV[1], Derraik JGB[1,2,3,4], Harwood M[5], Okesene-Gafa K[6], Beck K[7], Cameron-Smith D[1,8,9], Garg ML[9], O'Sullivan JM[1], Sundborn G[10], Pundir S[1], Mason RP[11], Cutfield WS[1,12], Albert BB[1,12]

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Comments: Obesity in pregnancy is associated with systemic inflammation and exaggeration of the normal insulin resistance that develops in the second half of pregnancy, which leads to excess delivery of lipid and glucose to the fetus. This underlies greater birth weight and body fat in the offspring and is associated with alterations in gene expression mediated by epigenetic changes that increase risk of metabolic dysfunction and disease in later life. Interventional strategies during pregnancy are a potential approach to alleviate and/or prevent obesity and obesity-related metabolic alterations in the offspring. Therefore, an anti-inflammatory and insulin-sensitizing treatment during pregnancy could be of great benefit to the metabolic and body compositional phenotype of the offspring.

Fish oil (FO), rich in omega-3 polyunsaturated fatty acids, exerts metabolic health benefits. The use of an omega-3 polyunsaturated fatty acid supplement was previously reported to improve insulin sensitivity [5]. Thus, the researchers of the current study hypothesized that supplementation during the second half of pregnancy and postpartum of overweight and obese women may help prevent the development of greater adiposity and metabolic dysfunction in children. However, they showed no effects of FO supplementation compared with olive oil supplementation on infant body fat percentage at age 2 weeks, and FO-supplemented infants had a higher body mass index Z-score and ponderal index at age 3 months. Although FO supplementation lowered significantly maternal triglycerides by 17% at 30 weeks of pregnancy and infant triglycerides by 21% at 3 months of age, it did not affect maternal or infant insulin resistance.

The study strengths are the double-blind randomized controlled design and the accurate measurement of body composition (body fat percentage) by dual-energy X-ray absorptiometry scan.

The study limitations include the treatment that was initiated from midpregnancy, and not preconception or throughout the entire duration of pregnancy, which may impact the results. We can assume that earlier supplementation may improve infant body composition. In addition, the relatively short period of follow-up of infants (only 3 months) does not allow to draw conclusions of the impact of FO supplementation during early childhood.

Nevertheless, there is a need to follow-up the offspring throughout later in life to determine whether the observed metabolic effects persist and to evaluate potential long-term effects of FO supplementation on body composition.

Maternal pre-pregnancy nutritional status and infant birth weight in relation to 0–2 year-growth trajectory and adiposity in term Chinese newborns with appropriate birth weight-for-gestational age

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Comments: The first 1,000 days of life, from conception until a child's second birthday, is a window of opportunity for promoting long-term health and well-being. Failure to meet nutritional needs in this period is strongly related to a statistically significant increased lifelong risk of obesity and noncommunicable diseases. The key role of diet-related interventions during this crucial phase of growth can be ascribed to at least three mechanisms operating at different levels. First, unmet demands in this critical phase of early development can affect the size and structure of organs, increasing the risk of developing hypertension, cardiovascular disease, type 2 diabetes, and obesity. Extensive growth and neurodevelopment take place in this period, and optimal development depends on the amount and quality of food and nutrients provided. Second, adverse nutritional conditions may permanently affect gene expression and program the body toward the development of noncommunicable diseases. Third, dietary preferences and food habits are formed early in life, influenced by feeding practices of parents and others, the variety of foods offered, and the socioeconomic, cultural, and educational context of the family. Although these factors have been largely reported in children born both small and large for gestational age [6], few studies have focused on those children born with appropriate birth weight for gestational age (AGA). Therefore, in this prospective cohort study, authors examined differential growth trajectories in the first 2 years by considering pre- and perinatal factors among AGA newborns. Results showed that AGA infants manifest differential growth trajectories by the combination of birth weight for gestational age and maternal body mass index. In fact, AGA infants with a combination of high birth weight tertile and maternal obesity/overweight identify a subset of subjects with elevated adiposity among AGA infants. In addition, excessive gestational weight gain was associated with higher values in all adiposity measures in AGA children at 2 years of age. Thus, this finding underscores that AGA term-born infants, who represent the majority of newborns, are heterogenous in their future risk of overweight and obesity and present opportunities for early intervention to prevent obesity. It is remarkable because infants born with AGA consist of ~80% of newborns. Thus, assessing factors in this large percentage of children refine infant obesity risk assessment at postnatal care for AGA infants during early childhood. Finally, evidence from this study supported the hypothesis that obesity prevention should start prior to conception and concurrently address multiple prenatal risk factors of adverse birth outcomes.

Nutrition during Infancy and Risk of Childhood Obesity

Exclusive breastfeeding for at least four months is associated with a lower prevalence of overweight and obesity in mothers and their children after 2–5 years from delivery

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Comments: Exclusive breastfeeding is the gold standard for infant feeding because it promotes adequate growth and development, excellent nutritional status, and appropriate psychological development. In addition, due to the special composition of breast milk in bioactive and immunogenic substances, it effectively protects against numerous infectious diseases and allergic processes. Breastfeeding has also been suggested as a preventive measure against obesity, which can further reduce long-term negative health outcomes for both women and children [7, 8].

The current study evaluated the role of breastfeeding on maternal and childhood overweight and obesity. The data showed that exclusive breastfeeding for at least 4 months was associated with a twofold lower risk for maternal and childhood overweight and obesity after 2–5 years from delivery, independent from maternal age, educational and economic status, and smoking habits.

The study strengths include the relatively large number of participants.

The main study limitation is its retrospective cross-sectional design, and therefore, associations but not causation can be derived from the data.
However, the study confirms the findings of previous studies about the role of exclusive breastfeeding for at least 4 months on protection from postpartum maternal weight gain and against childhood overweight and obesity.

Effects of a novel infant formula on weight gain, body composition, safety and tolerability to infants: the INNOVA 2020 study

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Comments: Despite efforts to promote breastfeeding, there are many social factors or maternal illness that cause many mothers to stop breastfeeding prematurely. Therefore, there is a need for infant formulas designed with an optimal nutritional composition essential to promote the adequate growth and development. Continuous research has led to the development of infant formula mimicking human milk with the incorporation of various food ingredients to meet the nutritional needs of infants and to contribute to better development. Based on certain studies suggesting that a high protein intake in the early stages of life may be the cause of obesity and increased risk of metabolic disease in later stages of life [9], the protein composition of infant formulas has been adjusted in both quality and quantity, reducing the protein intake and change in the whey/casein ratio. The development of infant formula containing bovine α-lactalbumin (part of the whey proteins) allowed the reduction in the protein content of the formula. Also, the relatively high content of long-chain polyunsaturated fatty acids of both the n-6 and n-3 series, especially arachidonic acid (20:4 n-6) and docosahexaenoic acid (22:6 n-3) in human milk and their proven effects on the cognitive development of infants [10], has led to the incorporation of these fatty acids into infant formulas.

The current study reports the results of a randomized controlled trial that aimed to evaluate a novel starting infant formula with reduced protein content and lower casein/whey protein ratio (by increasing the content of α-lactalbumin) compared to a standard formula on the safety, tolerability, and efficacy on weight gain and body composition of infants up to 6 and 12 months. Infants were divided into three groups: group 1 received the novel formula (INN, $n = 70$), with a lower amount of protein, a lower casein/whey protein ratio, a double amount of docosahexaenoic acid/arachidonic acid than the standard formula with the addition of thermally inactivated postbiotic (*Bifidobacterium animalis* subsp. *lactis*). Group 2 received the standard formula (STD, $n = 70$) and the third group was exclusively breastfed and used as a reference (BFD, $n = 70$). Weight gain was higher in both formula groups than in the BFD group at 6 and 12 months, whereas no differences were found between STD and INN groups either at 6 or at 12 months. Body mass index was higher in infants fed the two formulas compared with the BFD group. Nevertheless, body composition, length, head circumference, and tricipital/subscapular skinfolds were alike between groups. All groups showed similar digestive tolerance and infant behavior. However, a higher frequency of gastrointestinal symptoms was reported in the STD formula group, followed by the INN formula, and the BFD groups. Atopic dermatitis, bronchitis, and bronchiolitis were significantly more prevalent among infants who were fed the STD formula compared to those fed the INN formula or breastfed.

The strengths of the study are the multicenter, randomized controlled, double-blind clinical trial design and also the anthropometric measurements that were done at every study visit by a professional team.

The new formula (INN) seems to be a promising one, since it was considered safe and with fewer gastrointestinal symptoms compared with the STD formula, possibly due to the addition of thermally inactivated postbiotic. Also, weight gain and body composition with the consumption of the new formula were within the normal limits, according to WHO standards.

Different protein intake in the first year and its effects on adiposity rebound and obesity throughout childhood: 11 years follow-up of a randomized controlled trial

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Comments: There is compelling evidence from observational studies and some randomized clinical trials demonstrating that a high protein intake during the first year of life is associated with higher body mass index (BMI), higher fat mass, as well as increased risk of overweight or obesity later in life [11, 12].

It is hypothesized that higher protein intake stimulates growth and adipogenesis through the insulin growth factor 1 axis and the mammalian target of rapamycin pathway [13]. The "early protein hypothesis" was tested in a previous randomized clinical trial [14], which showed a lower concentration of insulinogenic amino acids and a lesser insulin growth factor 1 axis activation in breastfed infants and in infants fed with a lower protein content formula (similar to that of human milk) compared with infants fed with a higher protein content formula.

The current study examined whether protein supply in infancy affects the adiposity rebound, BMI, and overweight and obesity up to 11 years of age. The researchers randomized formula-fed term infants (n = 1,090) within the first 2 months of life to isoenergetic formula with higher or lower protein content within the range stipulated by EU legislation in 2001. A breastfed reference group (n = 588) was included. They found that compared to conventional high protein formula, feeding lower protein formula in infancy lowers BMI trajectories up to 11 years and achieves similar BMI values at adiposity rebound as observed in breastfed infants. Of note, timing of and BMI at adiposity rebound were strongly associated with later obesity. Thus, by using the lower protein formula, it can be possible to avoid excessive fat mass acquisition related to early adiposity rebound, and this may be an important opportunity for targeted effective strategies for promotion of later health.

The study strengths are the inclusion of a large number of infants from five European countries that makes data more generalizable, the double-blind randomized design of the study, and the long follow-up period up to 11 years.

This study corroborates previous data about the importance to avoid excessive protein intake in infancy, which may contribute to reduced burden of childhood obesity.

The effectiveness of interventions during the first 1,000 days to improve energy balance-related behaviors or prevent overweight/obesity in children from socio-economically disadvantaged families of high-income countries: a systematic review

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Comments: The nutrition of infants in the first 1,000 days of life, from conception through 2 years of age, has both immediate and long-term health consequences. These include nutrition-related metabolic, immune, neurocognitive, and epigenetic changes, which program long-term health [15]. The first 1,000 days is also an appropriate time to support parents to promote a healthy lifestyle and prevent obesity for their children.

This systematic review examined effectiveness of family-based interventions during the first 1,000 days of life in improving energy balance–related behaviors or preventing overweight/obesity in children from families experiencing socioeconomic disadvantage. Interestingly, after a search of five databases on published articles over three decades, only 33 articles were eligible for inclusion in this systematic review. They found 24 distinct interventions which were classified into three types: those specifically aimed at preventing overweight and obesity in children (*n* = 6); those mostly focused on promoting healthy feeding practices and diet (*n* = 5); and broad parent support programs aimed at enhancing the general health and bonding of the mother-child dyad (*n* = 13). The findings showed that there was some evidence of beneficial impact of interventions on obesity risk and associated behaviors (breastfeeding, responsive feeding, diet, sedentary and movement behaviors, and sleep). The most effective interventions aimed at promoting breastfeeding commenced antenatally; this was similar for the prevention of obesity, if the intervention continued for at least 2 years postnatally and was multibehavioral. This emphasizes the importance of early education and intervention to promote healthy lifestyle habits. Effective interventions were more likely to target first-time mothers and involve professional delivery agents, multidisciplinary teams, and peer groups.

Among ethnic/racial minorities, interventions delivered by lay agents had some impact on dietary behavior only. Cocreation with stakeholders, including parents, and adherence to frameworks were additional elements for more practical, comprehensive, and effective programs.

The strengths of this systematic review are that most included studies (~70%) were randomized controlled trials. Only studies that reported interventions required to target families experiencing socioeconomic disadvantage were included and interventions were required to be implemented prior to age of 2 years to really evaluate the effectiveness of interventions during the first 1,000 days.

Moreover, the search strategy of the studies was evaluated according to the PICOT framework: *Population* (parents experiencing socioeconomic disadvantage), *Intervention* (had to be delivered in the first 1,000 days with the aim of improving one or more of the outcomes), *Comparison* (intervention studies had to include a control group), *Outcome* (studies had to address one or more of the following outcomes in children: parental feeding practices, eating behaviors, dietary intake, physical activity and movement measures, sedentary behaviors, sleep, and anthropometric or growth measures), and *Timeframe* for follow-up (at least one of the eligible outcomes had to be assessed for effectiveness beyond the childbirth).
The main limitation of this systematic review is the inclusion of studies conducted only in high-income countries with possible impact on the generalizability of the findings.

Nutrition during Childhood and Risk of Childhood Obesity

Metabolic profiles of ultra-processed food consumption and their role in obesity risk in British children

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Comments: Childhood obesity is a growing health problem in many populations, hence the urgent need to unravel a large number of underlying mechanisms [16, 17]. Among all the risk factors related to childhood obesity, special attention should be certainly given to ultra-processed foods, which are industrial formulations and ready-to-eat or ready-to-heat foods containing additives, such as flavouring or colouring agents, emulsifiers, and preservatives. These products are typically energy dense and high in added sugars (e.g., fructose, high-fructose corn syrup, invert sugar, maltodextrin, dextrose, and lactose), salt, saturated or trans fatty acids, and other modified oils (hydrogenated or interesterified). Although several studies in adulthood and in childhood have demonstrated that the worldwide shift toward a dramatic increase in the consumption of ultra-processed foods appears partly responsible for the global obesity epidemic and may contribute to an increased risk of cardiometabolic diseases, the underlying mechanisms remain unclear. In this study performed in a large British population–based birth cohort, authors were able to describe a metabolic profile of ultra-processed food consumption in plasma. Particularly, by evaluating the plasma nuclear magnetic resonance metabolic profiles, authors have shown among British children that specific nutrient intake contributes to some of this ultra-processed food-associated metabolic profile. Particularly, higher levels of citrate, glutamine, and monounsaturated fatty acids and lower levels of branched-chain and aromatic amino acids may contribute to the association between a higher-level consumption of ultra-processed foods during childhood and an impaired metabolomic profiles and fat mass accumulation in children. These data clearly illustrated the need of a complete characterization of the metabolic effects of ultra-processed foods, which might affect multiple metabolic traits, many of which contribute to obesity risk in children and adolescents. Therefore, further studies characterizing the metabolic profiles associated with ultra-processed foods are still needed in order to elucidate the mechanisms linking diet, obesity, and disease development, even during childhood. A complete understanding of the molecular pathways underlying weight gain may facilitate interventions that prevent their initiation or interrupt their progression prior to clinical disease.

Effects of foods, beverages and macronutrients on BMI z-score and body composition in children and adolescents: a systematic review and meta-analysis of randomized controlled trials

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Comments: Diet is recognized as the essential component for the prevention and treatment of overweight and obesity among children and adolescents worldwide. Many dietary interventions targeting children and adolescents with overweight and obesity are leaning toward the Mediterranean diet [18, 19]. However, several studies have clearly shown that not only diet composition but also several independent factors including dietary patterns and adherence to a healthy dietary pattern might be challenging to children and adolescents with overweight and obesity because they often present with a relatively poor diet quality. Therefore, in this study, authors attempted to perform a comprehensive systematic review and meta-analysis to evaluate the independent effect of foods, beverages, and macronutrient composition on body composition in children and adolescents. Interestingly, authors revealed that consumption of higher dairy diets had a small beneficial effect on general body composition by increasing or preserving lean body mass and reducing body fat. Substitution of sugar-sweetened beverages with noncaloric beverages or flavoured milk had a small beneficial effect on body fat, but not on body mass index *Z*-score, and the composition of macronutrients had no effect on body mass index *Z*-score or body fat. Although the results reported in this systematic review and meta-analysis must be interpreted with caution due to the fact that the data are based on few studies and some meta-analysis presented with a high heterogeneity, the analysis shows some relevant information. In fact, reported data show that only studies investigating dairy, sugar-sweetened beverages, and macronutrient composition are available. Therefore, the effect of consuming other foods on body composition in children and adolescents with overweight and obesity has not been previously investigated in a randomized controlled setting emphasizing a gap of knowledge for future research. Given the high need for effective strategies to prevent and treat overweight and obesity in children and adolescents, studies and particularly trials investigating other types of foods need to be further performed to completely guide a scientific consensus on how to prioritize within healthy diets needs in order to prevent and treat overweight and obesity among children and adolescents.

Low dietary diversity for recommended food groups increases the risk of obesity among children: evidence from a Chinese longitudinal study

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Comments: Childhood obesity poses a global health, policy, and research challenge. In 1975, 32 million children under 5 years of age worldwide had overweight or obesity, growing to 42 million by 2020. Although during the last decade the prevalence of child and adolescent obesity has partially plateaued at high levels in most high-income countries, several reports have shown an increase in many low-income and middle-income countries. In addition, most of these epidemiological reports have been dramatically modified by COVID-19 pandemic. In fact, it has shown a substantial weight gain across all age groups in many countries, reflected by a significant increase in the 3-month change in body mass index standard deviation scores during this period [20], associated with profound alterations in glucose and insulin metabolism in children with obesity and overweight [21]. It is well known that obesity arises when a mix of genetic and epigenetic factors, behavioural risk patterns, and broader environmental and sociocultural influences induce an imbalance of the two body weight regulation systems, namely energy homeostasis and cognitive-emotional control. Although research has focused on the role of single nutrients in obesity, novel data have pointed out that dietary pattern analysis might represent a novel approach for assessing the association between diet and the risk of chronic diseases, including obesity. Dietary pattern analysis involves investigating the effects of the overall diet rather than individual nutrients or foods, and this approach may thus be more indicative of disease risk than individual foods or nutrients. Therefore, in this study, by evaluating the overall diet through the dietary diversity score, authors demonstrated that low dietary diversity for recommended food groups is associated with an increased risk of Chinese children being overweight and obese. Although some limitations related to the short period of evaluation and the impossibility to minimize the effects of confounding or confounding factors (such as physical activity, genetic factors, and other) on the analysis, these data add relevant information on diet approach for the prevention and treatment of childhood obesity. Therefore, not only unhealthy foods such as processed foods, refined foods, and sugar-sweetened beverages need to be discouraged but also a dietary diversity for recommended foods should be encouraged to improve dietary quality by ensuring adequate nutrient intake, balanced energy intake, and healthy growth. Therefore, more attention should be paid to the dietary diversification of recommended foods as a preventive measure for childhood obesity, and this should become a dietary habit for children.

Combined intake of sugar-sweetened beverages and sugar-containing ultra-processed foods is associated with an increase in body mass index during early childhood

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Comments: Sugar is a nutrient of concern mostly added to beverages. A large body of literature have studied the relationship between sugar-sweetened beverages and several non-communicable diseases, including not only obesity in childhood and adulthood but also cancer, diabetes, and cardiovascular diseases. Therefore, the WHO recommends limiting the intake of energy from free sugars (i.e., added sugars plus honey, syrups, and sugars in juiced or pureed fruit and vegetables) to less than 10% to prevent excess body weight and dental caries and to less than 5% for additional health benefits. Of note, sugar-sweetened beverages warrant special attention as there is consistent evidence from multiple study designs on its combined consumption with sugar-containing ultra-processed product, thus potentially and exponentially impacting the known adverse outcomes on weight, bone and joint health, sleep and psychological factors during childhood, and eventual adult diseases. Interestingly, in this study, authors attempted to examine the associations between intake of sugar-sweetened beverages and sugar-containing ultra-processed foods, both combined and individually, and 2-year changes of body mass index *Z*-scores (BMI*Z*) among children ages 2–7 years in Uruguay in a longitudinal cohort. Particularly, results showed that the consumption increased the BMI*Z* when the children had an early and current intake. The consumption of sugar-sweetened beverages and sugar-containing ultra-processed product foods rose between the two waves, and, by the end of the follow-up, 18.9% of children consumed sugar-sweetened beverages and 86.5% consumed sugar-containing ultra-processed product foods. Furthermore, changes in BMI*Z* between the two waves were higher in children with an intake of two or more sugar-sweetened beverages and sugar-containing ultra-processed product foods in the first wave. Additionally, changes in BMI*Z* and combined intake of sugar-sweetened beverages plus sugar-containing ultra-processed product foods may indicate that an additive risk in the presence of both sugar-containing products may have occurred. Thus, data further reinforce the importance of effective intervention approaches and public health strategies to prevent the excessive consumption of both sweetened beverages and sugar-containing ultra-processed product foods, in all ages and particularly in early ages. In fact, young children have an innate preference for sweet foods, which may contribute to increased consumption of sugar-containing ultra-processed foods, such as cookies, cakes, sweets, and sugar-sweetened beverages, thus representing a target crucial age in which strategies need to be started.

Nutrition and Risk of Obesity-Related Comorbidities

Scientific evidence of the association between oral intake of OMEGA-3 and OMEGA-6 fatty acids and the metabolic syndrome in adolescents: a systematic review

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Comments: Unique definition and particularly therapeutic scheme for metabolic syndrome in children and adolescents are not currently available [22]. Most of these gaps might be related to the fact that more than 40 definitions of metabolic syndrome in children and adolescents have been suggested in the literature; thus its diagnostic criteria have not been standardized yet. However, although uniform guidelines on its definition are still lacking, certainly insulin resistance, central obesity, dyslipidaemia, and hypertension are considered the main components of this syndrome. Although the first recommended approach to all these pathological conditions in children and adolescents is lifestyle intervention (diet and physical exercise), still robust data evaluating the role of several factors in the risk of developing metabolic syndrome are lacking. Among the diet-related risk factors, certainly the effects of some peculiar classes of fatty acids (namely omega-3 and omega-6) might have a relevant role due to their relevant effects on human health [23]. Fatty acids can be classified into three categories based on the number of double bonds present in side chains: saturated fatty acids (no double bonds), monounsaturated fatty acids (a single double bond), and polyunsaturated fatty acids (PUFA, more than 2 double bonds). Moreover, fatty acids can be classified by their carbon chain length and the position of the first double bond on methyl terminal (omega or n-fatty acids). PUFA, mainly categorized into omega-3 and omega-6 fatty acids, play key roles in regulating body homeostasis and cannot be produced endogenously. The biological properties of PUFA are still the focus of considerable attention as they are thought to play an important role in several conditions, such as cardiovascular diseases, cancer, depression, insulin resistance, lipid metabolism, and nonalcoholic fatty liver disease. Although, in adults, insufficient intake of omega-3 fatty acids has been associated with the risk of developing metabolic syndrome, but no significant results were found with omega-6 fatty acids, few data are still available in children and adolescents. Therefore, in this interesting systematic review of the literature on the scientific evidence, authors were able to summarize the main data available in childhood. Particularly, authors revealed that to date, scientific evidence is controversial on the association between omega-3 fatty acid oral intake and the metabolic syndrome in adolescents, due to the heterogeneity among studies and the divergence of results for the same components adopted in the definition of the syndrome. Results also showed that the effect of omega-3 fatty acids appears to be different between genders. Therefore, results of this analysis clearly show that longitudinal studies with omega-3 and omega-6 fatty acids are recommended to assist in understanding the association/effects with the metabolic syndrome. Thus, although the prevention and/or treatment of metabolic syndrome are complex processes, the nutritional interventions need to receive considerable attention, with being diet certainly a key component. The complete characterization of all the dietetic factors related to metabolic risk might properly guide the approach to children and adolescents with metabolic syndrome with the aim to prevent all the metabolic and cardiovascular complications.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Epigenetic DNA Methylation, Nutrition, and Growth

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Introduction

Epigenetics comprises different heritable biochemical DNA modifications that can alter gene transcription into RNA, and hence the degree of formation of the respective gene product, while the sequence of DNA is preserved. Key mechanisms of epigenetic DNA changes are histone modifications and DNA methylation, with the latter being the most widely studied epigenetic mechanism in human populations. DNA methylation occurs at DNA regions where cytosine is followed by guanine, which are referred to as CpG sites. Early life periods including embryonic, fetal, and infant development represent time windows when the human epigenome shows a high degree of plasticity and is particularly susceptible to external exposures. Accumulating evidence points to marked effects of environmental and nutritional cues in modulating epigenetic processes, which may induce long-lasting effects of later cell function, health, and disease risks. Considerable efforts are therefore invested into exploration of epigenetic mechanisms, susceptible time windows, as well as populations or patient groups, relevant exposures, effects and effect sizes, and their fluidity or persistence over time.

For this chapter, a search was performed in the US National Library of Medicine (PubMed) with the search terms "(epigenetic*) AND ((nutrit*) OR (growth))" and filter "humans" for the time period from June 30, 2022, to July 1, 2023. The first 1,000 hits were hand searched by the author, and the publications included here (shown below) were subjectively selected based on interest and a relation to human nutrition and growth.

Key articles reviewed for this chapter

Gestational weight gain in pregnant women with obesity is associated with cord blood DNA methylation, which partially mediates offspring anthropometrics
Jönsson J, Renault KM, Perfilyev A, Vaag A, Carlsen EM, Nørgaard K, Franks PW, Ling C
Clin Transl Med 2023;13:e1215

An examination of mediation by DNA methylation on birthweight differences induced by assisted reproductive technologies
Carlsen EØ, Lee Y, Magnus P, Jugessur A, Page CM, Nustad HE, Håberg SE, Lie RT, Magnus MC
Clin Epigenetics 2022;14:151

Altered epigenetic profiles in the placenta of preeclamptic and intrauterine growth restriction patients
Norton C, Clarke D, Holmstrom J, Stirland I, Reynolds PR, Jenkins TG, Arroyo JA
Cells 2023;12:1130

Prenatal social support in low-risk pregnancy shapes placental epigenome
Tesfaye M, Wu J, Biedrzycki RJ, Grantz KL, Joseph P, Tekola-Ayele F
BMC Med 2023;21:12

Cord blood epigenome-wide meta-analysis in six European-based child cohorts identifies signatures linked to rapid weight growth
Alfano R, Zugna D, Barros H, Bustamante M, Chatzi L, Ghantous A, Herceg Z, Keski-Rahkonen P, de Kok TM, Nawrot TS, Relton CL, Robinson O, Roumeliotaki T, Scalbert A, Vrijheid M, Vineis P, Richiardi L, Plusquin M
BMC Med 2023;21:17

Umbilical cord DNA methylation is associated with body mass index trajectories from birth to adolescence
Meir AY, Huang W, Cao T, Hong X, Wang G, Pearson C, Adams WG, Wang X, Liang L
EBioMedicine 2023;91:104550

Association of the DNA methylation of obesity-related genes with the dietary nutrient intake in children
Patel P, Selvaraju V, Babu JR, Geetha T
Nutrients 2023;15:2840

Racial disparities in methylation of *NRF1*, *FTO*, and *LEPR* gene in childhood obesity
Patel P, Selvaraju V, Babu JR, Wang X, Geetha T
Genes (Basel) 2022;13:2030

Environment- and epigenome-wide association study of obesity in 'Children of 1997' birth cohort
Zhao J, Fan B, Huang J, Cowling BJ, Au Yeung SLR, Baccarelli A, Leung GM, Schooling CM
Elife 2023;12:e82377

Is adiposity related to repeat measures of blood leukocyte DNA methylation across childhood and adolescence?
Wu Y, Montrose L, Kochmanski JK, Dolinoy DC, Téllez-Rojo MM, Cantoral A, Mercado-García A, Peterson KE, Goodrich JM
Clin Obes 2023;13:e12566

Differential methylation pattern in pubertal girls associated with biochemical premature adrenarche
Ponce D, Rodríguez F, Miranda JP, Binder AM, Santos JL, Michels KB, Cutler GB Jr, Pereira A, Iñiguez G, Mericq V
Epigenetics 2023;18:2200366

Long-term impact of paediatric critical illness on the difference between epigenetic and chronological age in relation to physical growth
Verlinden I, Coppens G, Vanhorebeek I, Güiza F, Derese I, Wouters PJ, Joosten KF, Verbruggen SC, Van den Berghe G
Clin Epigenetics 2023;15:8

Changes in DNA methylation of *clock* genes in obese adolescents after a short-term body weight reduction program: a possible metabolic and endocrine chrono-resynchronization
Rigamonti AE, Bollati V, Favero C, Albetti B, Caroli D, De Col A, Cella SG, Sartorio A
Int J Environ Res Public Health 2022;19:15492

Gestational weight gain in pregnant women with obesity is associated with cord blood DNA methylation, which partially mediates offspring anthropometrics

Jönsson J[1], Renault KM[2,3], Perfilyev A[1], Vaag A[4], Carlsen EM[5,6], Nørgaard K[4], Franks PW[7], Ling C[1]

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Clin Transl Med 2023;13:e1215
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Comments: Gestational weight gain (GWG) has been associated with the risk of the offspring for obesity, adiposity, and a variety of noncommunicable diseases in numerous studies. However, genome-wide studies on cord blood DNA methylation (DNAm) found no association with GWG in pregnant women with normal body weight. In contrast, this study with more than 200 pregnant women with obesity and a very wide variation of GWG found that GWG has been associated with cord blood DNAm. DNAm at 21 sites was associated with neonatal birthweight, and DNAm at 62 sites with neonatal body mass. Pathway analyses suggested the DNAm mediated 15–23% of the GWG effect on birthweight, and 14–27% of the GWG effect on lean body mass. Methylation quantitative trait loci, i.e., genetic variants that may affect the DNAm patterns of CpG sites, associated with GWG suggest associations to birthweight and to disease traits such as asthma, body mass index, and waist-to-hip ratio adjusted for body mass index. Overall, this study suggests that DNAm in the offspring may be differentially impacted by GWG in mothers with normal body weight and obesity, respectively. DNAm appears to have a mediating effect on neonatal birthweight and lean body mass, and interventions effectively lowering GWG in obese pregnant women have the potential to improve long-term health outcomes of the offspring.

An examination of mediation by DNA methylation on birthweight differences induced by assisted reproductive technologies

Carlsen EØ[1,2], Lee Y[1], Magnus P[1], Jugessur A[1,3], Page CM[1,4], Nustad HE[1,5], Håberg SE[1], Lie RT[1,3], Magnus MC[1]

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Clin Epigenetics 2022;14:151
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https://pubmed.ncbi.nlm.nih.gov/36443807/

Comments: Previous studies reported the effects of assisted reproduction on birthweight, with lower birthweight compared to natural conception in infants born after fresh embryo transfer and a slightly higher birthweight in infants born after frozen embryo transfer, respectively. It is unclear whether the assisted reproductive technologies and/or the hormonal treatment used to induce ovulation may underly these alterations of fetal growth. Since the application of assisted reproductive technologies occurs at the periconceptional time period when the early embryo undergoes extensive epigenetic reprogramming, this study examined whether cord blood DNA methylation (DNAm) mediated birthweight differences in infants born after fresh embryo transfer or natural conception in a large group of 764 newborns conceived by fresh embryo transfer, 126 newborns conceived by frozen embryo transfer, and 983 newborns conceived naturally form the Norwegian Mother and Child Cohort Study. The results show cord blood DNAm at 4 CpG sites to explain 44% of the birthweight difference between newborns conceived with fresh embryo transfer and/or conceived naturally and DNAm at 2 CpG sites to explain 22% of the birthweight difference between newborns conceived with fresh or frozen embryo transfer. One of the differentially methylated CpGs mediating the birthweight difference was located near LOXL1, the expression of which has previously been associated with premature rupture of membranes. Therefore, the authors speculate that assisted reproduction with fresh embryo transfer may increase the risk of premature rupture of membranes through methylation of this gene, resulting in lower gestational age and thereby lower birthweight, which however was not to be measured in this cohort.

Altered epigenetic profiles in the placenta of preeclamptic and intrauterine growth restriction patients

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Cells 2023;12:1130

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Comments: This pilot study examined DNA methylation in 6 frozen samples each of placentas from normal pregnancies and pregnancies complicated by intrauterine growth restriction (IUGR) or preeclampsia (PE), respectively, which were obtained from the Research Center for Women's and Infants' Health BioBank, Ontario, Canada. The study found three differentially methylated regions (DMR) in IUGR and six DMR in PE, compared to healthy pregnancies. Eight of the identified regions could be located on gene promoters or exons, but only two of these were common to both PE and IUGR pathologies. The data suggest hypomethylation at several gene promoters in placental DNA, including FAN-1 and HLA-L pseudogene, to be associated with IUGR and PE.

Prenatal social support in low-risk pregnancy shapes placental epigenome

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BMC Med 2023;21:12

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Comments: The degree of prenatal social support has previously been associated with adiposity during infancy and health in later life, as well as DNA methylation (DNAm) in maternal blood. In a subgroup of participants of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies cohort in whom placental tissue had been collected at the time of childbirth, self-reported social support was assessed with the Enhancing Recovery in Coronary Heart Disease Social Support Questionnaire, and Instrument, and perceived stress with the self-report ten-item Cohen's Perceived Stress Scale. Higher maternal social support during the first trimester of pregnancy was associated with higher methylation at 7 CpGs located within/near genes *HAUS3*, *ARHGEF7*, *VGF*, *FAM210B*, *SBF1*, *ILVBL*, and *EIF3F*. The social support-associated epigenetic signatures in placenta are independent of prenatal stress. There was a marked infant sex effect: in males, maternal social support was significantly associated with higher methylation at 9 CpGs and in females with higher methylation at 32 CpGs and lower methylation at 3 CpGs. The higher methylation at specific CPG sites was correlated with lower expression of *VGF,* a protein-coding gene highly expressed in parts of the brain and neuroendocrine cells and related to brain development, behavior, and regulation of energy metabolism, and with lower expression of *ILVBL* involved in fatty acid alpha-oxidation in the endoplasmic reticulum and the biosynthesis of isoleucine and valine. The genes annotated to the DNA methylation loci were found to be enriched for pathways involved in the immune system, placental growth and maturation, brain development, and energy metabolism. Continued research on molecular mechanisms of social support effects on offspring health could support in developing specific interventions targeting child neurodevelopment and other outcomes.

Cord blood epigenome-wide meta-analysis in six European-based child cohorts identifies signatures linked to rapid weight growth

Alfano R[1,2], Zugna D[3], Barros H[4], Bustamante M[5,6,7], Chatzi L[8], Ghantous A[9], Herceg Z[9], Keski-Rahkonen P[9], de Kok TM[10], Nawrot TS[2], Relton CL[11], Robinson O[1,12], Roumeliotaki T[13], Scalbert A[9], Vrijheid M[9], Vineis P[1], Richiardi L[3], Plusquin M[2]

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Comments: A large number of studies have associated the trajectories of weight or body mass index gain in early childhood, particularly an upward centile crossing of weight with a change greater than 0.67 standard deviation scores during the first two years of life, with an increased risk of later overweight, obesity, and other health outcomes. This study analyzed the link between cord blood DNA methylation (DNAm) and weight gain up to age 1 year in more than 2,000 children from six European child cohort studies. Rapid weight gain between birth and age 1 year was associated with 16 differentially methylated regions, even though only 3 CpGs reached genome-wide significance at the single CpG level. Children with greater gestational age acceleration had a lower risk of rapid weight gain. Adding DNAm to conventional risk factors resulted in a slight improvement in predicting rapid weight gain. A mediation analysis suggested that some DNAm signatures mediated the effect of gestational age on rapid weight gain.

Umbilical cord DNA methylation is associated with body mass index trajectories from birth to adolescence

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EBioMedicine 2023;91:104550

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Comments: This study of 831 mother-child pairs from the prospective Boston Birth Cohort related child body mass index trajectories from birth up to age 18 years to cord blood DNA methylation (DNAm). The four distinct body mass index trajectory patterns identified in this multiethnic cohort were associated with specific cord DNAm CpG sites. Interestingly, a higher number of significant findings was found in girls than in boys, with a decrease of the number of significant sex interactions at the age of 6 years. The results suggest that DNAm might be one underlying mechanism to explain the relationship between early weight gain and later overweight and obesity, which could offer novel opportunities for early risk prediction and targeted preventive approaches.

Association of the DNA methylation of obesity-related genes with the dietary nutrient intake in children

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Comments: In a small group of 113 children aged 6–10 years from Alabama (60 normal body weight, 53 overweight or obese), dietary intake was assessed by a parental 24-h recall record, and DNA methylation in saliva samples was assessed for three genes, *NRF1*, *FTO*, and *LEPR*. Significant associations between the estimated intake of different nutrients and the methylation of *NRF1*, *FTO*, and *LEPR* genes in various subgroups of children based on body weight and ethnicity were found. The authors suggest that intervention studies should be conducted to characterize the role of nutrient intake, specifically of dietary methyl donors, in DNA methylation and that possibly related risk of childhood obesity.

Racial disparities in methylation of *NRF1*, *FTO*, and *LEPR* gene in childhood obesity

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Comments: In the same study as reported in the publication cited above, children with overweight and obesity had significantly higher DNA methylation of *NRF1* and *FTO* and lesser methylation of *LEPR* than children with normal body weight. African American children showed higher methylation of *LEPR* than European American children. Only European American children had significantly higher levels of methylation in the *NRF1* and *FTO* genes than normal weight children. African American children with normal weight had higher methylation of the *LEPR* gene than the children with overweight of obesity. The reported ethic differences in the association between DNA methylation of the *NRF1*, *FTO*, and *LEPR* genes with childhood obesity should be considered in future studies.

Environment- and epigenome-wide association study of obesity in 'Children of 1997' birth cohort

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Elife 2023;12:e82377

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Comments: This large cohort study including Chinese children in Hong Kong found DNA methylation at *RPS6KA2* associated with both body mass index and waist-hip ratio, which is consistent with findings in previous studies on obesity in different populations. Associations with several other genes including *ZNF827*, *MIR7641-2*, *RAPTOR*, *KSR1*, *GTF3C3*, and *NFIC* previously associated with obesity or obesity-related disorders were also found. The cross-sectional design of the study does not allow to draw conclusions on the direction of causality.

Is adiposity related to repeat measures of blood leukocyte DNA methylation across childhood and adolescence?

Wu Y[1,2], Montrose L[3], Kochmanski JK[4], Dolinoy DC[2,5], Téllez-Rojo MM[6], Cantoral A[7], Mercado-García A[6], Peterson KE[2,5], Goodrich JM[5]

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Comments: Previous studies have suggested that altered DNA methylation (DNAm) might be a consequence rather than a cause of childhood obesity, which however remains somewhat controversial. This pilot study in 113 children in Mexico evaluated measures of DNAm at birth and early and late teenage and related it to childhood body mass index and adiposity measures at different ages. The observed inverse association between measures of childhood BMI and repeat measures of *H19* DNAm provides preliminary indications for an association between early-life adiposity and DNA methylation at *H19*. Potential interactions between age and early teen adiposity on *H19* and *HSD11B2* methylation are also suggested.

Differential methylation pattern in pubertal girls associated with biochemical premature adrenarche

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Comments: In 86 girls from the longitudinal Growth and Obesity Cohort Study in Chile, the dehydroepiandrosterone sulfate (DHEAS) concentration was measured in the fasting morning blood sample at ~7 years of age and during pubertal progression at Tanner breast stages T2 and T4. At the same time points, DNA methylation was assessed from buffy coat. The results show 69 differentially methylated positions that discriminate girls with high or low DHEAS at both Tanner stages. DNA methylation at four CpG sites also showed a significant association with measures of glucose metabolism. While the authors propose that DHEAS concentration may induce a consistent blood methylation signature and be a causal link between premature adrenarche and insulin resistance, the study design does not allow firm conclusions on the direction of causality.

Long-term impact of paediatric critical illness on the difference between epigenetic and chronological age in relation to physical growth

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Clin Epigenetics 2023;15:8

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https://pubmed.ncbi.nlm.nih.gov/36639798/

Comments: This impressive study builds on a previous study involving some of the same authors who demonstrated an association between critical illness and early administration of parenteral nutrition with altered leucocyte DNA methylation (DNAm), which was related to long-term developmental sequelae. "Epigenetic clocks" have been developed based on data indicating that chronological age can be predicted from certain

DNAm patterns. In a sizeable subgroup of the original multicenter randomized trial on nutritional management in the pediatric intensive care unit, the authors tested whether critical illness in childhood and its nutritional management affect the epigenetic age, and whether there is a relationship to child growth. The results show that critically ill children later were epigenetically younger, based on DNAm at 94 CpG sites, than their chronological age, particularly if the critical illness occurred at an age of 6 years or later. Critical illness also resulted in reduced length but not weight, again particularly in children with critical illness at age 6 years or later. The potential long-term consequences and underlying mechanisms deserve further investigation.

Changes in DNA methylation of *clock* genes in obese adolescents after a short-term body weight reduction program: a possible metabolic and endocrine chrono-resynchronization

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Comments: In this study, a 3-week body weight reduction program with a restricted calorie diet and enhanced physical activity in adolescents induced a significant body mass index reduction from 2.94 to 2.82 standard deviation score, along with hypermethylation of *clock* and *cry2* genes, hypomethylation of the *per2* gene, and no changes in methylation of *arntl, cry1, per1,* and *per3* genes in leucocytes. Appreciable gender-related differences were observed. It is tempting to speculate whether the methylation changes caused the observed cardiometabolic improvements or were the results thereof. The observed epigenetic remodeling of specific *clock* genes might be interpreted as partly correcting chronodisruption associated with obesity.

Conflict of Interest Statement

No conflict of interest is declared with respect to the contents of this manuscript, with no circumstances involving the risk that the professional judgment or acts of primary interest may be unduly influenced by a secondary interest.

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Nutrition and Growth in Preterm and Term Infants

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Introduction

This year, we decided to address for preterm infants three large trials on neonatal nutrition and six systematic reviews on enteral nutrition. For term infants, the review addressed six papers on breastfeeding, one paper on iodine nutrition, and two papers on food allergy.

Key articles reviewed for this chapter

Preterm Infants

Large Trials on Neonatal Nutrition

Early amino acids in extremely preterm infants and neurodisability at 2 years
Bloomfield FH, Jiang Y, Harding JE, Crowther CA, Cormack BE, for the ProVIDe Trial Group
N Engl J Med 2022;387:1661–1672

Bovine colostrum to supplement the first feeding of very preterm infants: the PreColos randomized controlled trial
Yan X, Pan X, Ding L, Dai Y, Chen J, Yang Y, Li Y, Hao H, Qiu H, Ye Z, Shen RL, Li Y, Ritz C, Peng Y, Zhou P, Gao F, Jiang PP, Lin HC, Zachariassen G, Sangild PT, Wu B
Clin Nutr 2023;42:1408–1417

Bovine colostrum as a fortifier to human milk in very preterm infants – a randomized controlled trial (FortiColos)
Ahnfeldt AM, Aunsholt L, Hansen BM, Hoest B, Jóhannsdóttir V, Kappel SS, Klamer A, Möller S, Moeller BK, Sangild PT, Skovgaard AL, van Hall G, Vibede LD, Zachariassen G
Clin Nutr 2023;42:773–783

Systematic Reviews on Enteral Nutrition

Oropharyngeal application of colostrum or mother's own milk in preterm infants: a systematic review and meta-analysis
Kumar J, Meena J, Ranjan A, Kumar P
Nutr Rev 2023;81:1254–1266

Mother's own milk compared with formula milk for feeding preterm or low birth weight infants: systematic review and meta-analysis
Strobel NA, Adams C, McAullay DR, Edmond KM
Pediatrics 2022;150(Suppl 1):e2022057092D

Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants
Young L, Oddie SJ, McGuire W
Cochrane Database Syst Rev 2022;1:CD001970

Fast feed advancement for preterm and low birth weight infants: a systematic review and meta-analysis
Yang WC, Fogel A, Lauria ME, Ferguson K, Smith ER
Pediatrics 2022;150(Suppl 1):e2022057092G

Routine monitoring of gastric residual for prevention of necrotising enterocolitis in preterm infants
Abiramalatha T, Thanigainathan S, Ramaswamy VV, Rajaiah B, Ramakrishnan S
Cochrane Database Syst Rev 2023;6:CD012937

Enteral nutrition in preterm infants (2022): a position paper from the ESPGHAN Committee on Nutrition and invited experts
Embleton ND, Jennifer Moltu S, Lapillonne A, van den Akker CHP, Carnielli V, Fusch C, Gerasimidis K, van Goudoever JB, Haiden N, Iacobelli S, Johnson MJ, Meyer S, Mihatsch W, de Pipaon MS, Rigo J, Zachariassen G, Bronsky J, Indrio F, Köglmeier J, de Koning B, Norsa L, Verduci E, Domellöf M
J Pediatr Gastroenterol Nutr 2023;76:248–268

Term Infants

Breastfeeding

Breastfeeding: crucially important, but increasingly challenged in a market-driven world
Pérez-Escamilla R, Tomori C, Hernández-Cordero S, Baker P, Barros AJD, Bégin F, Chapman DJ, Grummer-Strawn LM, McCoy D, Menon P, Ribeiro Neves PA, Piwoz E, Rollins N, Victora CG, Richter L on behalf of the 2023 Lancet Breastfeeding Series Group
Lancet 2023;401:472–485

Marketing of commercial milk formula: a system to capture parents, communities, science, and policy
Rollins N, Piwoz E, Baker P, Kingston G, Mabaso KM, McCoy D, Ribeiro Neves PA, Pérez-Escamilla R, Richter L, Russ K, Sen G, Tomori C, Victora CG, Zambrano P, Hastings G on behalf of the 2023 Lancet Breastfeeding Series Group
Lancet 2023;401:486–502

The political economy of infant and young child feeding: confronting corporate power, overcoming structural barriers, and accelerating progress
Baker P, Smith JP, Garde A, Grummer-Strawn LM, Wood B, Sen G, Hastings G, Pérez-Escamilla R, Ling CY, Rollins N, McCoy D on behalf of the 2023 Lancet Breastfeeding Series Group
Lancet 2023;401:503–524

Breastmilk or infant formula? Content analysis of infant feeding advice on breastmilk substitute manufacturer websites
Pomeranz JL, Chu X, Groza O, Cohodes M, Harris JL
Public Health Nutr 2023;26:934–942

Effectiveness of lactation cookies on human milk production rates: a randomized controlled trial
Palacios AM, Cardel MI, Parker E, Dickinson S, Houin VR, Young B, Allison DB
Am J Clin Nutr 2023;117:1035–1042

Systematic review and meta-analysis of breastfeeding and later overweight or obesity expands on previous study for World Health Organization
Horta BL, Rollins N, Dias MS, Garcez V, Pérez-Escamilla R
Acta Paediatr 2023;112:34–41

Iodine Nutrition

Infant iodine status and associations with maternal iodine nutrition, breast-feeding status and thyroid function
Næss S, Aakre I, Strand TA, Dahl L, Kjellevold M, Stokland AM, Nedrebø BG, Markhus MW
Br J Nutr 2023;129:854–863

Food Allergy

Timing of allergenic food introduction and risk of immunoglobulin E-mediated food allergy
Scarpone R, Kimkool P, Ierodiakonou D, Leonardi-Bee J, Garcia-Larsen V, Perkin MR, Boyle RJ
JAMA Pediatr 2023;177:489–497

Frequency of infant egg consumption and risk of maternal-reported egg allergy at 6 years
Wen X, Martone GM, Lehman HK, Rideout TC, Cameron CE, Dashley S, Konnayil BJ
J Nutr 2023;153:364–372

Large Trials on Neonatal Nutrition

Early amino acids in extremely preterm infants and neurodisability at 2 years

Bloomfield FH[1,3], Jiang Y[1,2], Harding JE[1], Crowther CA[1], Cormack BE[1,3], for the ProVIDe Trial Group

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https://pubmed.ncbi.nlm.nih.gov/36322845/

Bovine colostrum to supplement the first feeding of very preterm infants: the PreColos randomized controlled trial

Yan X[1], Pan X[2], Ding L[1], Dai Y[3], Chen J[4], Yang Y[5], Li Y[6], Hao H[7], Qiu H[8], Ye Z[9], Shen RL[2,10], Li Y[2,11], Ritz C[12], Peng Y[1], Zhou P[13], Gao F[2,14], Jiang PP[2], Lin HC[15], Zachariassen G[16], Sangild PT[2,10,16], Wu B[9]

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Bovine colostrum as a fortifier to human milk in very preterm infants – a randomized controlled trial (FortiColos)

Ahnfeldt AM[1], Aunsholt L[1,2], Hansen BM[3], Hoest B[4], Jóhannsdóttir V[5], Kappel SS[1,2], Klamer A[6], Möller S[7,12], Moeller BK[8], Sangild PT[1,2,5,12], Skovgaard AL[9], van Hall G[10], Vibede LD[11], Zachariassen G[5,7,12]

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Comments: One of the larger trials in neonatology, especially in the field of nutrition, was the ProVIDe multicenter randomized controlled trial conducted in New Zealand [1]. The trial included a total of 434 infants with a birth weight <1,000 g and who also had an umbilical arterial catheter in place and aimed to assess whether higher parenteral amino acid intake improves outcomes. The infants in the intervention group no longer received heparinized saline through the umbilical cord, but amino acids (with heparin) instead at a dose of 1 g per day in addition to usual nutrition for the first 5 days after birth. The primary outcome was survival free from neurodisability at 2 years. The results showed no significant difference between the intervention and placebo groups regarding this outcome (adjusted relative risk, 0.95; 95% confidence interval, 0.79 to 1.14; $p = 0.56$). Worrying signals came from the secondary outcomes in that infants in the intervention arm had higher probable or proven sepsis rates, as well as higher patent ductus arteriosus rates. Besides, the surviving infants suffered twice as frequent from moderate or severe neurodisability. Thus, the approach of adding an additional gram of amino acids per day (which would imply an extra 2 g/kg per day for those weighing 500 g) on top of all other regular parenteral nutrition was not beneficial. It must be noted that in this study, protein intakes were very high, amounting on average approximately 4 g/kg per day on day 4 of life from parenteral nutrition only, but many kids thus also received even higher dosages. Since electrolyte intake was not controlled, this probably resulted in a high rate of hypophosphatemia due to refeeding syndrome. Previously, the same phenomenon was presented in a study by Moltu et al., who also described refeeding syndrome features in premature infants not being supplemented with sufficient phosphate [2]. In fact, also in the ProVIDe study, several of the participating sites in the study provide only very minimal amounts of phosphate in parenteral nutrition during the first few days of life as was shown in a separate paper [3]. Moreover, a negative correlation was shown between amino acid intake and serum phosphate concentrations. In addition, those infants with refeeding syndrome in this trial suffered more frequently from sepsis and were three times as likely to die. Thus, all in all, the very high amino acid intakes in combination with low phosphate intakes may explain some of the negative outcomes in the infants.

Because human colostrum is so rich in immunoactive compounds, colostrum of bovine origin has also been suggested to be a beneficial supplement for preterm infants. Its use could be potentially advantageous in preterm infants whose mothers are not able to produce sufficient colostrum initially or could even serve as an adjunct to insufficient mother's own milk (MOM) or as a multinutrient fortifier to human milk. A Danish-Chinese research collaboration has recently investigated these usages in two separate trials, the PreColos and FortiColos trial [4, 5]. In the prior trial, 350 preterm infants (mean gestational age 30 weeks) were included in China [4]. They were randomized between either the standard feeding group, i.e., MOM supplemented with preterm formula, or the bovine colostrum group, which received a combination of MOM supplemented with bovine colostrum and possibly preterm formula in case the protein intake would exceed the maximum limit because of the high protein content of bovine colostrum. The intervention lasted 14 days in total. No differences were seen in the primary outcome, which was time to achieving 120 mL/kg per day of enteral nutrition. It must be noted, however, that feeding advancements in the study were very low compared to, for example, European practice, a feature described earlier [6]. During the first 2 weeks of life, the infants in both groups had received only 32 mL/kg per day of enteral feeding on average, and the median time to achieving 120 mL/kg per day of enteral nutrition lasted 28 days. After adjusting for confounders, the per protocol analysis even showed a significant delay of 4 days in achieving this goal in those who had received the bovine colostrum. Growth and incidence of clinical morbidities were not different between groups, except for possibly more infants suffering from periventricular hemorrhage in the intervention group. In conclusion, in these preterm infants, in whom enteral nutrition was only slowly advanced, partially replacing preterm formula with bovine colostrum in case of insufficient MOM does not seem to be a beneficial strategy.

In the FortiColos trial, bovine colostrum was used as an alternative to regular human milk fortifier [5]. In this randomized controlled trial, conducted in Denmark, 232 preterm infants (mean gestational age 28.5 weeks) were randomized to either a conventional bovine milk–derived multinutrient fortifier or powdered bovine colostrum, which was added to MOM or donor human milk in case of insufficient MOM. Total protein intake was targeted to be the same in both groups, but upon analysis, the infants in the bovine colostrum group received slightly higher protein intakes. The intervention lasted until 35 weeks postmenstrual age. Growth was the primary outcome, but there were no consistent differences between groups. Regarding secondary outcomes, there were also no clear differences in neonatal morbidities like late-onset sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, or retinopathy of prematurity. In conclusion, unlike preclinical studies in preterm piglets, in which beneficial effects of bovine colostrum were shown consistently [7–9], studies in human preterm infants have not been positive so far. It could be that this is due to the fact that piglets may absorb the immunoglobulin G intactly, whereas in humans, these either remain undigested or are broken down into smaller peptides, losing their bioactive function locally in the gut.

Systematic Reviews on Enteral Nutrition

Oropharyngeal application of colostrum or mother's own milk in preterm infants: a systematic review and meta-analysis

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Mother's own milk compared with formula milk for feeding preterm or low birth weight infants: systematic review and meta-analysis

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Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

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Fast feed advancement for preterm and low birth weight infants: a systematic review and meta-analysis

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Routine monitoring of gastric residual for prevention of necrotising enterocolitis in preterm infants

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Enteral nutrition in preterm infants (2022): a position paper from the ESPGHAN Committee on Nutrition and invited experts

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Comments: Several systematic reviews regarding neonatal nutrition in preterm infants have been updated last year and we will shortly discuss a few.

In the previous edition of this yearbook [10], we had also briefly discussed the application of buccal or oropharyngeal colostrum in preterm infants. The theory behind this practice is that this immunologically rich milk might boost the immune system and might aid in preventing several neonatal morbidities. The conclusion last year was that while administration of oropharyngeal colostrum to preterm infants appears safe and theoretically attractive from both an emotional and immunological point of view, no clear clinical benefits have consistently been proven unfortunately, especially in high-resource settings. However, in the last 2 years, several new studies mostly from Asian countries have been published, and this urged Kumar et al. to conduct an updated systematic review with meta-analysis [11]. The authors selected 17 randomized controlled trials (RCTs) in which 1,730 preterm infants were randomized between oropharyngeal colostrum versus placebo or standard care. Meta-analyzing available data suggests there might be a reduction in time to full enteral feeding and sepsis events, although GRADE shows this is with very low certainty of evidence mainly because of high study heterogeneity and inclusion of several nonblinded studies. Nonetheless, despite there is still a need for large multicentric adequately powered high-quality RCTs, buccal colostrum appears safe, is a cheap intervention, might stimulate parental involvement and even milk expression [12], has potential clinical benefits, and may thus be advised in neonatal intensive care units.

The latest Cochrane review assessing RCTs on the use of donor human milk versus (preterm) formula in case of insufficient MOM was published in 2019 [13]. It was concluded with moderate certainty evidence that donor human milk decreased the risk of necrotizing enterocolitis compared with formula. Last year, Strobel et al. published an updated systematic review in which 42 cohort studies were reviewed assessing nearly 90,000 preterm infants [14]. Groups of infants were stratified by whether they had received at least 50% formula or at least 50% MOM, so it must be noted that there was considerable overlap in both groups. Also, there were various study designs included and many studies came with a substantial risk of bias. Yet, it was concluded that infants who had received merely formula versus MOM during the first month of life had a threefold higher chance of suffering from necrotizing enterocolitis. Other morbidities and mortality rate were not significantly different between the groups.

Knowledge on the rate of advancing enteral nutrition in preterm infants has received a boost since the SIFT study was published in 2019 [15]. In relation to this, several systematic reviews have been updated. For one, a Cochrane review on the start of progressing enteral nutrition before or after 4 days of life showed that there was no increased risk of necrotizing enterocolitis or death of early progression, also not in subgroups [16]. On the contrary, delayed start of progression increased the risk of late-onset sepsis. Closely related is the rate of advancement hereafter. In an updated systematic review on 12 RCTs in which nearly 4,300 preterm infants were included, outcomes after aiming for a very rapid daily progression of enteral feeds (>30 mL/kg per day) versus slower daily progression (<30 mL/kg per day) were assessed. Faster advancement reduced the time to regain birth weight by almost 4 days and the duration of hospitalization by 3 days when compared with slow advancement rates. In addition, although statistical significance was not shown, slight reductions in the risk of mortality, necrotizing enterocolitis, and sepsis were demonstrated. Priorly, rapidly advancing enteral nutrition was often delayed because of routine assessment of gastric residuals, which were then interpreted as a sign of feeding intolerance. Based on new trials and physiological understanding, we now know this may be a misunderstanding. An updated Cochrane review on 5 RCTs in 423 preterm infants shows that omitting routine gastric residual assessment reduces time to full enteral feeding with 3 days and reduces sepsis risk by nearly 35%, while it has no effect on the incidence of necrotizing enterocolitis [17]. The conclusions of these systematic reviews are all in line with the recommendations given in the recent ESPGHAN position paper on enteral nutrition for preterm infants [18]. The group of authors in this document summarized many aspects of enteral nutrition (more than here described) and provided several practical recommendations for those working on a neonatal intensive care unit.

Term Infants

Breastfeeding

Breastfeeding: crucially important, but increasingly challenged in a market-driven world

Pérez-Escamilla R[1], Tomori C[2], Hernández-Cordero S[3], Baker P[4], Barros AJD[5], Bégin F[6], Chapman DJ[7], Grummer-Strawn LM[8], McCoy D[9], Menon P[10], Ribeiro Neves PA[5], Piwoz E[11], Rollins N[12], Victora CG[5], Richter L[13] on behalf of the 2023 Lancet Breastfeeding Series Group

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Marketing of commercial milk formula: a system to capture parents, communities, science, and policy

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The political economy of infant and young child feeding: confronting corporate power, overcoming structural barriers, and accelerating progress

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Breastmilk or infant formula? Content analysis of infant feeding advice on breastmilk substitute manufacturer websites

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Effectiveness of lactation cookies on human milk production rates: a randomized controlled trial

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Systematic review and meta-analysis of breastfeeding and later overweight or obesity expands on previous study for World Health Organization

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Comments: **Public Health Policies, Breast Milk Substitutes Marketing and Breastfeeding**. There are many reasons for the low rates and short durations of breastfeeding worldwide. Among these, the impact of breast milk substitute (BMS) industry on parents, care providers, and policymakers plays an important role. It is the topic of the three papers of the "Breastfeeding 2023" series published in the Lancet.

In 1981, the World Health Assembly adopted the International Code of Marketing of BMS, the "Code," a set of standards to promote and protect breastfeeding [19]. It includes prohibition of advertising of BMS to the public or promotion within healthcare systems; banning provision of free samples to mothers, healthcare workers, and health facilities; no promotion of formula within health services; and no sponsorship of health professionals or scientific meetings by the BMS industry. Of note, WHO is increasingly advocating the use of the term commercial milk formula instead of BMS to highlight the artificial and ultra-processed nature of formula products. Forty-two years later, there is still a long way to go. As of March 2022, a total of 144 (74%) of the 194 WHO Member States (MS) have adopted legal measures to implement at least some of the provisions in the Code [20]. Of these, 32 MS have measures in place that are substantially aligned with the Code. A further 41 MS have measures that are moderately aligned and 71 have included some provisions, while 50 have no legal measures at all. The WHO African, Eastern Mediterranean, and Southeast Asian regions have the highest percentage of countries substantially aligned with the Code.

The first paper of the "Breastfeeding 2023" series from Pérez-Escamilla et al. describes what policies and interventions are needed to achieve optimal breastfeeding [21]. A synthesis of reviews published between 2016 and 2021 and country-based case studies indicate that breastfeeding practices at a population level can be improved with interventions across the socioecological model and settings. Parents and healthcare providers often misinterpret baby behaviors (e.g., crying, fussiness, posseting, poor nighttime sleep) as signs of milk insufficiency or infant pathology.

The second paper from Rollins et al. addresses how BMS marketing operates as a system to capture parents, communities, science, and policy [22]. This paper summarizes the history of BMS and its marketing, e.g., trends in BMS sales and marketing expenditures, and describes the development of the BMS industry marketing playbook and how BMS marketing takes advantage of deficiencies in public health policies and regulations. The increasing use of digital media and tools for the marketing of BMS is of concern. Digital marketing has become the primary means by which BMS manufacturers and distributors promote their brands and products, representing as much as 70% of total advertising spent on these products. Digital marketing platforms enable advertisers to reach beyond national borders, adding further challenges to enforcement of national laws.

The third paper from Baker et al. examines the social, political, and economic reasons for this problem [23]. This paper highlights the power of the BMS industry to influence policy at both national and international levels in ways that grow BMS markets. Baker et al. propose six recommendations on social, political, and economic reforms.

The United States is one of the few countries that has not adopted any portion of the International Code of Marketing of BMS into law. Therefore, marketing and labelling techniques that are not allowed in many other countries are regularly used to sell BMS in the United States. The study by Pomeranz et al. examines how BMS companies communicate with the public about the benefits and challenges of breastfeeding and BMS feeding on their US websites directed to consumers [24]. The authors identified messages and images about breastfeeding/breast milk and BMS feeding, including benefits or issues associated with each of them, and marketing practices that could discourage breastfeeding. Data were collected for US websites of five BMS manufacturers. Websites contained more screenshots about breastfeeding/breast milk (n = 303) than BMS (n = 263), but these screenshots were significantly more likely to mention benefits of BMS (44%) than breastfeeding/breast milk (26%), including significantly more statements that BMS provides brain, neural, and gastrointestinal benefits. Issues related to breastfeeding appeared on 40% of screenshots mentioning breastfeeding (e.g., breast milk supply, infant latching, sore nipples). Twice as many screenshots compared BMS brands favorably to breast milk than as superior to other brands.

Pomeranz et al. concluded that their study corroborates previous research finding that BMS marketing expressly discourages breastfeeding.

Duration of Breastfeeding. A large variety of commercially available products claim to improve lactation. Lactation cookies (LCs) contain galactagogues, i.e., substances believed to enhance breast milk production. The objective of the study by Palacios et al. was to assess the efficiency of commercially available LCs [25]. They performed a 1-month, randomized controlled trial among exclusively lactating mothers (n = 176) of healthy, term, 2-month-old infants living in the United States. Participants were randomly assigned to eat daily 56.5 g of either LCs with "galactagogues" (oatmeal, brewer's yeast, flax seeds, and fenugreek) or conventional cookies containing similar weight, calories, and presentation but lacking galactagogues. No significant differences were observed on baseline-to-endline changes in human milk production rate (primary outcome), perceived insufficient milk, or breastfeeding self-efficacy (secondary outcomes). Recommendations to consume LCs for increasing objective or subjective milk supply are likely to be misleading.

Breastfeeding and Later Risk for Overweight or Obesity. The primary aim of this systematic review and meta-analysis by Horta et al. was to update the evidence on the association of breastfeeding with a reduced risk for overweight or obesity [26]. They also assessed the likelihood of residual confounding. The review comprised 159 studies published between August 2014 and May 2021, with 169 estimates on the association of breastfeeding with overweight or obesity. Most studies (n = 130) were performed in children aged 1–9 years. Breastfeeding was associated with a protection against overweight or obesity (pooled odds ratio: 0.73, 95% confidence interval: 0.71, 0.76). Among the 19 studies that were less susceptible to publication bias, residual confounding, and misclassification, a benefit was still observed (pooled odds ratio: 0.85, 95% confidence interval: 0.77, 0.93), suggesting that the observed association is causal. Among the studies that were clearly susceptible to positive confounding by socioeconomic status, a benefit of breastfeeding was observed even after adjusting for socioeconomic status (pooled odds ratio: 0.76, 95% confidence interval: 0.69, 0.83). This study by Horta et al. confirmed that breastfeeding reduces the odds of overweight or obesity and that this association is unlikely to be due to publication bias and residual confounding.

Iodine Nutrition

Infant iodine status and associations with maternal iodine nutrition, breastfeeding status and thyroid function

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Comments: Iodine is an essential component of thyroid hormones. Iodine deficiency (ID) is particularly of concern in pregnant and lactating women, infants, and young children because of the importance of thyroid hormone for normal growth and neurodevelopment both in in utero and early life. Breast milk iodine concentration (BMIC) is dependent on maternal iodine intake; therefore, in exclusively breastfed infants, iodine intake is dependent entirely on maternal iodine intake.

The study by Næss et al. assessed the iodine status in a cohort of Norwegian infants and its association with maternal iodine nutrition, breastfeeding status, and thyroid function [27]. A total of 113 infants were followed up at ages 3, 6, and 11 months. Mean maternal age was 29.3 years, and mean gestational age was 40 years, with 5% preterms. At age 3 months, 80% of the infants were breastfed (all of them were exclusively breastfed), while 15% were mixed milk fed and 5% exclusively formula fed. Infant and maternal urinary iodine concentration (UIC), maternal iodine intake, breastfeeding status, BMIC, and infant thyroid function tests were assessed. The median infant UIC was 82 µg/L at the age of 3 months, below the recommended WHO cutoff of 100 µg/L, indicating insufficient iodine status at group level. Infant UIC was adequate later in infancy (median 110 µg/L at ages 6 and 11 months). Infant UIC was associated positively with maternal UIC, maternal iodine intake, and BMIC. The associations were strongest at the age of 3 months. Breastfed infants had significantly lower median UIC compared with formula-fed infants at ages 3 months (76 vs. 190 µg/L) and 6 months (105 vs. 315 µg/L) but not at age 11 months. No consequences on thyroid function were found at any age. In this study, median BMIC at 3 months postpartum was 77 µg/L, which is considerably lower than the iodine concentration in ready-to-use infant formula on the European market (about 130 µg/L). Assuming a breast milk intake of 0·75 L per day at the age of 3 months, a BMIC of 77 µg/L would correspond to an iodine intake of 58 µg per day in fully breastfed infants in the present study. This is much lower than the WHO recommendation of 90 µg per day. Næss et al. concluded that breastfed infants in Norway are at risk of insufficient iodine intake during the first months of life. In Norway, iodine supplementation has been recommended from 2018 for lactating women if intake of the most important iodine sources (dairy products and lean fish) is low.

Of note, the high variability in the dietary iodine intake of individuals results in very high day-to-day variation in UIC. Therefore, UIC from spot samples is not appropriate for the diagnosis of ID in an individual but is considered as a reliable biomarker to evaluate the iodine status at a population level. There is an urgent need for biomarkers that could be used to assess iodine status at the individual level. Two 2017 and 2019 Cochrane systematic reviews found no evidence that iodine supplementation in women before, during, or after pregnancy improved infant and child cognitive development in areas with mild to moderate ID [28]. Likewise, a 2019 Cochrane systematic review concluded that there was no evidence of a positive impact of iodine supplementation on morbidity, including cognitive impairment, and mortality in preterm infants [28].

Food Allergy

Timing of allergenic food introduction and risk of immunoglobulin E-mediated food allergy

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Frequency of infant egg consumption and risk of maternal-reported egg allergy at 6 years

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Comments: The prevalence of food allergy (FA) is increasing, especially in high-income countries, where up to 10% of the population may experience FA. Findings from recent studies on dietary interventions for FA prevention have led to revised guidelines, moving from an avoidance approach of allergenic foods to actively recommending introduction of allergenic foods in the first 4 to 6 months of life. It has also been shown that earlier introduction of egg and peanut probably reduces the risk for egg and peanut allergy, respectively. Evidence to support earlier introduction of other food allergens before the age of 4 months is still lacking.

Scarpone et al. performed a meta-analysis of randomized clinical trials (RCTs) assessing the age at introduction of allergenic foods (milk, egg, fish, shellfish, tree nuts, wheat, peanuts, and soy) during infancy and immunoglobulin E (IgE)–mediated FA from 1 to 5 years of age [29]. Primary outcomes were risk of IgE-mediated allergy to any food from 1 to 5 years of age and withdrawal from the intervention. Secondary outcomes included allergy to specific foods.

The study populations were infants enrolled from birth to 12 months of age. RCTs that compared earlier and later allergenic food introduction and different doses and types of exposure were included, as were RCTs using breastfeeding or breast milk, amino acid formula, other low-allergen exposures, or standard care as the comparator. Non-RCTs, trials of timing of solid food introduction that did not use allergenic foods, and trials in specific populations, such as very preterm infants, were excluded.

Data were extracted from 23 RCTs (56 articles, 13,794 randomized participants). There was moderate certainty evidence from 4 RCTs (3,295 participants) that introduction of multiple allergenic foods from 2 to 12 months of age (median age, 3–4 months) was associated with reduced risk of FA (risk ratio [RR], 0.49; 95% CI, 0.33–0.74; $I^2 = 49\%$). There was moderate certainty evidence from 5 RCTs (4,703 participants) that introduction of multiple allergenic foods from 2 to 12 months of age was associated with increased withdrawal from the intervention (RR, 2.29; 95% CI, 1.45–3.63; $I^2 = 89\%$). There was high-certainty evidence from 9 RCTs (4,811 participants) that introduction of egg from 3 to 6 months of age was associated with reduced risk of egg allergy (RR, 0.60; 95% CI, 0.46–0.77; $I^2 = 0\%$) and high-certainty evidence from 4 RCTs (3,796 participants) that introduction of peanut from 3 to 10 months of age was associated with reduced risk of peanut allergy (RR, 0.31; 95% CI, 0.19–0.51; $I^2 = 21\%$). Evidence for timing of introduction of cow milk and risk of cow milk allergy was of very low certainty. The study by Scarpone et al. provides more evidence on the beneficial role of earlier introduction of egg and peanut on the risk of egg and peanut allergy, respectively [29]. This study also suggests that earlier introduction of multiple allergenic foods may be beneficial for the risk of FA. However, the high rate of withdrawal from the intervention precludes to draw firm conclusions and therefore update the current guidelines.

Egg allergy is the second most common FA in early childhood after cow milk allergy, affecting about 2.5% of young children. The egg consumption that is needed to induce the beneficial effect of the earlier introduction of egg is unknown. Wen et al. analyzed data of 1,252 children from the Infant Feeding Practices Study II (2005–2012), a longitudinal prebirth cohort study run by the US Food and Drug Administration in collaboration with the Centers for Disease Control and Prevention [30]. Mothers reported the frequency of infant egg consumption at 2–7, 9, 10, and 12 months of age and the status of their child's egg allergy at the 6 years of follow-up. The risk of maternal-reported egg allergy at 6 years significantly ($p = 0.004$) decreased with infant egg consumption frequency at 12 months: 2.05% for infants not consuming eggs, 0.41% for those consuming eggs <2 times per week, and 0.21% for those consuming eggs >2 times per week. A similar but not significant trend was observed at 10 months of age. After adjusting for socioeconomic confounders, breastfeeding, complementary food introduction, and infant eczema, infants who consumed eggs >2 times per week at 12 months had a significantly lower RR of maternal-reported egg allergy at 6 years (confounder-adjusted RR: 0.11; 95% CI: 0.01, 0.88; $p = 0.038$), whereas those who consumed <2 times per week (confounder-adjusted RR: 0.21; 95% CI: 0.03, 1.67; $p = 0.141$) did not have a significantly lower risk than those who did not consume eggs at all. This study adds another piece of information to the most appropriate feeding patterns regarding the prevention of egg allergy. However, some limitations need to be pointed out. The diagnosis of egg allergy was reported by the mother and not after oral egg challenge or diagnosed by a physician. The preparation method (cooked or baked) of the eggs was not available in the surveys. IFPS II data were relatively old with the last follow-up in 2012, which may limit the generalizability of the results. Particularly, there was a low frequency of egg consumption at 9 months or earlier; both the small sample size and the statistical power did not allow to examine its association with the risk of egg allergy at 6 years.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Introduction

The chapter includes articles published from July 1, 2022 up to June 30, 2023, focusing on the connections between infant and children nutrition and cognition. Original articles on nutrition and cognition comprising randomized controlled trials (RCTs), observational studies, and reviews have been selected. The selected articles fall into two macroareas, subdivided into two main categories, subdivided in turn into further topics:

1. Mother-infant dyad, subdivided into macronutrients, iodine, vitamin B_{12}, other nutrients, and gut microbiome
2. Infants and children, subdivided into dietary habits and food and nutrients

The studies concerning intrauterine life and lactation stage, respectively, are mostly concentrated to maternal dietary intakes of single nutrients, but growing interest is taking place for maternal intakes of macronutrients and dietary habits. These studies are also growing in the postlactational stages, from the start of complementary feeding onward up to later pediatric ages (comprehensive of adolescence). This approach is consistent with the general issues of *sustainability*, considering diet a correlate of lifestyle, setting, socioeconomic conditions, and local resources as part of the exposome, the sum of external factors that, in association with gene-related predisposition, is a major determinant of growth and development during childhood.

We have reported the selected papers by using a rather homogeneous approach to underline differences in topic, effects (for RCTs) and/or associations (for prospective and observational studies and reviews), settings, approach, and results on developmental parameters as separated outcome, in order to allow a clearer interpretation of the results while contextualizing the research in an appropriate way.

The specific comments will follow any section, while a short final overview will summarize the possible evolution steps of the research in nutrition and development.

Key articles reviewed for this chapter

Mother-Infant Dyad

Macronutrients

Neurodevelopment, vision and auditory outcomes at age 2 years in offspring of participants in the 'Women First' maternal preconception nutrition randomized controlled trial
Fernandes M, Krebs NF, Westcott J, Tshefu A, Lokangaka A, Bauserman M, Garcés AL, Figueroa L, Saleem S, Aziz SA, Goldenberg RL, Goudar SS, Dhaded SM, Derman RJ, Kemp JF, Koso-Thomas M, Sridhar A, McClure EM, Hambidge KM, The Women First Preconception Nutrition Trial Study Group
Arch Dis Child 2023;108:622–631

The association between maternal ultra-processed food consumption during pregnancy and child neuropsychological development: a population-based birth cohort study
Puig-Vallverdú J, Romaguera D, Fernández-Barrés S, Gignac F, Ibarluzea J, Santa-Maria L, Llop S, Gonzalez S, Vioque J, Riaño-Galán I, Fernández-Tardón G, Pinar A, Turner MC, Arija V, Salas-Savadó J, Vrijheid M, Julvez J
Clin Nutr 2022;41:2275–2283

Processed foods and diet quality in pregnancy may affect child neurodevelopment disorders: a narrative review
Zupo R, Castellana F, Boero G, Matera E, Colacicco G, Piscitelli P, Clodoveo ML, Rondanelli M, Panza F, Lozupone M, Sardone R
Nutr Neurosci 2023;1–21. DOI: 10.1080/1028415X.2023.2197709. Online ahead of print

Prenatal exposure to trans fatty acids and head growth in fetal life and childhood: triangulating confounder-adjustment and instrumental variable approaches
Zou R, Labrecque JA, Swanson SA, Steegers EAP, White T, El Marroun H, Tiemeier H
Eur J Epidemiol 2022;37:1171–1180

Circulating levels of short-chain fatty acids during pregnancy and infant neurodevelopment
Hernández-Martínez C, Canals J, Voltas N, Martín-Luján F, Arija V
Nutrients 2022;14:3946

The impact of maternal high-fat diet on offspring neurodevelopment
Urbonaite G, Knyzeliene A, Bunn FS, Smalskys A, Neniskyte U
Front Neurosci 2022;16:909762

Iodine

A scoping review of iodine and fluoride in pregnancy in relation to maternal thyroid function and offspring neurodevelopment
Griebel-Thompson AK, Sands S, Chollet-Hinton L, Christifano D, Sullivan DK, Hull H, Carlson SE
Adv Nutr 2023;14:317–338

Prenatal iodine supplementation and early childhood neurodevelopment: the PoppiE Trial – study protocol for a multicentre randomised controlled trial
Best KP, Gould JF, Makrides M, Sullivan T, Cheong J, Zhou SJ, Kane S, Safa H, Sparks A, Doyle LW, McPhee AJ, Nippita TAC Afzali HHA, Grivell R, Mackerras D, Knight E, Wood S, Green T
BMJ Open 2023;13:e071359

Vitamin B_{12} and Related Compounds

Association between maternal choline, fetal brain development, and child neurocognition: systematic review and meta-analysis of human studies
Obeid R, Derbyshire E, Schön C
Adv Nutr 2022;13:2445–2457

Maternal choline supplementation: a potential therapy for developmental manganese exposure?
Howard SL, Beaudin SA, Strupp BJ, Smith DR
bioRxiv 2023 Jun 26;2023.06.23.546356. DOI: 10.1101/2023.06.23.546356. Preprint

Associations between maternal folate status and choline intake during pregnancy and neurodevelopment at 3–4 years of age in the Alberta Pregnancy Outcomes and Nutrition (APrON) study
Irvine N, England-Mason G, Field CJ, Letourneau N, Bell RC Giesbrecht GF, Kinniburgh DW, MacDonald AM, Martin JW, Dewey D and APrON Study Team
J Dev Orig Health Dis 2023;14:402–414

Maternal vitamin B_{12} status during pregnancy and early infant neurodevelopment: the ECLIPSES study
Cruz-Rodríguez J, Díaz-López A, Canals-Sans J, Arija V
Nutrients 2023;15:1529

Other Nutrients

Maternal vitamin D levels during pregnancy and offspring psychiatric outcomes: a systematic review
Upadhyaya S, Ståhlberg T, Silwal S, Arrhenius B, Sourander A
Int J Mol Sci 2022;24:63

Neuroprotective role of lactoferrin during early brain development and injury through lifespan
Schirmbeck GH, Sizonenko S, Sanches EF
Nutrients 2022;14:2923

Gut Microbiome

Maternal anxiety, depression and stress affects offspring gut microbiome diversity and bifidobacterial abundances
Galley JD, Mashburn-Warren L, Blalock LC, Lauber CL, Carroll JE, Ross KM, Hobel C, Coussons-Read M, Schetter CD, Gur TL
Brain Behav Immun 2023;107:253–264

Mechanisms of maternal diet-induced obesity affecting the offspring brain and development of affective disorders
Radford-Smith DE, Anthony DC
Metabolites 2023;13:455

Infants and Children

Dietary Habits

Children with lower ratings of executive functions have a greater response to the portion size effect
Keller KL, Pearce AL, Fuchs B, Hallisky K, Rolls BJ, Wilson SJ, Geier C, Rose EJ
Appetite 2023;186:106569

Is adherence to the Mediterranean diet associated with good sleep duration in primary-school children?
Buja A, Grotto G, Zampieri C, Mafrici SF, Cozzolino C, Baldovin T, Brocadello F, Baldo V
Front Pediatr 2022;10:959643

Are dietary patterns related to cognitive performance in 7-year-old children? Evidence from a birth cohort in Friuli Venezia Giulia, Italy
Michela Marinoni M, Giordani E, Mosconi C, Rosolen V, Concina F, Fiori F, Carletti C, Knowles A, Pani P, Bin M, Ronfani L, Ferraroni M, Barbone F, Parpinel P, Edefonti V
Nutrients 2022;14:4168

Unfavorable behaviors in children run in packs! Dietary and non-dietary modulators of attentional capacity
Drozdowska A, Falkenstein M, Lücke T, Kersting M, Jendrusch G, Platen P, Sinningen K
Nutrients 2022;14:5264

Foods and Nutrients

Macronutrient intake during infancy and neurodevelopment in preschool children from the EDEN mother-child cohort
Marinho AR, Correia D, Bernard JY, Heude B, Lopes C, de Lauzon-Guillain B
Eur J Clin Nutr 2023;77:668–676

Nutrient trajectories during infancy and their associations with childhood neurodevelopment
Toh JY, Cai S, Lim SX, Pang WW, Godfrey KM, Shek LP, Tan KH, Yap F, Lee YS, Chong YS, Eriksson JG, Broekman BFP, Rifkin-Graboi A, Chong MFF
Eur J Nutr 2023;62:2429–2439

Defining the relationship of gut microbiota, immunity, and cognition in early life – a narrative review
Kartjito MS, Yosia M, Wasito E, Soloan G, Agussalim AF, Basrowi RW
Nutrients 2023;15:2642

New perspectives on the associations between blood fatty acids, growth parameters, and cognitive development in global child populations
Cardino VN, Goeden T, Yakah W, Ezeamama AE, Fenton JI
Nutrients 2023;15:1933

Macronutrients

Neurodevelopment, vision and auditory outcomes at age 2 years in offspring of participants in the 'Women First' maternal preconception nutrition randomized controlled trial

Fernandes M[1,2,3], Krebs NF[4], Westcott J[4], Tshefu A[5], Lokangaka A[5], Bauserman M[6], Garcés AL[7], Figueroa L[7], Saleem S[8], Aziz SA[8], Goldenberg RL[9], Goudar SS[10], Dhaded SM[10], Derman RJ[11], Kemp JF[4], Koso-Thomas M[12], Sridhar A[13], McClure EM[13], Hambidge KM[4]; The Women First Preconception Nutrition Trial Study Group

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Arch Dis Child 2023;108:622–631
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Macronutrient: lipids
Setting: rural Democratic Republic of the Congo, Guatemala, India, and Pakistan
Effect: no
Study: RCT
Treatment/methods: Maternal lipid-based nutrient supplement initiated preconceptionally (arm 1, *n* = 217), at 12 weeks of gestation (arm 2, *n* = 230), or not (arm 3, *n* = 220); intervention stopped at delivery.
Age-related effects: Prenatal maternal nutrition supplementation was not associated with any neurodevelopmental outcomes at age 2 years. Maternal education, family environment, and length-for-age *Z*-score at 24 months predicted early child development.

The association between maternal ultra-processed food consumption during pregnancy and child neuropsychological development: a population-based birth cohort study

Puig-Vallverdú J[1,2], Romaguera D[2,3,4], Fernández-Barrés S[1,2,5], Gignac F[1,2], Ibarluzea J[6,7,8,9], Santa-Maria L[6,7,8], Llop S[5,10], Gonzalez S[11,12], Vioque J[5,12], Riaño-Galán I[3,13,14], Fernández-Tardón G[5,13], Pinar A[1,2,15], Turner MC[1,2,5], Arija V[16,17], Salas-Savadó J[3,17,18], Vrijheid M[1,2,5], Julvez J[1,2,5,15,18]

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Clin Nutr 2022;41:2275–2283
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Macronutrient/food: ultra-processed food (UPF)
Setting: Spain
Association: partial
Study: prospective cohort study
Treatment/methods: Food frequency questionnaire during weeks 12 and 32 of gestation. The NOVA classification was used to identify UPFs. Child neuropsychological development was assessed with the Bayley Scales of Infant and Toddler Development and the McCarthy Scales of Children's Abilities.
Age-related associations: Adverse association between maternal consumption of UPF during pregnancy and verbal functioning in early childhood (4–5 years of age)

Processed foods and diet quality in pregnancy may affect child neurodevelopment disorders: a narrative review

Zupo R[1], Castellana F[2], Boero G[3], Matera E[4], Colacicco G[5], Piscitelli P[6], Clodoveo ML[1], Rondanelli M[7,8], Panza F[5], Lozupone M[5], Sardone R[2,9]

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https://pubmed.ncbi.nlm.nih.gov/37039128/

Macronutrients/food: ultra-processed food (UPF)
Setting: the United Kingdom, Europe, the United States (mostly)
Associations: yes
Study: review
Treatment/methods: PubMed, MEDLINE, EMBASE, Scopus, Ovid, and Scholar databases were searched for original articles.
Age-related associations: Child cognitive development was negatively impacted by a maternal diet with many UPFs, saturated fats, and total sugars (especially those added or hidden in packaged carbonated beverages). Conversely, a Mediterranean diet led to better neurodevelopment, particularly verbal intelligence and executive functions, in middle childhood.

Prenatal exposure to trans fatty acids and head growth in fetal life and childhood: triangulating confounder-adjustment and instrumental variable approaches

Zou R[1,2,3], Labrecque JA[4], Swanson SA[4,5], Steegers EAP[6], White T[1,7,8], El Marroun H[1,9], Tiemeier H[1,10]

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Macronutrient: lipids/trans-fatty acids (TFAs)
Setting: the Netherlands
Association: partial
Study: prospective cohort study
Treatment/methods: Maternal plasma TFA concentration was assessed using gas chromatography in midgestation. Offspring head circumference (HC) was measured in the second and third trimesters using ultrasonography; childhood brain morphology was assessed using magnetic resonance imaging at age 10 years.
Age-related associations: A higher gestational TFA level was associated with a smaller fetal HC in the third trimester and lower fetal HC growth rate from the second to the third trimester. No association between prenatal TFA exposure and nonverbal IQ at age 6 years. No association between prenatal exposure to TFAs and fetal HC in the second trimester or global brain volume at age 10 years.

Circulating levels of short-chain fatty acids during pregnancy and infant neurodevelopment

Hernández-Martínez C[1,2,3], Canals J[1,2,3], Voltas N[1,2,3,4], Martín-Luján F[5], Arija V[1,3]

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Nutrients 2022;14:3946
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Macronutrient: lipids/short-chain fatty acids (SCFAs)
Setting: Spain
Associations: yes
Study: prospective cohort study (ECLIPSES)
Treatment/methods: Serum SCFA concentrations were assessed in the first and third trimester of pregnancy by liquid chromatography with tandem mass spectrometry; infant cognitive development and temperament have been assessed by Bayley Scales of Infant Development-III and the Early Infancy Temperament Questionnaire.
Age-related associations: Lower serum levels of acetic, butyric, and isobutyric acid, mainly during the first trimester, were related to better language and psychomotor development and, in the case of butyric acid, better intensity behavior in infants. Medium levels of propionic acid were related to better scores for development, mood, and temperament, at 40 days of age.

The impact of maternal high-fat diet on offspring neurodevelopment

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https://pubmed.ncbi.nlm.nih.gov/35937892/

Macronutrients: fats
Setting: animal studies (RCTs and observations)
Effects: unclear
Study: review (partly systematic)
Treatment/methods: Recent findings from rodent models and from human studies have been reviewed to study the potential effect of maternal high-fat diet (mHFD) on neurodevelopment of the offspring, including both male and female animals in biological studies; therefore, most recent publications started describing female phenotype as well.
Age-related effects: The effect of mHFD on brain remains underinvestigated, particularly on females. Most of the intervention research is performed on animal models and we are in pressing need of human studies.

Comments: Within this area of growing interest, the unique RCT selected comes from developing countries, showing no effect of a prenatal maternal nutrition supplementation of lipids with any neurodevelopmental outcomes at age 2 years, while environmental factors accounted for most of the observed differences. The results suggest the need to consider confounders even in settings where malnutrition is a common condition and any type of supplementation is usually considered as positive. The authors conclude that "a multisectoral approach is needed to maximize opportunities to improve children's early development." Two observational studies (one as review) from rich, well-developed settings underline negative associations between the maternal consumption of ultra-processed foods (UPFs) in pregnancy and later developmental measures in middle childhood. A poor environmental setting cannot be excluded from observational studies, in a cause-reverse relationship, mainly due the lower cost of UPF compared to whole, fresh foods. Finally, two observational papers on fatty acids have been included, out of the usual long-chain polyunsaturated fatty acids (LC-PUFA) issue, and focused on trans-fatty acids (TFA, showing negative associations even at long term) and short-chain fatty acids (SCFA, positive associations for propionic acid at short term), respectively, and developmental achievements. Experimentally, the role of total fat intakes is controversial and possibly underinvestigated as far as brain development. On the whole, more research on the role of fats and supposed "minor" fatty acid families is actually needed on the role in neurodevelopment, besides the overinvestigated role of PUFA and LC-PUFA.

Iodine

A scoping review of iodine and fluoride in pregnancy in relation to maternal thyroid function and offspring neurodevelopment

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https://pubmed.ncbi.nlm.nih.gov/36796438/

Micronutrients: iodine and fluoride
Setting: Europe, Asia (mostly)
Associations: unclear
Study: scoping review
Treatment/methods: Scoping review of the literature on iodine and fluoride exposure during pregnancy and their individual effects on thyroid function and offspring neurodevelopment. Just one study has been found associating both the exposures.
Age-related associations: Fluoride intake might interfere with iodine status and adversely affect thyroid function during a critical intrauterine period of brain development, but more studies are needed, for sure.

Prenatal iodine supplementation and early childhood neurodevelopment: the PoppiE trial – study protocol for a multicentre randomised controlled trial

Best KP[1,2], Gould JF[1,2], Makrides M[1,2], Sullivan T[1,3], Cheong J[4,5], Zhou SJ[6], Kane S[5,7], Safa H[8,9], Sparks A[10], Doyle LW[7,11], McPhee AJ[1], Nippita TAC[12,13], Afzali HHA[14], Grivell R[15], Mackerras D[16], Knight E[1,3], Wood S[17,18], Green T[1,2]

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BMJ Open 2023;13:e071359
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Micronutrient: iodine
Setting: Australia
Effects: ongoing study up to 24 months of age
Study: RCT
Treatment/methods: A total of 754 women (377 per group) less than 13 weeks' gestation with an iodine intake of ≥165 µg per day from food have been randomized to receive either a low iodine (20 µg per day) multivitamin and mineral supplement or an identical supplement containing 200 µg per day (amount commonly used in prenatal supplements in Australia), from enrolment until delivery. Neurodevelopment of infant will be assessed using the Cognitive Scale of the Bayley-IV and behavioral and emotional development of infants using the Infant Toddler Social Emotional Assessment.
Age-related effects: Ongoing study, effects on children of 24 months of age

Comments: The role of iodine (I) deficiency in maternal thyroid function and offspring neurodevelopment is well known. Effects of iodine on cognition are however underestimated, particularly in well-developed countries. The first review highlights the possible interference of fluoride (F) on maternal iodine status, with a consequent adverse association with the thyroid function during a critical prenatal period of brain growth. Since both iodine and fluoride may be prescribed to pregnant women, further data are needed to define recommendations for iodine intake and fluoride exposure for pregnant women. The second article is a protocol of an RCT trial to evaluate maternal iodine supplementation during pregnancy and its role on early childhood neurodevelopment. The study is the first RCT to investigate childhood neurodevelopmental outcomes following reduced prenatal iodine supplementation in an iodine-sufficient population living in Australia.

Vitamin B_{12} and Related Compounds

Association between maternal choline, fetal brain development, and child neurocognition: systematic review and meta-analysis of human studies

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https://pubmed.ncbi.nlm.nih.gov/36041182/

Micronutrient: choline
Setting: mostly well-developed countries
Effects/association: yes
Study: systematic review and meta-analysis
Treatment/methods: A total of 30 articles have been selected (including case-control studies, RCT, and observational studies) addressing neural tube defects (NTDs) and associations between prenatal and early postnatal choline intake, brain development, and neurocognitive function of children.
Age-related effects/associations: Low maternal choline intake/circulating serum total choline in early pregnancy was associated with a 36% higher odds ratio for NTDs. In general, RCTs providing up to 1 g choline per day to women during the second part of the pregnancy showed favorable effects on few neurocognitive domains of the child.

Maternal choline supplementation: a potential therapy for developmental manganese exposure?

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bioRxiv 2023 Jun 26;2023.06.23.546356. DOI: 10.1101/2023.06.23.546356. Preprint
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https://pubmed.ncbi.nlm.nih.gov/37425833/

Micronutrient: choline
Setting: animal studies
Effects: partial
Study: RCT
Treatment/methods: Starting at gestational day 3, pregnant dams were given standard diet or diet with additional choline throughout gestation and lactation until offsprings were weaned. Pups were exposed orally to 0 or 50 mg Mn/kg per day during early postnatal life. In adulthood, animals were tested in the five-choice serial reaction time task and the Montoya staircase task, to assess impulsivity, focused and selective attention, behavioral reactivity to errors or omission of an expected reward, and sensorimotor function.
Age-related effects: The maternal choline supplementation (MCS) was partially effective in protecting against Mn-induced deficits, particularly in the domains of attentional function and behavioral reactivity (at 12–24 hours after birth). Collectively, these findings demonstrate that MCS may hold promise as nutritional intervention to protect against the neurotoxic impacts of elevated Mn exposure. These findings, taken with evidence from other studies demonstrating the benefit of MCS to offspring and the fact that ~90% of women consume less than the adequate intake of choline, inform the recommendation that MCS should be considered for pregnant women.

Associations between maternal folate status and choline intake during pregnancy and neurodevelopment at 3–4 years of age in the Alberta Pregnancy Outcomes and Nutrition (APrON) study

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Micronutrient: folate and choline
Setting: Canada
Associations: no
Study: prospective cohort study (APrON)
Treatment/methods: Maternal-child pairs (n = 309) from the APrON study have been enrolled. During the second trimester of pregnancy, maternal red blood cell folate was measured from blood samples and choline intake was estimated using a 24-h dietary recall. Their children's neurodevelopment was assessed using the Wechsler Preschool and Primary Scales of Intelligence – Fourth Edition[CND], NEPSY-II language and memory subtests, four behavioral executive function tasks, and the Movement Assessment Battery for Children – Second Edition.
Age-related associations: Maternal folate status and choline intake during the second trimester of pregnancy were not associated with children's intelligence, language, memory, or motor outcomes at 3–4 years of age; however, their interaction may have an influence on children's executive functions.

Maternal vitamin B_{12} status during pregnancy and early infant neurodevelopment: the ECLIPSES study

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Micronutrient: Vitamin B_{12}
Setting: Spain
Associations: yes
Study: prospective cohort study (ECLIPSES)
Treatment/methods: A total of 434 mother-infant pairs from the ECLIPSES study have been enrolled, to examine maternal vitamin B_{12} status at the beginning and end of pregnancy and the neurodevelopmental outcomes of infants 40 days postpartum using the Bayley Scales of Infant Development-III (BSID-III, cognitive, language, and motor skills).
Age-related associations: Medium maternal first-trimester vitamin B_{12} levels (312 to 408 pg/mL, tertile 2) were associated with better neonatal performance in the motor, gross motor, language, and cognitive skills with respect to tertile 1 (<312 pg/mL), at 40 days after birth. The probability of obtaining a neonatal motor, gross motor, and receptive language score >75th percentile was significantly higher also in the tertile 2 group.

Comments: Neural tube defects (NTDs) still occur among some women who consume 400 μg of folic acid for prevention. Since intakes of methyl donors and other micronutrients involved in one-carbon metabolism may further protect against NTDs, we have considered together papers on B_{12}, folate, and choline. Within this context, a positive influence on neurodevelopment is biologically plausible.

In the first paper, the authors underline the association between maternal choline intake and child neurocognition/neurodevelopment. Despite limitations of available trials and observational studies, higher maternal choline intakes may be associated with better child achievements and should be considered in pregnancy and lactation since because most young women are not achieving the reference intake of choline. Furthermore, maternal choline supplementation shows neuroprotective effects too in rodent model. The last two studies reported here show limited associations of maternal folate and choline intake in the second trimester of gestational age (GA) and positive effects of moderately higher maternal vitamin B_{12} levels in the first trimester of GA on neurocognitive functions at either long (3–4 years ages) or short (40 days) term, respectively. A higher degree in homogeneity study designs is recommendable, to derive practical suggestions on time of intakes and outcomes to suggest appropriate dietary recommendations to mothers in pregnancy.

Other Nutrients

Maternal vitamin D levels during pregnancy and offspring psychiatric outcomes: a systematic review

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Micronutrient: vitamin D
Setting: mostly developed countries
Associations: partial
Study: systematic review
Treatment/methods: Systematic searches have been conducted using MEDLINE, Embase, PsychINFO, and Web of Science for studies to examine the associations between maternal vitamin D levels, measured as circulating 25(OH)D levels in pregnancy or at birth, and offspring neuropsychiatric and psychiatric outcomes. Twenty-nine studies have been included.
Age-related effects: A small amount of evidence shows associations between prenatal vitamin D deficiency and autism spectrum disorders. When studies with larger sample sizes and stricter definitions of vitamin D deficiency were considered, positive associations of vitamin D deficiency were found for attention deficit/hyperactivity disorder and schizophrenia.

Neuroprotective role of lactoferrin during early brain development and injury through lifespan

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Micronutrient: lactoferrin
Setting: mostly animal studies
Associations: yes, for biologic plausibility
Study: narrative review
Treatment/methods: In this narrative review, the role of several nutrients during neurodevelopment has been investigated, particularly focusing on lactoferrin in experimental studies, underlying its presence in human milk and the biological plausibility on brain functions.
Speculation: New evidence, mostly on experimental basis, indicates that early neuroprotective pathways modulated by lactoferrin could prevent neurodegeneration through anti-inflammatory

and immunomodulatory processes. At present, the study supports speculations about functional effects of lactoferrin on the immune response (the same as vitamin D, for instance) on neurodevelopment too.

Comments: In the narrative review on vitamin D, 29 studies have been considered and the author found positive associations of low maternal vitamin D levels with attention deficit/hyperactivity disorder and schizophrenia in the offspring. The findings could have important implications for public health, as vitamin D deficiency can be readily prevented with vitamin supplements. The second narrative review underlines the potential role of lactoferrin during a period of high cerebral vulnerability, speculating on effects to ensure optimal neurodevelopment, to be confirmed in humans too. Since there is general agreement on the positive effects of either vitamin D or lactoferrin on immune responses, positive effects of both compounds on brain development could support the hypothesis of a shared collaborations between two main integrated networks, that is, the immune and the nervous system, respectively, possibly deriving from a close origin at the level of embryonic tissues.

Gut Microbiome

Maternal anxiety, depression and stress affects offspring gut microbiome diversity and bifidobacterial abundances

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Brain Behav Immun 2023;107:253–264
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Nutrient related: infant microbiome
Setting: well-developed area (California)
Associations: yes
Study: longitudinal study

Treatment/methods: In the pre- and postnatal period, maternal stress, anxiety, and depression have been assessed with standardized instruments (the OASIS, PHQ, and PSS, respectively) and maternal inflammatory cytokine levels analyzed. Offspring microbiome have been characterized by using full-length 16S sequencing on infant stool samples.
Age-related associations: The diversity and composition of the infant stool microbiome between 5 and 13 months of age are associated with maternal anxiety, depression, and stress metric levels both during pregnancy and the postpartum.

Mechanisms of maternal diet-induced obesity affecting the offspring brain and development of affective disorders

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Nutrient related: infant microbiome
Setting: animal experiments and humans mostly in well-developed countries (North Europe, Australia)
Associations: yes
Study: review (at preclinical and clinical level)
Treatment/methods: Overview of preclinical and clinical studies investigating mechanisms of maternal diet–induced obesity and association between maternal obesity, microbiome, and altered behavioral outcomes in children
Age-related associations: Current literature supports preclinical evidence that the maternal microbiota is associated with offspring development and behavior. Clinical studies have shown associations between childhood maltreatment with altered neurobiology and behaviour. The gut microbiome may act as a key modifiable, and therefore treatable feature of the relationship between maternal obesity and the offspring and infant brain function.

Comments: These selected studies focused on maternal and infant/offspring microbiome composition and possible associations with development. Specific microbial taxa involved in maintaining proper brain and immune function are lower in those born to mothers with mental health disorders, and, at the same time, a direct modification of the maternal microbiota seems to be associated with metabolic and/or mood disorders in the offspring. Once more, the collaboration between an immune-related system (microbiota composition) and brain function may be hypothesized.

Dietary Habits

Children with lower ratings of executive functions have a greater response to the portion size effect

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Nutrient related: portion size
Setting: well developed (Pennsylvania)
Associations: yes
Study: prospective longitudinal study
Treatment/methods: Parental ratings of child executive functions (EFs) from the Behavior Rating Inventory of Executive Function 2 (BRIEF2) and children's measured food intake across four meals to assess intake in response to increasing portion size
Age-related associations: EFs moderated the portion size effect such that lower, including Behavioral (BRI) and Emotional (ERI), indices were associated with increases in intake as portions increased. As amount of food increased, children in the lowest functioning tertiles increased intake by 35% and 36%, respectively, compared to children in the higher tertiles, at 7–8 years of age, independent of child and parent weight status. Accordingly, an intervention on EF behaviors could help children to moderate excess intake in response to large portions of energy-dense foods.

Is adherence to the Mediterranean diet associated with good sleep duration in primary-school children?

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Front Pediatr 2022;10:959643
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Nutrient related: Mediterranean diet (MD)
Setting: Italy
Effects: yes

Study: cross-sectional study
Treatment/methods: The "adherence to the MD" in association with the quality of sleep has been poorly investigated in children from the primary school. In Italian primary school children, the association has been indagated through questionnaires administered to mothers and derived from the Italian version of the KidMed index.
Age-related associations: For children with a good sleep duration, the odds ratio of a poor-to-moderate adherence to the MD was very low, with an average score of 0.282 (95% CI, 0.109–0.681, $p < 0.05$), at 6 years of age.

Are dietary patterns related to cognitive performance in 7-year-old children? Evidence from a birth cohort in Friuli Venezia Giulia, Italy

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Nutrient related: dietary patterns (DPs)
Setting: Italy
Effect: partial
Study: cross-sectional study
Treatment/methods: Dietary patterns were identified through a principal component factor analysis based on 37 nutrients from children's 3-day dietary records. The Wechsler Intelligence Scale of Children (WISC-IV) test provided measures of cognitive performance, including the full-scale intelligence quotient (FSIQ) and single index scores.
Age-related associations: No significant relationships were observed with the FSIQ score; positive associations were found between the "Seafood" DP and Verbal Comprehension Index or Perceptual Reasoning Index. The "Meat and Potatoes" and "Dairy Products" DPs were inversely associated with the Verbal Comprehension Index and Processing Speed Index scores, respectively, in children aged 7 years.

Unfavorable behaviors in children run in packs! Dietary and non-dietary modulators of attentional capacity

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https://pubmed.ncbi.nlm.nih.gov/36558423/

Nutrient related: breakfast
Setting: Germany
Association: partial
Study: cross-sectional study (CogniDROP intervention study)
Treatment/methods: Children performed a simple computerized Visual Attention Task and answered a questionnaire about behavioral patterns, i.e., skipping breakfast on a school day, frequency of physical activity (PA) outside school, and nighttime sleep.
Age-related associations: Almost 11% of children, at 10–11 years of age, (grade 5–6 of school in Germany) left home in the morning without breakfast, more than 9.5% of children reported poor sleep quality, 24.9% slept less than the recommended 9 h, and girls were insufficiently physically active. Sleep duration, bedtime, and PA correlated with skipping breakfast. Better sleep quality was positively related to reaction time in the Visual Attention Task. Skipping breakfast in the morning seems to be associated with other unfavorable habits.

Comments: Dietary patterns and associations with neurodevelopment and behavior are an emerging area of interest, according to the interpretation that we do not eat foods, but whole foods, varying in composition, and within the wide diversity of local dietary patterns. Food form and tradition, based on local resources, are consistent also with the concept of *sustainable nutrition*. Adequate portion size at meals, eating breakfast, adherence to healthy local models of diet such as the Mediterranean diet, and eating fish show associations with favourable scores of functional developmental achievements, including good sleeping habits. Reverse causality cannot obviously be excluded, based on prospective and cross-sectional studies (considering parents' socioeconomic status, instruction achievement, and lifestyle).

Foods and Nutrients

Macronutrient intake during infancy and neurodevelopment in preschool children from the EDEN mother-child cohort

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Nutrient: macronutrient
Setting: France
Effect: no
Study: prospective cohort study (EDEN study)
Treatment/methods: Macronutrient intake was assessed by 3-day food records at 12 months of age. Neurodevelopment was assessed using the French version of the Ages and Stages Questionnaire (ASQ) and the French version of the Wechsler Preschool and Primary Scale of Intelligence – Third Edition.
Age-related associations: Macronutrient intake at 12 months was not associated with neurodevelopmental scores in children at 3 and 5–6 years. No association was found between polyunsaturated fatty acid intake and overall neurodevelopmental scores, after accounting for multiple testing.

Nutrient trajectories during infancy and their associations with childhood neurodevelopment

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Nutrient: trajectories of macronutrient intake
Setting: Singapore
Effects: partial
Study: prospective cohort study (GUSTO study)
Treatment/methods: One-day food records were collected to assess dietary intakes, while Bayley Scales of Infant and Toddler Development-III and Kaufman Brief Intelligence Test-2 were conducted to assess child neurodevelopment.
Age-related associations: Protein, total fat, and carbohydrate intake trajectories from 6 to 12 months of infancy had significant but heterogeneous and even opposing associations with childhood language and motor development, while dietary fiber intake trajectory was positively associated with fine motor development at age 24 months. Total energy trajectory showed no significant associations with neurodevelopment outcomes. No associations were found between nutrient trajectories and neurodevelopment outcomes at 54 months of age.

Defining the relationship of gut microbiota, immunity, and cognition in early life – a narrative review

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Nutrient: microbiota
Setting: narrative review (experimental and human studies)
Effects: yes
Study: review
Treatment/methods: A comprehensive literature search was conducted in March 2022 across databases including Google Scholar, PubMed, EMBASE, and Cochrane.
Age-related effects: Gut microbes influence neurogenesis, myelin formation, and immune and cognitive functions. While limited, evidence shows how gut microbiota affects innate and adaptive immunity as well as cognition. This review underlines the need for increased awareness of gut microbiota's role in health, particularly given the observed impacts during the first 1,000 days of life.

New perspectives on the associations between blood fatty acids, growth parameters, and cognitive development in global child populations

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Nutrients: fatty acids
Associations: yes
Setting: global, focusing on low- and middle-income countries – Africa, Asia
Study: narrative review
Treatment/methods: Comparison of polyunsaturated fatty acid (PUFA) levels between global child populations; PUFAs and growth parameters; PUFAs and cognitive development; highly unsaturated fatty acids, growth parameters, and cognitive development
Age-related associations: It would be beneficial to utilize a unified approach to collect and measure fatty acids, focusing on levels of those predictive of, or indicating, malnutrition. The observed data could reflect the children's nutritional status and also aid in the direct comparison between values in comparative studies. The observations could help to develop appropriate interventions to reverse essential fatty acid deficiency during sensitive developmental periods, with the aim to promote proper growth and cognition throughout childhood, adolescence, and adulthood.

Comments: The selected studies reflect the absolute need (in this case) to collect data on the role of macronutrient intakes, microbiota, and fatty acids at a global level (in either well-developed and developing countries). The intakes here collected concern the most relevant nutrients and nutrient-related topics (macronutrients, microbiome, and long-chain fatty acids). We should ensure the access to intakes of major nutrients able to sustain growth and neurodevelopmental achievements for all children throughout the world. The heterogeneity and the paucity of data and associations now available indicate to concentrate efforts toward this direction. As final observation, the last paper reported here reinforces the hypothesis of a close relationship between the immune function and cognition in the first stages of life, with a mediatory effect of the infant microbiome.

Overview: Independent roles of single nutrients, compounds, foods, and dietary patterns starting from the maternal-fetal/infant dyad up to later childhood on cognitive functions represent hot topics. Available data are mainly derived from well-developed, rich, Western countries, but more knowledge from developing countries is needed to plan effective nutritional strategies. Most study designs are highly heterogeneous, whichever the setting, preventing to draw conclusive remarks. To disentangle the role of nutrients and/or diet on cognition in a short time, the usual sentence, "more data are needed from well-done RCTs with adequate sample size," should be supported, or even overcome, by newer methodological and analytical approaches such as those derived from machine learning models.

Conflict of Interest Statement

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Author Contributions

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Nutrition and Growth in Chronic Diseases

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Introduction

Nutrition plays a pivotal role in enabling adequate growth and achieving the full growth potential. This optimal growth requires proper intake of macro- and micronutrients and hormonal axis that acts in its full capacity without interruption. Unfortunately, in chronic diseases, children suffer from inadequate intake of nutrients and insufficient utilization of energy and nutrients, while inflammation interferes with the proper action of hormonal stimuli. For this chapter, we have selected and reviewed 12 leading articles published over the last year, evaluating different nutritional and growth aspects in some major chronic diseases of childhood: celiac disease, cystic fibrosis, inflammatory bowel disease, and chronic kidney disease. These articles are a selected sample of manuscripts published this year on the interplay between chronic disease, nutrition, and growth and are an appetizer for the reader to dive into this intriguing aspect of nutrition and growth.

Key articles reviewed for this chapter

Celiac Disease

Factors associated with low bone mineral density at the time of diagnosis in children with celiac disease
Çamtosun E, Varol Fİ, Güngör Ş, Selimoğlu MA
J Clin Res Pediatr Endocrinol 2023;15:62–68

Nutrient deficiencies in children with celiac disease during long term follow-up
Kreutz JM, Heynen L, Vreugdenhil ACE
Clin Nutr 2023;42:1175–1180

Nutritional imbalances in Polish children with coeliac disease on a strict gluten-free diet
Szaflarska-Popławska A, Dolińska A, Kuśmierek M
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Inflammatory Bowel Disease

Can we rely on resting metabolic rate equations? Large variance in Crohn disease pediatric patients
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Sex-specific pathways lead to statural growth impairment in children with Crohn's disease
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J Pediatr 2022;249:75–83.e1

Growth after menarche in pediatric inflammatory bowel disease
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Chronic Kidney Disease

Associations of longitudinal height and weight with clinical outcomes in pediatric kidney replacement therapy: results from the ESPN/ERA Registry
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Pediatr Nephrol 2023;38:3435–3443

Evaluation of height centile growth patterns compared with parental-adjusted target height following kidney transplantation
Ng NSL, Gajendran S, Plant N, Shenoy M
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Celiac Disease

Factors associated with low bone mineral density at the time of diagnosis in children with celiac disease

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Comments: The association between celiac disease (CeD) and poor bone health is well reported, and in children and adolescents, it is manifested as reduced bone mineral density (BMD) in newly diagnosed CeD [1]. The etiology may be multifactorial combining intestinal and nonintestinal factors, including malabsorption of macro- and micronutrients, as well as increased production of pro-inflammatory cytokines causing bone turnover and remodeling imbalance [2, 3].

In this study by Çamtosun et al. [4], 86 newly diagnosed children with CeD (mean age 8.06 ± 4.08 years) were retrospectively evaluated for BMD and possible risk factors. BMD *Z*-scores were calculated according to both chronological age (CA) and height age (HA).

The BMD *Z*-score according to CA was found to be ≤ -2 in 26.7% of the patients, and the BMD *Z*-score according to HA was found to be ≤ -2 in 12.8%. A positive correlation was found between the BMD *Z*-score CA and both weight-for-age and height-for-age *Z*-scores (r_S: 0.373 and 0.380, respectively). When BMD was evaluated based on HA, no association was found between BMD and clinical parameters (presenting symptoms), laboratory parameters (celiac serology levels, vitamins and micronutrients levels, liver enzymes), or histopathological stage. A positive correlation was only found with age at diagnosis (r_S: 0.269).

The correction of BMD *Z*-score according to HA is especially important in children with short stature, which was prevalent in one-third of this cohort. These findings emphasize the importance of BMD result interpretation, because without this correction, BMD *Z*-scores might be misleadingly low [5]. Nonetheless, this study highlights the significant prevalence of reduced BMD in children with a new diagnosis of CeD, regardless of clinical symptoms of malabsorption or different laboratory parameters, emphasizing the current lack of established risk factors in this population.

Nutrient deficiencies in children with celiac disease during long term follow-up

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Nutritional imbalances in Polish children with coeliac disease on a strict gluten-free diet

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Risk of obesity during a gluten-free diet in pediatric and adult patients with celiac disease: a systematic review with meta-analysis

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Comments: Gluten-free diet (GFD) is currently the sole treatment for celiac disease (CeD), and lifelong strict adherence is recommended to avoid persistent intestinal inflammation and CeD-related complications. As gluten-containing grains serve as the primary grain in most cereal-based foods nowadays, following a GFD often involves major changes in dietary patterns, and can be challenging for patients and families alike.

The 2022 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) position paper on the management and follow-up of children and adolescents with CeD [6] recommends testing for micronutritional status at time of diagnosis, correcting deficiencies, and continued follow-up until normalization of celiac serology. Although maintaining GFD results in improvement of most nutritional deficiencies in patients with CeD, there is some concern about the nutritional balance of GFD, especially when relying on commercial and processed gluten substitutes [7–9].

In the current study by Kreutz et al. [10], serial data were retrospectively analyzed from 130 children with CeD, followed by a single center in the Netherlands. Follow-up visits were performed from 3 months after CeD diagnosis, and then yearly up to 10 years. The mean age at diagnosis was 6.2 years, with 59% girls. Celiac antibody normalization was documented in 66, 75, and 77% of patients after 1, 2, and 3 years of GFD, respectively. Overall, no vitamin B_6 deficiency or hypocalcemia was found. Low levels of ferritin, vitamin D, vitamin B_{12}, folate, and zinc were present in 22, 21, 2, 4, and 8% of measurements, respectively. The frequency of a ferritin and iron deficiency decreased over time in this cohort. Low ferritin prevalence declined from 36% at 3 months after GFD initiation to 9.5% after 5 years of follow-up. Vitamin D insufficiencies and deficiencies seemed to arise randomly with no specific trend over time. The frequencies of deficiency in vitamin B_{12}, folate, and zinc were too sporadic to identify a trend overtime. As some of the deficiencies observed after 3 months were also reported at the time of diagnosis, that could have influenced the pooled results of this study. Moreover, there were some missing data with limited availability of measurements per nutrient.

Szaflarska-Popławska et al. [11] reported data from a single-center prospective cohort in Poland, comparing 48 children with CeD on a strict GFD (mean duration 5.02 ± 3.87 years) with 50 children without CeD. The study included anthropometric measurements, 3-day food records, and laboratory tests of hemoglobin, calcium, magnesium, folic acid, and vitamin B_1, B_2, B_6, and B_{12} level. Compared to children with no CeD, children with CeD had significantly lower levels of serum calcium, vitamin B_1, and folic acid. Mean calcium, folic acid, and vitamin D intake was below the dietary recommendations in both CeD and non-CeD subjects. The mean dietary intake of proteins and carbohydrates in the CeD group exceeded the recommended levels, but was similar to controls. The prevalence of underweight was significantly higher, and the prevalence of overweight/obesity was significantly lower among patients with CeD, compared to controls. There was no effect of GFD duration on the intake of most macro- and micronutrients, except for vitamin B_1 that declined overtime.

The systematic review and meta-analysis by Barone et al. [12] aimed to assess the prevalence of body mass index (BMI) categories at disease presentation and their variation in patients on a GFD overtime, among children and adults with CeD. A total of 45 studies (22 in pediatric patients and 23 in adults) met the eligibility criteria and were included in the meta-analysis. The analysis included 7,959 patients with CeD and 20,524 healthy individuals. The mean BMI of patients at diagnosis was significantly lower than that of controls, with an overall reduced risk to be in the overweight/obese category at diagnosis. During follow-up on a GFD, patients with CeD significantly increased their mean BMI. The pooled prevalence of patients in different BMI categories during a GFD showed that the percentages of patients in the overweight and obese categories remained similar to those observed at disease presentation: 13 and 7%, respectively. The data demonstrated that only 9% have changed to a higher BMI category during GFD; however, it was significantly more common in adults than in children (12 vs. 6%, respectively, p = 0.013). However, 20% of the entire population changed from the overweight/obese category to the underweight/normal category, more commonly in the pediatric vs adult population (34 vs. 8%, respectively, p < 0.001). The results emphasize that after initiation of GFD, an increase in BMI category is significantly more frequent in adults, while the opposite is observed in children. Overall, this current meta-analysis shows that GFD does not increase the risk of developing overweight or obesity.

All three publications highlight the importance of a comprehensive dietary consultation when initiating GFD in patients with CeD, in order to guide how to not only eliminate gluten from the diet but also maintain a balanced and nutritionally adequate diet supporting normal body weight and growth and avoiding long-term nutritional deficiencies.

Cystic Fibrosis

Trajectories of early growth and subsequent lung function in cystic fibrosis: an observational study using UK and Canadian registry data

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Early life growth trajectories in cystic fibrosis are associated with lung function at age six

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Nutritional status and lung function in children with pancreatic-sufficient cystic fibrosis

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Comments: Cystic fibrosis (CF) is strongly associated with poor nutritional status, caused by the underlying genetic mutation, malabsorption and decreased nutrient intake, higher energy needs and increased losses, as well as recurrent infections [13]. As poor nutritional status is associated with lower lung function and long-term morbidity and mortality, optimizing nutritional status and adequate growth is one of the most important management goals in CF. Moreover, CF guidelines recommended monitoring patients' growth trajectories aiming for target weight-for-length *Z*-score or body mass index (BMI) *Z*-score (before and after the age of 2 years, respectively) above the 50th percentile, to prevent disease progression [14].

In the first study, Macdougall et al. [15] have used data from two national CF registries (1,974 patients from the United Kingdom and 791 patients from Canada) to characterize the association between weight trajectories in early childhood (1–5 years) and lung function at age 6 years. In both registries, weight-for-age *Z*-score at age 1 year (intercept) and change over time (slope) were associated with forced expiratory volume in 1 s percent predicted (FEV_1pp) later at 6 years. At 1 year, an increase in one weight-for-age *Z*-score was associated with an increase of 3.2–3.8 FEV_1pp, and an increase of one BMI *Z*-score was associated with an increase of 3.7–4.1 FEV_1pp. These results are consistent with previous studies and highlight the importance of nutrition status of patients with CF during infancy, considering later disease outcomes.

In the second study [16], Psoter et al. have used a group-based trajectory modeling to characterize early life growth patterns and their association with lung function at the age of 6 years, utilizing data from the Cystic Fibrosis Foundation Patient Registry in the United States. Patients ($n = 6809$) were divided to six groups by growth trajectories: three groups that began with growth parameters >50th percentile, termed "always high," "gradual decliner," and "rapid decliner," and three groups that began with growth parameters <50th percentile, termed "rapid riser," "gradual riser," and "always low." Trajectories consistently above the 50th percentile (always high and gradual decliner) had higher FEV_1pp at age 6 compared to trajectories consistently below the 50th percentile (always low), with nearly 10% difference in FEV_1pp between always high and always low trajectory. The different trajectory classes were associated with sex, ethnicity, newborn screening, and pancreatic function.

The third interesting study by Madde et al. [17] focuses on patients with CF without pancreatic insufficiency (PI). It is known that only 10–15% of children with CF retain pancreatic sufficiency (PS) overtime, and hence this subgroup is poorly represented in CF cohort studies. As PI leads to intestinal malabsorption, it is a major cause of malnutrition and poor growth in children with CF. This is the first large cohort study to evaluate the association between BMI and FEV_1pp in children with PS-CF, and to compare to the association in PI-CF. The study included children diagnosed with CF before the age of 2 years, who had data on BMI and FEV_1pp after the age of 6 years. Overall, 424 children with PS-CF and 7,849 children with PI-CF were identified from the Cystic Fibrosis Foundation Patient Registry. Pancreatic status was defined based on pancreatic enzyme replacement therapy.

The association between BMI and FEV_1 differed significantly by pancreatic status: each 10% higher BMI was associated with 2% higher FEV_1pp in PI-CF, compared to just 0.9% in PS-CF. Moreover, in PS-CF, overweight/obesity was associated with decreasing FEV_1pp. In addition, the decline in lung function between 6 and 20 years of age was evaluated according to pancreatic status and BMI groups. In the PI cohort, all BMI groups showed a significant decline in FEV_1 with age (−1.34% per year), with steeper decline in the lower BMI groups. However, among the PS cohort, the FEV_1 decline with age was modest (−0.48% per year), and mean FEV_1pp remained >90% by age 20 years regardless of BMI group. This study highlights the importance of maintaining good nutritional status in CF to benefit lung function over time, in both pancreatic subgroups; however, the effect in PS patients is more modest. Finally, the finding of a decrease in FEV_1 among PS patients with BMI above 85th percentile should be taken into consideration in this specific group, to avoid overweight and obesity, which could be detrimental to lung function.

Inflammatory Bowel Disease

Can we rely on resting metabolic rate equations? Large variance in Crohn disease pediatric patients

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Comments: Resting metabolic rate (RMR), which represents resting energy expenditure, is the energy required by the body in resting conditions and is the largest component of the total energy expenditure. Multiple factors can impact RMR, including age, sex, genetic factors, and endocrine function. However, it has become clear that fat-free mass (FFM) is the best single determinant of RMR, accounting for the majority of its between-subject variance [18].

The RMR characteristics in children with inflammatory bowel disease (IBD), and specifically Crohn disease (CD), are poorly established. A reduction in RMR in CD [19] can result from anorexia or food avoidance, as well as from poor nutritional state that may alter body composition. On the contrary, RMR may also be elevated in patients with IBD due to active inflammation and increased metabolic requirements. Determining resting energy expenditure and total energy requirements is particularly important in children with IBD, both for nutritional management and rehabilitation, as well as for specific treatments in CD using enteral nutrition.

In this study by Marderfeld et al. [20], RMR was evaluated in pediatric patients with CD using an indirect calorimetry, and the results were compared to estimated RMR using the Schofield equation (which considers the patient's age, sex, weight, and height). FFM was measured by bioelectrical impedance analysis. The study included 73 children, aged 7–18 years, with various stages of CD. Of the total, 29% patients were underweight, 2.8% were overweight, and 9.7% had short stature at the time of assessment. Children with moderate/severe disease score had lower weight *Z*-scores, lower body mass index *Z*-scores, and lower RMR. No association was found between RMR/FFM ratio and disease activity. There was a wide variance in RMR in the study population, and the ratio of measured RMR to estimated RMR varied between 0.7 and 1.5. This ratio was higher than 1 in the mild CD group and highest among patients in remission. This study highlights the wide variation and the limited ability to predict RMR in this population, implying that accurate individual assessment using the appropriate equipment and trained personnel is needed for establishing energy needs in CD.

Sex-specific pathways lead to statural growth impairment in children with Crohn's disease

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Growth after menarche in pediatric inflammatory bowel disease

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Comments: Growth impairment is common in pediatric inflammatory bowel disease (IBD), mostly in children with Crohn disease (CD) [21, 22]. The growth impairment is a result of multifactorial pathophysiology combining the effects of the chronic inflammatory process, chronic malnutrition, and treatment-related factors including the use of corticosteroids. The growth hormone (GH)–insulin-like growth factor 1 (IGF-1) axis is negatively affected by the elevation of pro-inflammatory cytokines, causing GH resistance and impaired linear growth [23, 24]. In addition, chronic malnutrition may occur due to decreased dietary intake and intestinal malabsorption, as well as an increase in energy requirements. The impact of pediatric-onset IBD on final height in modern era, however, is debatable [25–27].

It has been suggested that statural growth impairment is more common in male patients with CD than in females [28], although other studies showed different results [27]. This current study by Gupta et al. [29] prospectively examined serum cytokines and hormone levels in pediatric CD multicenter longitudinal cohort. Height *Z*-score difference was computed as height *Z*-score based on chronological age minus height *Z*-score based on bone age.

Overall, 122 children with CD (63% male) were included. The magnitude of the mean height *Z*-score difference was greater in females (±0.94) than males (−0.87 vs. −0.27; $p = 0.005$), indicating growth was better in females. Specific serum cytokine levels did not differ by sex; however, different associations were found between specific cytokines and hormones levels (evaluated as bone age *Z*-scores) in males and females. Among females, negative associations were identified between interleukin (IL)-8 and IL-12p70 with gonadotropin; IL-8, IL-12p70, and interferon-γ with sex hormone; and IL-8 and interferon-γ with IGF-1. Among males, IL-1β and IL-6 were negatively associated with IGF. These findings suggest that the primary pathway of growth impairment is the GH–IGF-1 axis in males and the hypothalamic-pituitary-gonadal axis in females. It also highlights the need to include specific serum inflammatory proteins in risk models to establish which males and which females are at greatest risk for growth impairment in CD.

In the second study by Salguero et al. [30], the impact of age at menarche on final height was investigated in female patients with IBD diagnosis prior to menarche. The study identified 146 patients (76% with CD), with mean age at diagnosis of 10.7 years, mean age at menarche of 14.3 years, and mean age upon final height of 19.6 years (with no significant differences between patients with CD and ulcerative colitis).

There was a significant negative correlation between age of menarche and magnitude of linear growth after menarche. Patients who had menarche before 12.5 years had significantly increased linear growth than those who had menarche after 13.5 years. However, there was a significant positive association between age at menarche and final height, but not the final height *Z*-score.

Delayed menarche (age ≥ 14.5 years) occurred in 41 and 35% of patients with CD and ulcerative colitis, respectively, and was associated with maternal delayed menarche and with lower weight *Z*-score at diagnosis.
Growth impairment was associated with surgery before menarche, jejunal disease, low mid-parental height, hospitalization (only for CD), and recurrent corticosteroid or anti–tumor necrosis factor alpha therapy. The study highlights the multifactorial etiology for growth impairment in IBD, irrespective of age at menarche.

Chronic Kidney Disease

Associations of longitudinal height and weight with clinical outcomes in pediatric kidney replacement therapy: results from the ESPN/ERA Registry

Bonthuis M[1,2], Bakkaloglu SA[3], Vidal E[4], Baiko S[5], Braddon F[6], Errichiello C[7], Francisco T[8], Haffner D[9], Lahoche A[10], Leszczyńska B[11], Masalkiene J[12], Stojanovic J[13], Molchanova MS[14], Reusz G[15], Barba AR[16], Rosales A[17], Tegeltija S[18], Ylinen E[19], Zlatanova G[20], Harambat J[21], Jager KJ[1,2]

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Comments: There is a significant high burden of morbidity and mortality among pediatric patients with end-stage kidney disease on kidney replacement therapy (KRT, i.e., hemodialysis, peritoneal dialysis, hemofiltration, and hemodiafiltration) [31]. Short stature in these patients is common, reported in approximately 40% [32, 33], and results from numerous factors including genetic alternations, malnutrition, growth hormone re-

sistance and delayed puberty, inflammatory process, and chronic acidosis [34]. Previous studies have suggested association between both extremes of body mass index (BMI), as well as short stature, and higher mortality risk in pediatric KRT [35, 36].
In this study, Bonthuis et al. [37] have evaluated the association of height and BMI with clinical outcomes, in a large European cohort of pediatric patients with KRT (33 countries, 11,873 patients). During a median follow-up of 4.7 years, short stature was observed in 42.7% of patients, whereas only 1.4% had tall stature. Most patients had normal weight (67.7%), followed by overweight (17.9%), obesity (9.6%), and underweight (4.9%). Patients with both short and tall statures had a lower likelihood of receiving kidney transplantation compared to patients with normal stature, as were patients with underweight compared to patients with normal weight. Moreover, kidney transplant recipients with short or tall statures had an increased risk of graft failure. All-cause mortality was associated with short stature, underweight, and obesity. Specifically, patients with short stature showed an increased risk of death from infections. The risk of cardiovascular mortality was also higher among patients with short stature, underweight, overweight, and obesity.
The major limitation of this registry-based observational study is the inability to determine causality, while the course of disease and complications could influence growth and weight, rather than the opposite direction. In addition, in children with end-stage kidney disease, characteristics of the underlying disease could influence anthropometric indices, including genetic etiologies and height or fluid balance and weight. Nevertheless, this is an important large-scale multicenter study that demonstrates that extremities of height and BMI are associated with poorer outcomes in children with KRT. These results suggest the need for a multidisciplinary approach in this population, including close nutritional management, possibly growth hormone treatment in persistent short stature, and lifestyle modification.

Evaluation of height centile growth patterns compared with parental-adjusted target height following kidney transplantation

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Comments: Kidney transplantation (KT) is effective in correcting metabolic and endocrine disorders contributing to uremic growth failure in children with end-stage kidney disease. However, catch-up growth following KT has been infrequently observed [38].
In this current study, Ng et al. [39] have evaluated growth of children after KT, compared to their target height, which was defined as parental-adjusted height standard deviation score (SDS) within ±1.55. Height SDS was assessed at the time of transplant and at 1, 2, 3, and 5 years following KT. The study included 48 children (29% females), with median age of 5.3 years at first KT. Children with conditions known to have genetic predisposition to short stature were excluded. At the time of KT, 60% of children had normal height (SDS ≥ −1.88), with only 48% children achieving their target height

based on adjusted parental height. The percentage of children achieving normal height increased to 75, 83.3, 86.5, and 88% at 1, 2, 3, and 5 years following KT, respectively. The percentage of children achieving target height increased to 68.8, 73.8, 73, and 80% at 1, 2, 3, and 5 years after KT, respectively ($p = 0.01$). Although children aged <6 years at KT had the highest prevalence of growth impairment at time of transplant, they also demonstrated the most significant increase in the proportion of children achieving their target height at 1, 2, 3, and 5 years after KT (72, 81.8, 85, and 92.3%, respectively, $p = 0.023$). Only 16% of children with short stature at the time of KT received growth hormone therapy after KT. Maintenance steroid immunosuppression was given to 42% of the cohort at latest follow-up; however, it was not associated with failure to achieve target height. The only identified risk factor of failure to achieve target height was duration of dialysis >12 months.

Although this study reports encouraging results as the vast majority of children attained normal height during the first 5 years after KT, still 20% had not achieved their target height. Since dialysis prior to KT was identified as the major risk factor for failure to achieve target height, a focus should be given to obtain adequate growth prior to KT in children with advanced kidney disease.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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

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Introduction

Healthy nutrition during the first years of life is critical for optimal growth and development in the short and long term. Growth patterns in infancy are influenced by feeding practices and have been investigated extensively. Papers examining early nutrition and its effects on growth, body composition, and later obesity cover a range of topics including maternal diet, breast milk (BM) components, formula and especially the protein content in formula, and complementary feeding (CF) with studies conducted in low- and middle-income countries as well as high-income countries. This year we have focused on BM composition, protein content in formula, and sources of protein in CF in relation to growth and risk of later obesity. The studies are mainly from high-income countries, but a study from a middle-income country is also included. We have selected 10 publications published between July 1, 2022 and June 30, 2023, which we find of special interest. The original articles comprise randomized controlled trials, observational studies, and reviews and have been grouped into three categories: BM composition and infant growth (two studies), protein content of infant formula and infant growth (four studies), and CF and growth (four studies).

Key articles reviewed for this chapter

Breast Milk Composition and Infant Growth

Metabolizable energy content of breastmilk supports normal growth in exclusively breastfed Icelandic infants to age 6 months
Thorisdottir B, Odinsdottir T, Gunnlaugsson G, Eaton S, Fewtrell MS, Vázquez-Vázquez A, Kleinman RE, Thorsdottir I, Wells JC
Am J Clin Nutr 2023;118:468

Associations between breast milk intake volume, macronutrient intake and infant growth in a longitudinal birth cohort: the Cambridge Baby Growth and Breastfeeding Study (CBGS-BF)
Olga L, Vervoort J, van Diepen JA, Gross G, Petry CJ, Prentice PM, Chichlowski M, van Tol EAF, Hughes IA, Dunger DB, Ong KK
Br J Nutr 2023;130:56

The Effect of Protein Content and Quality of Infant Formula on Infant Growth

Low-protein infant formula and obesity risk
Kouwenhoven SMP, Muts J, Finken MJJ, Goudoever JBV
Nutrients 2022;14:2728

Protein and growth during the first year of life: a systematic review and meta-analysis
Milani GP, Edefonti V, De Cosmi V, Bettocchi S, Mazzocchi A, Silano M, Pietrobelli A, Agostoni C
Pediatr Res 2023;94:878–891

Infant feeding choices during the first post-natal months and anthropometry at age seven years: follow-up of a randomized clinical trial
Demmelmair H, Fleddermann M, Koletzko B
Nutrients 2022;14:3900

The effect of goat-milk-based infant formulas on growth and safety parameters: a systematic review and meta-analysis
Jankiewicz M, van Lee L, Biesheuvel M, Brouwer-Brolsma EM, van der Zee, Szajewska H
Nutrients 2023;15:2110

Complementary Feeding and Growth

A randomized, controlled trial of a Nordic, protein-reduced complementary diet in infants: effects on body composition, growth, biomarkers, and dietary intake at 12 and 18 months
Johansson U, Öhlund I, Lindberg L, Hernell O, Lönnerdal B, Venables M, Lind T
Am J Clin Nutr 2023;117:1219

Quantity and source of protein during complementary feeding and infant growth: evidence from a population facing double burden of malnutrition
Kittisakmontri K, Lanigan J, Wells JCK, Manowong S, Kaewarree S, Fewtrell M
Nutrients 2022;14:3948

Impact of complementary feeding on obesity risk
Kittisakmontri K, Fewtrell M
Curr Opin Clin Nutr Metab Care 2023;26:266–272

Do vegetarian diets provide adequate nutrient intake during complementary feeding? A systematic review
Simeone G, Bergamini M, Verga MC, Cuomo B, D'Antonio G, Iacono ID, Mauro DD, Mauro FD, Mauro GD, Leonardi L, Miniello VL, Palma F, Scotese I, Tezza G, Vania A, Caroli M
Nutrients 2022;14:3591

Breast Milk Composition and Infant Growth

Metabolizable energy content of breastmilk supports normal growth in exclusively breastfed Icelandic infants to age 6 months

Thorisdottir B[1,2], Odinsdottir T[2], Gunnlaugsson G[3], Eaton S[4], Fewtrell MS[5], Vázquez-Vázquez A[5], Kleinman RE[6], Thorsdottir I[1,2], Wells JC[5]

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Comments: It is inevitable that energy content of breast milk (BM) contributes to infant growth. The content is often assessed by the bomb calorimetry technique or by adding energy contributions from each macronutrient. These methods do not take into account that not all energy is utilized as energy for the infant, i.e., a fraction of the energy goes to bacterial growth, maturation of gut and immune function or is simply not absorbed in the infant's gut. Thus, energy availability through BM may be overestimated when used in assessments of infant growth.

The study by Thorisdottir et al. uses data from an Icelandic prospective longitudinal study investigating breastfeeding and BM content among infants exclusively breastfed (EBF) for 6 months. The authors used the doubly labeled water (DLW) technique to estimate both metabolizable energy content of BM, BM intake, and infant body composition to assess whether energy content in BM is sufficient to support infant growth up to 6 months. Using this method, total energy expenditure and subsequently BM intake, BM content of metabolizable energy, and fat mass (FM) and fat-free mass (FFM) were assessed. The authors estimated the metabolizable energy to 2.61 kJ/g BM, which they concluded is in accordance with current literature (2.56–2.60 kJ/g). Importantly, the comparable literature uses either bomb calorimetry or direct measurements of macronutrient contributions to estimate BM content without consideration of absorption. Thus, these methods may be considered valid for estimation of energy availability for the infant through BM. Furthermore, Thorisdottir et al. estimated a mean BM intake of 983 ± 169.7 g per day at 6 months, which was also considered comparable to current literature using the same method. However, a recent systematic review and meta-analysis investigating BM intake throughout lactation reported a mean BM intake of 729 mL per day (95% confidence interval: 713–745) at 6 months [1]. Considering a density of BM of 1.03 g/mL [2], the 983 g per day corresponds to 954 mL per day, which is higher than the intake reported in the systematic review and meta-analysis. However, this review included studies using the 24-h test weighing method (n = 113), deuterium dilution (n = 49), and/or both (n = 5). These methods have their limitations and especially the most used 24-h test weighing may underestimate BM intake due to underreporting of feeds. In this regard, another strength of the study by Thorisdottir et al. is the avoidance of a BM sample normally used to determine energy content. The method of milk sample collection influences the composition of BM especially with regard to macronutrient such as fat. Hindmilk samples, in comparison to foremilk samples, have higher fat concentration, which increases energy content and may overestimate the total energy availability for the infant. A recent systematic review investigating BM composition and later risk of obesity emphasized that (1) the protocol of BM sample collection and analyses as well as (2) estimation of BM intake are essential methodological challenges to consider in order to end up with representable and comparable data [3]. Despite using the DLW technique which is a strength to the present study, comparing the results with results from other studies using a BM sample and/or other BM intake assessments may be difficult due to the abovementioned challenges.

Regarding infant growth and body composition, infants in the present study showed weight, length, and body mass index Z-scores within the normal range compared to the WHO reference. This supports that EBF for 6 months and the BM content were sufficient to support healthy growth. Furthermore, FFM Z-score was 0.22, while FM Z-score was 0.78, with only the latter being significantly different from 0. This further indicates that EBF up to 6 months increased fat deposition, but not FFM accretion, compared to a reference population from the United Kingdom.

Despite a low sample size of n = 27 infants and only n = 22 infants included in the final analyses, the study uniquely investigates energy sufficiency in BM up to 6 months postpartum using the DLW technique. The results support WHO recommendations of EBF up to 6 months with regard to infant growth and body composition. The study uses techniques for assessing both infant body composition and BM composition with high accuracy, which strengthens the study conclusions. However, the results should be compared to infants EBF up to 4 months or a group of infants receiving infant formula or mixed fed to further investigate the influence of infant feeding mode on growth. In addition, the Icelandic study was conducted in a high-income setting with participants highly motivated to breastfeed, and thus, the study should be replicated in other settings in order to improve generalizability of the results.

Associations between breast milk intake volume, macronutrient intake and infant growth in a longitudinal birth cohort: the Cambridge Baby Growth and Breastfeeding Study (CBGS-BF)

Olga L[1], Vervoort J[2], van Diepen JA[3], Gross G[3], Petry CJ[1], Prentice PM[1], Chichlowski M[3], van Tol EAF[3], Hughes IA[1], Dunger DB[1,4], Ong KK[1,4,5]

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Comments: The study by Olga et al. investigates whether breast milk (BM) intake and/or BM composition are associated with measures of infant growth (weight, length) and adiposity (skinfold thickness) within the first year of life. The study includes 94 mother-infant dyads, although only 46 pairs had complete data. BM intake was assessed using the dose-to-mother deuterium method, BM composition (triglycerides [fat], lactose [carbohydrate], and protein) was assessed in postfeed (i.e., hindmilk) samples collected 6 weeks postpartum, and anthropometry was assessed repeatedly up to 12 months of age. The main findings of the present study include positive associations between BM carbohydrate and protein and early (0–6 weeks) adiposity gains, while an inverse association was found between BM carbohydrate and protein and late (3–12 months) adiposity gains. The authors did not find any association with BM fat concentration or intake and suggest that BM carbohydrate and protein may be a stronger predictor for later growth and adiposity.

The study highlights an important challenge within the research area of breastfeeding and BM composition, namely whether to use nutrient concentrations or intakes in associations with infant outcomes. The choice of exposure may rely in the research question being asked. However, using BM nutrient intakes may be more prone to reverse causality as it is more plausible that infant growth outcomes predict BM intakes (i.e., a larger infant drinks more milk) compared to BM concentrations (i.e., a larger infant changes BM composition). Thus, it is worth to consider adjusting for the total energy intake as this might confound the results when using BM intake as exposure. This is rarely described in the literature and should be considered in future studies. In line with the discussion of the previous study, the method of milk sample collection in the present study has limitations, which is also highlighted by the authors. The postfeed samples have higher concentrations of fat, and possibly protein, compared to prefeed samples or samples from full expressions [4]. As a result, concentrations might be overestimated, which could result in the lack of associations for fat. For protein, an overestimation of protein concentration could explain the inverse association seen during 3–12 months. As mentioned above, the method of BM sample is one of the main challenges within BM research, and standardized protocols are needed to align studies for comparison of results.

Regarding infant growth assessment, weight is potentially influenced by hydration status and/or weight loss shortly after birth, where infants born with a higher birth weight seem more prone to a higher weight loss compared to infants with normal or low birth weight [5]. In addition, length measurements are less accurate at earlier ages, e.g., birth length. Furthermore, positive associations between BM nutrient intakes and infant growth during 0–6 weeks might reflect breastfeeding practice, i.e., successful breastfeeding establishment early on compared to problematic breastfeeding establishment. In summary, assessment of very early growth (0–6 weeks) may be less accurate to estimate adiposity, whereas assessment from 3 to 12 months might be more reliable as the inaccuracy has likely been evened out.

As the authors emphasize, the long-term consequences of more rapid versus slower growth within the first 12 months are yet unestablished. Generally, it is recognized that a high weight gain or adiposity among EBF infants is not a concern, while overweight among infants receiving formula can be concerning. Although the evidence is sparse, high protein concentration in formula has been associated with rapid weight gain and thus contributes to the risk of later overweight in certain studies. In this regard, accurate assessment of BM protein concentration becomes highly important to either support or reject these findings.

One of the main strengths of the study is the use of dose-to-mother deuterium method to assess BM intake. The authors argue that a correlation between BM protein concentration and BM intake is not confounding the results of the positive association between BM protein intake and infant growth. While this argument seems valid in relation to the results, several other factors such as infant age and/or sex may influence the correlation between BM macronutrient concentration and BM intake. As most statistical approaches combine few variables of interest, many more seem to influence the complete picture of BM composition, BM intake, and infant outcomes. Novel statistical approaches such as machine leaning techniques could be interesting when exploring this area.

The Effect of Protein Content and Quality of Infant Formula on Infant Growth

Low-protein infant formula and obesity risk

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Comments: This review by Kouwenhoven et al. provides a very detailed and interesting discussion about many relevant aspects of how low-protein infant formula may influence obesity risk in the infants. Although the paper does not include a systematic review, the authors conclude that there is a need for new trials examining protein quality and effects of a further reduction in protein content. Also, there is a need to explore the possible underlying mechanisms behind how early protein intake can influence infant growth and later health.

The level of protein intake is of course a key issue, but they conclude that it is only when the protein intake is very high, that there is an effect on obesity risk. They mention the very high protein content of 4.4 g per 100 kcal given from age 6–12 months in the high-protein group in the European ChildHood Obesity Project (CHOP) study, whereas the content in the control group in other studies was 2.7 g per 100 kcal or lower [6]. At the 6-year follow-up, the high-protein group had considerably higher body mass index and a risk of obesity, which was more than two times higher than the low-protein group [7]. The systematic review by Milani et al., which is discussed below, also supports that only very high protein intake has an effect on growth.

An important methodological aspect is also mentioned in the review. Macronutrient content of the infant formula may influence intake of formula. A low-protein content may result in a higher intake, as the infant may compensate for the lower protein content. Therefore, it is important to measure volume intake, if possible, by using stable isotopes.

It is also mentioned that a high protein intake early in life might have a negative effect on kidney function. In the CHOP study, kidney size was increased in the high-protein group compared to the groups with lower protein formula or breastfeeding at 6 months [8]. Interestingly, a new study followed up a subgroup from the CHOP study, including participants from Spain and Poland, at the age of 11 years. They examined the long-term effect of high protein intake on kidney volume [9]. Those in the high-protein group still had higher kidney volume, which could have negative long-term effects as pointed out by the authors. Furthermore, those in the high-protein group also had a higher systolic blood pressure, which was partially mediated by the kidney volume. However, at the age of 11 years, there was no difference in weight, length, and body mass index.

In the review, it is mentioned that a higher content of plant proteins in infant formula will benefit the environment. However, it is also underlined that using plant-based protein in infant formula involves lower protein quality and possibly impaired digestibility, which have to be addressed.

At the end of the review, there is a brief description of an intervention study the authors were planning. It is a large multicenter long-term randomized controlled trial of infants born to overweight or obese mothers, as these infants have an increased risk of adiposity. The main outcomes are growth and body composition. The protein level of the new formula will be closer to that of BM and part of the protein will be plant based to support environmental sustainability.

Protein and growth during the first year of life: a systematic review and meta-analysis

Milani GP[1,2], Edefonti V[2], De Cosmi V[2], Bettocchi S[1], Mazzocchi A[2], Silano M[3], Pietrobelli A[4,5], Agostoni C[2,6]

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Comments: This systematic review and meta-analysis by Milani et al. provides a good overview of the current status within the field of protein intake and infant growth. They compared the growth effect of interventions with cow's milk formulas with different protein content during the first year of life. In the meta-analysis they included intervention studies which compared infant formula with a high (>2.0 g/100 kcal) versus low (≤2.0 g per 100 kcal) protein content. They identified 12 papers for the systematic review and 5 of them were also included in the meta-analysis. There was considerable heterogeneity, and the overall conclusion of the systematic review with the 12 studies was that there were no clear-cut effects of protein intake on growth. The conclusion from the meta-analysis of the five studies with formula interventions was also that it does not support an effect of protein intake on growth. Interestingly, the ChildHood Obesity Project (CHOP) study, which showed major differences in growth up to the age of 6 years [7], was not included in the meta-analysis because one of the inclusion criteria was that the intervention with formula should have started before 30 days after birth. In the CHOP study, start of intervention was allowed until the age of 2 months.

Infant feeding choices during the first post-natal months and anthropometry at age seven years: follow-up of a randomized clinical trial

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Comments: This paper is a 7-year follow-up of the Belgrade-Munich Infant Milk Trial (BeMIM) study. In this study, healthy term infants were randomized to protein-reduced infant formula with alfa-lactalbumin-enriched whey and long-chain polyunsaturated fatty acids (1.89 g protein/100 kcal) or a control formula with 2.30 g protein/100 kcal. The formula was given from 30 to 120 days after birth and a breastfed group was included as reference. At 4 months of age, infants in the low-protein formula group had a higher length gain compared to the control group, which could be because of the enrichment. At follow-ups at 4 and 7 years, there were no differences in anthropometry between the groups. So, this result is in line with most of the studies comparing formulas with a relatively small difference in protein content. However, of special interest was that the insulin-like growth factor 1 (IGF-1) values at 4 months were significantly associated with weight, height, and body mass index Z-scores at 7 years. Thus, how early diet influences IGF-1 levels might have a long-term programming effect on growth.

The effect of goat-milk-based infant formulas on growth and safety parameters: a systematic review and meta-analysis

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Comments: There has been an increasing interest in the use of goat milk infant formula, and it has been approved as an infant formula by the European Food Safety Authority. In the present review, it is stated that production of goat milk requires lower feeding requirements and lower production cost compared to cow milk. There is also some evidence that there is an increased rate of gastric emptying compared to cow milk, which could influence stool frequency. Using strict inclusion criteria, 4 randomized controlled trails where a goat milk formula was compared to a cow milk-based formula were included. All four studies were funded by industry. There were no significant differences in weight, length, or head circumference between the groups. In the review, there are no information on or discussion of the amount of protein content in the formulas. Going through the 4 papers included, there were no major difference in the amount of protein comparing goat and cow milk formula in three of the studies. However, in the largest study, the protein content in the goat formula was about 20% higher corresponding to 1.7 versus 1.35 g/100 kcal in the cow milk formula [10]. In that study, the weight gain in the goat milk group tended to be higher. However, it was not discussed in the original paper if the difference could be caused by the higher protein content. Based on the four studies in the meta-analysis, it is concluded that goat milk formula is safe and well tolerated. Stool frequency was not different between the groups.

A randomized, controlled trial of a Nordic, protein-reduced complementary diet in infants: effects on body composition, growth, biomarkers, and dietary intake at 12 and 18 months

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Quantity and source of protein during complementary feeding and infant growth: evidence from a population facing double burden of malnutrition

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These papers are commented on together below.

Comments: There is a growing interest in plant-based foods worldwide, especially plant protein due to environmental concerns and possible health benefits. A report by the EAT-Lancet Commission on healthy foods and sustainable food production recommend a predominantly plant-based diet and low amount of animal source foods for reduction of greenhouse gases and preventing noncommunicable diseases [11]. The protein intake is very critical for growth and should be balanced. During the complementary feeding (CF) period, the protein intake increases typically from 5% to about 15% percent of energy (%PE). In high-income countries (HICs), the protein intake is often of animal origin and, according to the "early protein hypothesis," high amounts of early protein would stimulate growth, especially fat tissue, which could lead to later increased risk of later obesity [12]. In low- and middle-income countries (LMICs), there is a risk of undernutrition and stunting due to a low intake of high-quality protein. The effect of different protein sources, e.g., plant-based protein, dairy protein, and meat protein, on growth is not widely investigated during the CF period. We have selected two publications examining the association between the source and quantity of protein intake and growth during infancy and early childhood in a HIC (Sweden) and LMIC (Thailand). The papers contribute substantially to the understanding of the importance of protein sources, which is becoming more and more crucial because of sustainability.

In the study by Johansson et al., the Nordic diet with reduced protein intake was investigated in a randomized controlled trial. The Nordic diet is characterized by a high intake of plant-based foods including fruit, vegetables, legumes, and whole grains and a reduced intake of red meat, meat products, and saturated fat [13]. They included 250 healthy term-born infants between 4 and 6 months of age (baseline). They were randomized to either a Nordic diet group (NG) or a conventional group (CG), which followed the Swedish dietary guidelines. Children in the NG received taste portions of Nordic fruit, berries, and vegetables following a schedule from 4 to 6 months. From 6 to 18 months, the parents were offered recipes on Nordic homemade baby food and protein-reduced baby food products. Measurements were performed at baseline, 12, and 18 months including body composition by deuterium dilution as primary outcome, anthropometry, biomarkers, and dietary intake. They found no difference between groups regarding body composition, growth, or energy intake, but lower levels of insulin-like growth factor 1 (IGF-1) and blood urea nitrogen, used as an adherence biomarker, and higher levels of folate, also an adherence biomarker in the NG group compared to the CG. The biomarkers complied with the dietary intake. For both groups, weight-for-age and BMI-for-age *Z*-scores were around 0.6–0.8 at 12 and 18 months, which seemed to support healthy growth. The protein intake at 12 and 18 months was 9.2 and 12.4 %PE for the NG group and 12.5 and 14.6 %PE for the CG group, respectively. Intake of fruit and vegetables were 42 and 45% higher in the NG group at 12 and 18 months though it declined in both groups by 14–16% over time. The energy intake was the same in both groups. It is notable that the protein intake is rather low for both groups. At 12 months, it is just below the Nordic nutrition recommended range of 10–15 %PE for the NG group and below 15% for the CG, which has previously been reported as an upper limit for protein intake in early childhood to avoid altered growth [14]. The authors suggest that the low protein intake in the CG may partly explain why no difference in body composition or growth was found. Another issue is higher attrition in the NG (24%) compared to the CG (12%), which may reduce the power. Furthermore, the high dropout rate in the NG underlines that adopting new and unfamiliar foods and eating habits even in highly educated, motivated, and well-resourced families is not straightforward, and the study illustrates that this should be addressed in the transition to a more plant-based and sustainable diet. Nevertheless, this well-conducted randomized controlled trial suggests that reducing protein intake and increasing plant-based foods during the CF period are safe and do not compromise growth. It seems beneficial to introduce local and plant-based foods during the CF period as this age is important for accepting new flavors and textures and thus may contribute to favor a more plant-based diet later in life in HIC. Future studies should examine the long-term health effects of protein-reduced diets with more plant-based protein in early childhood and how it can be implemented in the daily life.

The other study by Kittisakmontri et al. focused on protein intake during CF in relation to the double burden of malnutrition (DBM), describing the coexistence of under- and overnutrition, which is often present at different time points. Optimizing CF might contribute to overcome this problem. From a prospective cohort, 145 healthy term infants between ages 4 and 6 months mainly from middle-class families in Thailand were included. Infant growth and dietary assessments took place at 6, 9, and 12 months and a blood sample was taken at 12 months. Households with underweight infants and overweight/obese parents indicating DBM were present in 6.2% of the families. The protein intake increased markedly from 6 to 12 months, i.e., PE% was 7.8, 12.6, and 15.6% at 6, 9, and 12 months, respectively. Furthermore, protein intake was positively associated with weight and BMI *Z*-score, but not associated with length. The main protein sources were animal based and mostly from infant formula. The protein sources differed in associations with growth. While plant-based protein showed no associations, dairy protein showed stronger associations with weight-related growth outcomes than nondairy animal-based protein. Also, dairy protein intake was positively correlated with IGF-1 levels.

It is interesting that the protein intake at 12 months in this study is actually higher than in the Swedish study mentioned above, both compared to the NG and the CG, and as the authors note also above the recommendations in Thailand and by WHO [15, 16]. This indicates that CF in some middle-income countries is altered toward a more Western diet with higher intake of animal source protein. This may also challenge the transition to a more sustainable diet globally. The authors suggest an upper limit of protein intake for international recommendations taking the increase of overweight in childhood in many LMICs into consideration. The Thai study lacks a more detailed description of the plant-based protein consumed at this age. It is mentioned that is was mainly cereals, which may be of lower nutritional quality than protein from legumes and grains, which was part of the Nordic diet in the Swedish study. Shifting toward a more plant-based diet during CF should comprise high-quality protein and adequate micronutrients to secure optimal growth and development. The follow-up time for the Thai study is very short and therefore information on long-term effects of amount and source of protein are lacking. These studies illustrate the different kind of problems middle- and high-income settings may experience in relation to achieving high-quality and sustainable foods during the CF period. Finally, future studies should be conducted or repeated in diverse settings regarding socioeconomic conditions to be able to assess if the findings are valid in general.

Impact of complementary feeding on obesity risk

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Comments: This review is distinguished by giving a short and accurate overview of the latest literature regarding various aspects of complementary feeding (CF) on obesity risk including timing, composition, and feeding methods. The authors have preferably included systematic reviews; however, the majority of studies are observational, implying the risk of confounding. Whereas the timing of introduction of CF does not seem to influence the risk of later obesity, the content seems more critical. Most evidence concerns protein consumption in Western populations. The protein content especially in formula, which constitutes a large part of the diet particularly in the beginning

of the CF period, may contribute to rapid weight gain and later risk of obesity [17, 18]. Studies on the effects of other sources of protein, both plant-based and nondairy animal-based protein, are limited and need to be investigated further. Likewise, there is limited evidence for the effect of sugar and sugar-sweetened beverage, but as the authors conclude, the intake should be low as there is no nutritional requirement. The authors also include studies on methods of CF. Regarding baby-led weaning, there is limited evidence of the effect on growth and obesity risk, and findings from the studies are inconclusive. On the other hand, responsive feeding, which includes education of the parents to respond adequately to the infant's signs for appetite and satiety, seems to support healthy growth in some studies. However, the duration of the studies was relatively short and studies with longer follow-up are warranted.
Another strength of the review is that it also underlines the shortcomings of the present knowledge and the need for high-quality studies conducted in both high-income countries and low- and middle-income countries. As commented above, the double burden of malnutrition in low- and middle-income countries should be given special attention in relation to CF.

Do vegetarian diets provide adequate nutrient intake during complementary feeding? A systematic review

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This article is also reviewed in the chapter by Yackobovitch-Gavan et al. [this vol., pp 1–21].

Comments: The WHO recommends exclusive breastfeeding for the first 6 months of life and partly breastfeeding to continue up to 2 years or beyond. After 6 months, the breast milk no longer contains enough energy and nutrients to support optimal growth and development of most infants. The infant needs, in addition to milk, food with a higher nutrient content in this important age with high growth and development. The complementary feeding (CF) period where the infant starts to get solid food is a critical period with a high demand of nutrients and the WHO strongly recommends a healthy diet during infancy containing all essential nutrients [19].

In the last decades, vegetarianism has become more popular in many Western countries. However, only few reliable studies on the prevalence in Western countries exist. Children tend to follow their family's dietary pattern, and it is expected that the prevalence of infants, children, and adolescents eating vegetarian diets will increase.

The attitudes among nutrition societies in Western countries have been very different, where many support the use of vegetarian diets at all life stages if nutrient supplements are taken when needed. Contrary, other countries recommend that diet should include all food groups, including animal-based food especially during pregnancy, lactation, and childhood. In cases where vegetarian or vegan diet is followed in children, supplementation and medical monitoring are recommended to discover any nutrient deficiency. With growing interest for vegetarian and vegan diets, more pediatricians are asked by parents if these diets are safe.

The first 1,000 days are especially vulnerable and important for later metabolic and neurodevelopmental outcomes. The authors therefore consider a systematic review of literature on the outcomes of vegetarian/vegan diet during CF of paramount importance. The aim of this systematic review was to examine the findings on the influence of vegetarian diets during CF on different outcomes like growth, neurodevelopment, risk of wasting and/or stunting, overweight, and obesity. Additional outcomes are risk of deficiency of vitamins and micronutrients, infections, development of type 2 diabetes, and hypertension later in life. The authors planned to include (1) intervention and observational studies from industrialized countries, (2) studies where intervention or exposure was present during the CF period (6–24 months of age), and (3) studies comparing vegetarian diets (lacto-ovo vegetarian, vegan, macrobiotic, and others, completely free of animal protein) and healthy diets (e.g., Mediterranean diet). The authors underline that the comparator/control should be healthy CF including food of animal origin.

Only four studies (one guideline, one systematic review, and two studies) were included, indicating that there are very few studies with infants/children during the CF period evaluating vegetarian and vegan diets. For obvious ethical reasons, there were no intervention studies assessing the impact of nonsupplemented vegetarian/vegan diets. However, there are several observational or case studies investigating the influence on individual nutrient deficiency. Especially, deficiency in vitamin B_{12}, DHA, and iron can cause irreversible damage of the neurosystem. Furthermore, vegetarian and vegan diets during CF period have no documented positive effects on noncommunicable disease. The authors concluded that current evidence suggests that risks of critical micronutrient deficiency or insufficiency and growth retardation are high when exposed to vegetarian or vegan diets and these are therefore not considered safe.

Consequently, vegetarian and vegan diet cannot be recommended during the CF period. Following the authors' conclusion, pediatricians and nutritionists should be very aware of infants where parents insist to give their child vegetarian diets with very little or no food of animal origin. This is also in accordance with an ESPGHAN Position Paper from 2017 [20] stating that these children should have supplementation ensuring sufficient supply of vitamin B_{12}, vitamin D, iron, zinc, folate, n-3 long-chain unsaturated fatty acids, and protein, and their growth and neurodevelopment should be monitored close. It should be ensured that parents understand the serious consequences of not following these advices.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Pregnancy: The Impact of Maternal Nutrition on Intrauterine Fetal Growth

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Introduction

This chapter of the 2024 edition of the yearbook on *Nutrition and Growth* reviews important manuscripts published between July 2022 and June 2023 addressing the association of maternal nutrition during pregnancy and intrauterine fetal growth. In the current edition, ten studies with high impact were chosen. The studies demonstrate the influence of macro- and micronutrition on maternal diet and of different diet composition on fetal growth. We also included several animal studies, which should be noticed due to major findings through basic science or strict methodology in areas without enough evidence among human studies. We hope that this chapter will help us improve the medical care we can provide to our patients and will also give researchers new ideas for future studies.

Key articles reviewed for this chapter

Human Studies

Periconceptional maternal protein intake from animal and plant sources and the impact on early and late prenatal growth and birthweight: the Rotterdam Periconceptional Cohort
van Zundert S, van der Padt S, Willemsen S, Rousian M, Mirzaian M, van Schaik R, Steegers-Theunissen R, van Rossem L
Nutrients 2022;14:5309

Maternal association of maternal HDL2-c concentration in the first trimester and the risk of large for gestational age birth
Huang D, Zhu H, Zhu Y, Dang Q, Yang Q, Zhang Y, Cai X, Zhao X, Liang N, Wang H, Yu H
Lipids Health Dis 2022;21:71

Dietary protein intake during pregnancy and birth weight among Chinese pregnant women with low intake of protein
Yang J, Chang Q, Tian X, Zhang B Zeng L, Yan H, Dang S, Li YH
Nutr Metab (Lond) 2022;19:43

Does trans fatty acid affect low birth weight? A randomised controlled trial
Alamolhoda SH, Asghari G, Mirabi P
J Obstet Gynaecol 2022;42:2039–2045

Effect of iodine nutrition status on thyroid function and pregnancy outcomes
Zha H, Yu L, Tang Y, Sun L, Yuan Q
Biol Trace Elem Res 2023;201:5143–5151

Exposure to ultra-processed foods during pregnancy and ultrasound fetal growth parameters
Lourenço BH, Castro MC, de Morais Sato P, Neves PAR, Vivanco E, Lima DL, Cardoso MA, MINA-Brazil Study Group
Br J Nutr 2023 May 16;1–10. doi:10.1017/S0007114523001204. Online ahead of print

Maternal seafood consumption and fetal growth: a birth cohort study in urban China
Wei Z, Li W, Lei C, Caixia A, Chuan Z, Jianqin W
BMC Pregnancy Childbirth 2023;23:253

The effect of pre-pregnancy obesity on gut and meconium microbiome and relationship with fetal growth
Cömert TK, Akpinar F, Erkaya S, Durmaz B, Durmaz R
J Matern Fetal Neonatal Med 2022;35:10629–10637

Animal Studies

Association between high-fat diet during pregnancy and heart weight of the offspring: a multivariate and mediation analysis
Wang W, Huo Y, Zhang J, Xu D, Bai F, Gui Y
Nutrients 2022;14:4237

Effect of a maternal high-fat diet with vegetable substitution on fetal brain transcriptome
Claycombe-Larson KJ, Bundy AN, Kuntz T, Hur J, Yeater KM, Casperson S, Brunelle DC, Roemmich JN
J Nutr Biochem 2022;108:109088

Periconceptional maternal protein intake from animal and plant sources and the impact on early and late prenatal growth and birthweight: the Rotterdam Periconceptional Cohort

van Zundert S[1,2], van der Padt S[1], Willemsen S[1,3], Rousian M[1], Mirzaian M[2], van Schaik R[2], Steegers-Theunissen R[1], van Rossem L[1]

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Comments: Most studies demonstrated a positive association between maternal protein intake and birth weight, but only a few of them distinguished between animal-based and plant-based proteins. Therefore, this study was conducted to determine the associations of periconceptional maternal protein (animal and plant) intake and embryonic growth. In this cohort study which includes 501 pregnancies, data were taken from the Rotterdam Periconceptional Cohort. Only women who completed periconceptional Food Frequency Questionnaire with living nonanomalous singleton pregnancies were included. The study found that periconceptional protein intake, and in particular animal source protein, was positively associated with embryonic growth. Beside one cohort study that found a nonlinear association between maternal protein intake and birth weight, other past studies showed that maternal protein intake was associated with a reduced risk of fetal growth restriction and a higher birth weight, which strengthens this study findings. An analysis including an "animal/plant protein intake" ratio showed that consuming more animal proteins relative to plant proteins was associated with increased prenatal growth and birth weight. To our knowledge, this is the first study that investigated the effect of protein sources on embryonic growth. This finding might be explained by the fact that animal proteins usually provide all essential amino acids, while plant proteins are deficient in one or more (such as lysine and threonine). It is important to consider the complex effect of maternal nutrition on prenatal growth. Therefore, residual unobserved/unknown factors might act as confounders. Future research on amino acid composition, nutrient metabolism, digestibility, and the interaction with microbiota are warranted to further investigate the association between protein sources and prenatal growth and birth weight.

Maternal association of maternal HDL2-c concentration in the first trimester and the risk of large for gestational age birth

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Lipids Health Dis 2022;21:71

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Comments: Maternal high-density lipoprotein cholesterol (HDL-c) levels throughout gestation were negatively associated with birth weight. However, whether HDL2-c concentration correlates with large for gestational age (LGA) incidence has not yet been determined. In addition, early pregnancy is a critical period for fetal development, and it is important to pay attention to maternal lipid levels during this time. In this prospective study performed in China, 549 women were evaluated and had their blood collected during 6–14 weeks of pregnancy. The study found that LGA mothers had significantly lower serum HDL-c concentrations than appropriate for gestational age (AGA) mothers and that maternal HDL-c concentration was negatively associated with the risk of LGA. Based on the difference in density, HDL can be divided into HDL2 and HDL3. Which of the two plays a critical role in fetal growth and birth weight is unclear. In the study, HDL2-c concentrations of LGA mothers were significantly lower than those of AGA mothers, but HDL3-c concentrations were similar between the groups. A logistic regression model showed that after adjusting for maternal age, prepregnancy body mass index, and parity, HDL2-c concentration was negatively correlated with the risk of LGA. As for the study limitations, it important to mention that small for gestational age infants were excluded for the evaluation of HDL2-c. Furthermore, there was no information on women's lifestyle, such as diet or physical activity. To conclude, we should consider evaluating maternal first trimester HDL2-c levels.

Dietary protein intake during pregnancy and birth weight among Chinese pregnant women with low intake of protein

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Comments: Animal studies have shown that both insufficient and excessive dietary protein intake during pregnancy produced low-birth-weight offspring. However, human observational studies on the effect of dietary protein intake during pregnancy on birth weight are inconsistent. A few studies alone have evaluated the associations of dietary protein intake from different sources and fetal growth. The current study aimed to explore the associations of different dietary protein sources with birth weight. In this population-based cross-sectional study, which was performed in China, 7,310 women were evaluated. Maternal dietary intake was collected by semiquantitative food frequency questionnaire at 0–12 months after delivery. Higher intake of dietary protein, in particular animal protein, but also from dairy products, was found to be associated with higher birth weight and lower risks of low birth weight, small for gestational age, and intrauterine growth restriction. The different effects of animal and plant protein on fetal growth may be due to differences in amino acid composition. Animal protein can provide all nine indispensable amino acids, while plant protein can be deficient in one or more indispensable proteins such as lysine or threonine. Another explanation for the effects of different sources of protein may be due to the fact that pregnant women with higher intake of animal protein may have a much better baseline protein status. Some limitations to mention are, first, the dietary information was retrospective. Second, since blood samples were not taken, the effects of amino acids status could not be evaluated. Future studies on body amino acids or protein status are still warranted.

Does trans fatty acid affect low birth weight? A randomised controlled trial

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Comments: This is a randomized controlled trial that was conducted to examine the effect of low trans-fatty acid (TFA) dietary patterns on the development of low birth weight (LBW), below 2,500 g. In the study, which was performed in Iran, 800 healthy women with singleton pregnancy, before 8 weeks and with normal body mass index, were randomized to two groups: a diet with TFA content <1% of total daily energy intake and a routine pregnancy dietary recommendation. All women received supplementation with folic acid, multivitamins, and iron. A 24-h diet log was performed at the end of each trimester. The risk of LBW in the intervention group was decreased by about 50%, with incidence of 12% in the intervention group versus 19% in the control group. Conflicting results were described in some cohorts and case-control studies, which did not demonstrate the same association between maternal TFA intake and birth weight, but with lower sample size. Several other cohorts did observe an association between higher levels of TFAs and reduced birth weight. Some limitations to mention are that there was no objective evaluation of maternal serum TFA level. Secondly and more important, the study population had a narrow intake range for industrial TFAs, which might limit the results only to specific populations that do not consume industrialized TFAs. To conclude, this novel randomized controlled trial demonstrated that by limiting the level of TFAs, we might be able to lower the rate of LBW babies.

Effect of iodine nutrition status on thyroid function and pregnancy outcomes

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Comments: Iodine is essential for synthesizing triiodothyronine (T3) and thyroxine (T4). Pregnant women are recommended to consume approximately 250 µg per day of iodine by the World Health Organization with a median urinary iodine concentration (UIC) < 150 µg/L defined as iodine deficiency during pregnancy. Whether iodine nutrition status itself could lead to adverse pregnancy outcomes was still controversial. The study aims to explore whether iodine nutrition status is correlated with thyroid function and to analyze its effect on pregnancy outcome. In this prospective study performed in China, 212 euthyroid women were evaluated between 18 and 32 weeks pregnancy. UIC/urinary creatinine (UCr) was used to evaluate the iodine nutrition status. The study found an association between UIC/UCr and the incidence of low-birth-weight infants. A low UIC/UCr was found to be a risk factor for low birth weight and was also found to be associated with higher free thyroxine and lower thyroid stimulating hormone. Lower UIC/UCr might be associated with an increased risk of autonomous production of thyroid hormone through goiters, leading to lower thyroid stimulating hormone levels. Both excessive and deficiency of iodine intake may negatively influence thyroid function, though the conjunction between the two remains contentious. Maternal iodine deficiency is known to have a long-term effect on fetal growth, especially on the nervous system. However, its short-term effect during pregnancy remains controversial. An important limitation to be mentioned is that there was no quantitative analysis of autoimmune antibodies, which could affect thyroid function and pregnancy outcomes. To conclude, it is recommended to take care of iodine supplementation during pregnancy. Also, in future studies, attention should be paid to the effects of iodine nutrition status.

Exposure to ultra-processed foods during pregnancy and ultrasound fetal growth parameters

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Comments: This study aimed to evaluate the influence of ultra-processed food (UPF) consumption on embryonic growth. It was a cohort study, including 417 women in Brazil. Participants completed structured interviews and UPF was defined within the NOVA classification system. Frequency of food group's consumption in the previous month was categorized as no/monthly/weekly/daily. Ultrasound biometry evaluation was performed at 27.5 (interquartile range: 26.9, 28.6) weeks. The study demonstrated that increased frequency of UPF consumption was negatively associated with fetal head circumference (HC) and femur length (FL). Daily maternal consumption of UPF was particularly unfavorable with significant negative differences of HC compared with the lowest frequency of UPF consumption. Those findings are supported with past studies that identified impairment of embryonic growth following exposure to higher UPF consumption. On the other hand, in the current study, a detailed dietary assessment was performed with fetal evaluation during the third trimester. Unlike another study which reported that each 1% increase in energy intake from UPF in the second trimester was associated with a 0.62% higher neonatal total body adiposity, this study could not ascertain a significant relationship between the frequency of UPF consumption and abdominal circumference (AC). There are several limitations to mention. Pregnant women who missed ultrasound examinations were from poorer households and more frequently smoked. Also, it is important to mention that the outcomes were depicted according to a single ultrasound scan, as multiple measurements in late pregnancy were not available. To conclude, negative associations between maternal UPF consumption and skeletal components of HC and FL were observed but were not apparent for AC. These findings reinforce the relevance of maternal diet in a life course approach for promoting healthier infant growth trajectories, with potential repercussions on body composition.

Maternal seafood consumption and fetal growth: a birth cohort study in urban China

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Comments: This study was aimed to examine the association between seafood consumption and fetal growth. In this cohort study, 10,179 women with singleton child were recruited in China and completed a Food Frequency Questionnaire 1–3 days after delivery. The study demonstrated that higher consumption of seafood had a beneficial effect on low birth weight, mainly driven by freshwater fish and shellfish. Among women who consumed more than 75 g of seafood/week, significant reduced rates of low birth weight were found compared to women with no or very low intakes. Gestation weight gain partially mediated the association between seafood consumption and birth weight. Those findings are supported by several previous epidemiological studies that showed that increased seafood intake was associated with increased fetal growth measures. The n-3 long-chain polyunsaturated fatty acids that widely exist in seafood promote the shift of the prostacyclin/thromboxane A balance to a more antiaggregatory and vasodilator state, which may increase the placental flow and, therefore, fetal growth. Contamination of fish has frequently been suggested as an explanation for the negative associations of fish intake with fetal growth. The differences in the associations between seafood consumption with fetal growth were probably explained by the different effects between beneficial nutrients, mainly docosahexaenoic acid, and pollutants present in each meal. One limitation is a low rate of gestational diabetes mellitus of 1.01%, which might be explained by the low living standards of the sample. The study population are less likely to have high-calorie, high-fat, and low-fiber diets, which are characteristic in areas with higher rates of gestational diabetes mellitus. Another limitation is that the nutritional assessment might be subject to recall bias. The study findings suggest to recommendation for intervention programs to improve birth outcomes through the improvement of seafood consumption.

The effect of pre-pregnancy obesity on gut and meconium microbiome and relationship with fetal growth

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Comments: The intestinal microbiota serves important physiological functions, including the absorption of dietary fats and fat-soluble vitamins, digestion of complex carbohydrates and plant-based polysaccharides, and bile acid metabolism. All these processes affect the development of obesity, and in addition, short-chain fatty acids resulting from the digestion of dietary fiber in the gut are responsible of regulating appetite. This study investigated the effects of pre-pregnancy body weight on maternal stool and newborn meconium microbiota and fetal growth. In the study, which was performed in Turkey, 20 women with normal weight before pregnancy (body mass index 18.5–24.9) and 20 obese women (body mass index >30), without any pregnancy complications, all with adequate gestational weight gain (11.5–16 and 5–9 kg) were enrolled. All women delivered vaginally and at term. Maternal stool samples were collected in the first trimester and meconium samples were collected after birth. Among the obese women, a relative abundance of Firmicutes was found with lower amount of Proteobacteria compared to normal weight women. Among the meconium samples of the newborns of pre-pregnancy obese mothers, lower abundances of Firmicutes, *Bacteroides*, and *Prevotella* and higher relative abundances of Proteobacteria were found compared to those of newborns from mothers with normal body weight. The birth weight, weight/height ratio of newborns, and maternal gut microbiota alpha diversity indices were associated. Dysbiosis occurring during pregnancy at an advanced age may be associated with an increased risk for hypertension, gestational diabetes, and pregnancy loss. The fact that type of food consumption was not considered is a limitation of the study results. The results demonstrate that pre-pregnancy body weight may influence the microbiome composition of the maternal gut in the first trimester and meconium of the newborn, though there is still a need for studies on microbiota in which variables are equalized.

Association between high-fat diet during pregnancy and heart weight of the offspring: a multivariate and mediation analysis

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Comments: Cardiac remodeling caused by maternal obesity has been found to be associated with many factors such as diet, placenta, sex, and fetal weight. However, the level of effect of these factors remains unclear. Therefore, this animal study was performed to evaluate, by mouse models, the maternal obesity and high-fat diet supplementation effect on myocardial remodeling. Twenty mice were randomly divided into 4 groups of feeding – before/during pregnancy of high-fat/normal diet. Pregnant mice were subjected to a cesarean section on day 18.5 of gestation with delivery of 97 pups. Combined with multifactorial analysis and based on gradual screening, it was found that fetal weight and a pregnancy high-fat diet were two important factors affecting heart weight/body weight (HW/BW). It was demonstrated that a pregnancy high-fat diet has a greater effect on the myocardial remodeling of offspring. A sex difference was also noted with the male offspring of the pregnancy high-fat diet mothers who had higher HW/BW. The authors of the study also performed a qRT-PCR to examine the myocardial-related indicators and they found that the genes *Nppa*, *Nppb*, and *Mef2c* were highly expressed among the pregnancy high-fat diet mice. *Nppa* and *Nppb* genes were found to play a role in the development of cardiac hypertrophy and are used as significant markers of cardiac hypertrophy. *MEF2C* is involved in cardiac morphogenesis and myogenesis and regulates the expression of cardiac proteins. The results of this study demonstrate the important influencing factors of the effect of the maternal nutrition model on fetal heart weight and HW/BW. This study also demonstrates that a high-fat diet during pregnancy, rather than before pregnancy, is more closely associated with cardiac remodeling in offspring.

Effect of a maternal high-fat diet with vegetable substitution on fetal brain transcriptome

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Comments: Both maternal high-fat diet (HFD) and low vegetable intake are associated with low birth weight. However, whether intrauterine growth restriction–associated abnormal neuronal development, caused by a maternal HFD, can be ameliorated by vegetable supplementation is still unknown. In this animal study, 2-month-old female mice were fed a diet containing either normal fat, HFD, or 45% fat substituted with 5% energy from vegetables (HF+VS) prior to and during pregnancy. Fetuses and placentas were harvested in mid and late gestation. RNA was isolated from fetal whole brains and sequenced using Illumina HiSeq. HF+VS diet prevented maternal HFD-induced decreases in placental weight at day 19. Feeding of a maternal HFD was associated with 79 differentially expressed genes, while maternal vegetable substitution was associated with 131 differentially expressed genes. The vegetable substitution diet decreased *Apold1*, *Spata2l*, and *Celsr1* expression compared to HFD. In previous studies, it was found that expression of *APOLD1* is increased in postmortem brains of human schizophrenia patients. As for *Spata2l*, there is no information about its function in the brain. *Celsr1* belongs to the adhesion receptor cadherin family of proteins, and it is expressed in the nervous system with expression upregulated in the adipose tissue of obese mice. The study's limitation is that it did not address for a specific maternal nutrient deficiency, and also it has not yet determined whether the mentioned differentially expressed genes in the fetal brain cause postnatal cognitive and behavioral alterations. In conclusion, this study suggests that vegetable supplementation might have a protective effect against abnormal placental and fetal growth due to maternal HFD.

Overall Commentary

Maternal nutrition affects fetal growth in various mechanisms. Both macro- and micronutrients during pregnancy affect fetal outcome. A balanced maternal diet, including the source of protein and the type of fat consumed, should be evaluated to improve the offspring's outcome. But we should remember that nutrition's impact is attenuated by genetic, demographic, and behavioral factors. Therefore, we need to try to achieve a personalized approach while giving medical care.

Conflict of Interest Statement

The authors report no conflict of interest.

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