World Review of Nutrition and Dietetics

Volume
128

Nutrition and Growth

Yearbook 2025

Editors
Moshe Phillip
Dominique Turck
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Berthold Koletzko

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World Review of Nutrition and Dietetics

Vol. 128

Series Editor

Berthold Koletzko Munich

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Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and PubMed/MEDLINE.

Printed on acid-free and non-aging paper (ISO 9706)
ISSN 0084–2230
e-ISSN 1662–3975
ISBN 978–3–318–07388–1
e-ISBN 978–3–318–07389–8

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp IX (DOI: 10.1159/000541844)

Preface

Linear growth, weight gain, and body composition are influenced by a complex interplay of factors, with nutrition playing a pivotal role. However, understanding the interaction between nutrition and growth remains a challenge for pediatricians, neonatologists, pediatric nutrition specialists, endocrinologists, gastroenterologists, pediatric dietitians, and other healthcare professionals caring for children.

Extensive research efforts worldwide are focused on unraveling the causes of growth failure, determining optimal dietary compositions for children's growth, and developing appropriate nutritional interventions for undernourished or malnourished children at all ages.

This yearbook aims to shed light on the intricate relationship between diet, nutrients, and growth, in health and disease, by presenting diverse clinical settings including preventive measures, optimal nutrition in health and disease, long term follow-up, and insights gained by basic research, all of these exploring the various aspects of nutrition and growth.

The experts contributing to this book have carefully selected a limited number of peer-reviewed manuscripts published between July 2023 and June 2024, offering valuable insights and commentary. While we regret not being able to include more studies due to space constraints, we hope this compilation will inspire readers to delve deeper into the field of nutrition and growth and that our comments will serve as a catalyst for increased interest and further research.

We are grateful to our associate editors for their valuable contributions and for taking the time to share their insights with our readers.

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 1–15 (DOI: 10.1159/000541845)

Malnutrition and Catch-Up Growth during Childhood and Puberty

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Introduction

The world continues to struggle with the double burden of malnutrition, characterized by the coexistence of undernutrition and overweight/obesity across populations. In 2022, over a billion people aged five and above were living with obesity, while more than half a billion were underweight. Among children under five, 148 million were stunted, 45 million were wasted, and 37 million were overweight. Despite progress in reducing stunting and wasting since 1990, global efforts are offtrack to meet the 2030 nutrition targets. Since 2000, few countries have reduced the prevalence of stunting among children under 5 years of age as dramatically as Peru, where it is estimated to have declined from a very high prevalence of 31.1% in 2000 to 10.1% in 2022, which is now considered a medium prevalence. Peru offers a successful example of reducing stunting through multisectoral interventions, particularly by addressing socio-economic inequalities. Double-duty actions, which leverage shared drivers of malnutrition, are essential for efficiently tackling both undernutrition and obesity and can be implemented through policies that focus on improving dietary guidelines,

healthcare, food systems, and social support, ensuring nutrition security across all forms of malnutrition [1].

This chapter reviews the most recent data on childhood malnutrition and catch-up growth, published between July 1, 2023, and June 30, 2024. This year's chapter primarily addresses different nutritional interventions for the treatment and prevention of malnutrition, which were assessed in several meta-analyses and clinical trials, including lipid-based nutrient supplements [2], zinc supplementation [3], protein intake in formula-fed infants [4], probiotic supplementation [5], locally produced ready-to-use therapeutic foods [6], bioactive glycans in microbiome-directed complementary food [7, 8], and L-carnitine supplementation [9]. Additionally, long-term outcomes of SAM survivors [10], the interplay between gut microbiota and childhood bone growth [11], as well as the relationship between childhood infections and linear growth [12, 13] are discussed.

Key articles reviewed for this chapter

Lipid-based nutrient supplements for prevention of child undernutrition: when less may be more
Dewey KG, Arnold CD, Wessells KR, Stewart CP
Am J Clin Nutr 2023;118:1133–1144

The effect of zinc supplementation on anthropometric measurements in healthy children over two years: a systematic review and meta-analysis
Monfared V, Salehian A, Nikniaz Z, Ebrahimpour-Koujan S, Faghfoori Z
BMC Pediatr 2023;23:414

Higher versus lower protein intake in formula-fed term infants
Gonzalez-Garay AG, Serralde-Zúñiga AE, Medina Vera I, Velasco Hidalgo L, Alonso Ocaña MV
Cochrane Database Syst Rev 2023;11:CD013758

Probiotic supplementation for promotion of growth in undernourished children: a systematic review and meta-analysis
Imdad A, Pandit NG, Ehrlich JM, Catania J, Zaman M, Smith A, Tanner-Smith EE, Zackular JP, Bhutta ZA
J Pediatr Gastroenterol Nutr 2023;77:e84–e92

Ready-to-use therapeutic foods (RUTFs) based on local recipes are as efficacious and have a higher acceptability than a standard peanut-based RUTF: a randomized controlled trial in Indonesia
Rachmadewi A, Soekarjo DD, Bait BR Suryantan J, Noor R, Rah JH, Wieringa FT
Nutrients 2023;15:3166

Bioactive glycans in a microbiome-directed food for children with malnutrition
Hibberd MC, Webber DM, Rodionov DA, Henrissat S, Chen RY, Zhou C, Lynn HM, Wang Y, Chang HW, Lee EM, Lelwala-Guruge J, Kazanov MD, Arzamasov AA, Leyn SA, Lombard V, Terrapon N, Henrissat B, Castillo JJ, Couture G, Bacalzo NP Jr, Chen Y, Lebrilla CB, Mostafa I, Das S, Mahfuz M, Barratt MJ, Osterman AL, Ahmed T, Gordon JI
Nature 2024;625(7993):157–165

A microbiota-directed complementary food intervention in 12-18-month-old Bangladeshi children improves linear growth
Mostafa I, Hibberd MC, Hartman SJ, Hafizur Rahman MH, Mahfuz M, Hasan SMT, Ashorn P, Barratt MJ, Ahmed T, Gordon JI
EBioMedicine 2024;104:105166

Effects of L-carnitine supplementation on the rate of weight gain and biomarkers of environmental enteric dysfunction in children with severe acute malnutrition: a double-blind randomized controlled clinical trial
Alam J, Fahim SM, Islam MR, Alam MA, Gazi MA, Ahmed T
J Nutr 2024;154:949–961

Long-term outcomes after severe childhood malnutrition in adolescents in Malawi (LOSCM): a prospective observational cohort study
Kirolos A, Harawa PP, Chimowa T, Divala O, Freyne B, Jones AG, Lelijveld N, Lissauer S, Maleta K, Gladstone MJ, Kerac M; for the CHANGE study collaborators group
Lancet Child Adolesc Health 2024;8:280–289

Gut microbiota in regulation of childhood bone growth
Lui JC
Exp Physiol 2024;109:662–671

Shigella and childhood stunting: evidence, gaps, and future research directions
Bagamian KH, Anderson Iv JD, Blohm G, Scheele S
PLoS Negl Trop Dis 2023;17:e0011475

Childhood growth during recovery from acute illness in Africa and South Asia: a secondary analysis of the childhood acute illness and nutrition (CHAIN) prospective cohort
Bourdon C, Diallo AH, Mohammad Sayeem Bin Shahid AS, Khan MA, Saleem AF, Singa BO, Gnoumou BS, Tigoi C, Otieno CA, Oduol CO, Lancioni CL, Manyasi C, McGrath CJ, Maronga C, Lwanga C, Brals D, Ahmed D, Mondal D, Denno DM, Mangale DI, Chimwezi E, Mbale E, Mupere E, Salauddin Mamun GM, Ouédraogo I, Berkley JA, Njunge JM, Njirammadzi J, Mukisa J, Thitiri J, Walson JL, Jemutai J, Tickell KD, Shahrin L, Mallewa M, Hossain MI, Chisti MJ, Timbwa M, Mburu M, Ngari MM, Ngao N, Aber P, Harawa PP, Sukhtankar P, Bandsma RHJ, Bamouni RM, Molyneux S, Mwaringa S, Shaima SN, Ali SA, Afsana SM, Banu S, Ahmed T, Voskuijl WP, Kazi Z
EClinicalMedicine 2024;70:102530

Lipid-based nutrient supplements for prevention of child undernutrition: when less may be more

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Am J Clin Nutr 2023;118:1133–1144

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https://pubmed.ncbi.nlm.nih.gov/37742931/

Comments: This study, by Dewey et al. [2], evaluated the impact of small-quantity (SQ-LNS) and medium-quantity lipid-based nutrient supplements (MQ-LNS) on preventing child undernutrition in low- and middle-income countries. Through a systematic review and meta-analysis of randomized controlled trials, it was found that MQ-LNS slightly improved weight-for-length Z-scores (WLZ) and reduced wasting but had no significant effect on length-for-age Z-scores (LAZ) or stunting. Only two studies compared MQ-LNS with SQ-LNS, and the evidence suggests no added benefits of MQ-LNS over SQ-LNS, which are more cost-effective and similarly beneficial in improving growth outcomes.

The studies included in this systematic review varied in duration, with some providing supplementation for 3–5 months (short-term) and others for 6–18 months (longer-term). The main limitations included the heterogeneity of study designs, variations in intervention duration, and differences in outcome measurement methods. Additionally, blinding was not possible due to the nature of the interventions. The meta-analysis also faced challenges with incomplete consumption of MQ-LNS rations, particularly in younger children, which might have affected nutrient intake and growth outcomes. The research highlights the need for further research, particularly rigorous research on the seasonal use of MQ-LNS, the use of MQ-LNS in highly food-insecure settings, and studies directly comparing MQ-LNS with SQ-LNS.

The effect of zinc supplementation on anthropometric measurements in healthy children over two years: a systematic review and meta-analysis

Monfared V[1], Salehian A[1], Nikniaz Z[2], Ebrahimpour-Koujan S[3], Faghfoori Z[4]

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BMC Pediatr 2023;23:414

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https://pubmed.ncbi.nlm.nih.gov/37612628/

Comments: This study by Monfared et al. [3] systematically reviewed and conducted a meta-analysis of the effects of zinc supplementation on the anthropometric measurements of healthy children over 2 years old. It identified eight randomized

controlled trials (RCTs) with 1,586 participants. The results indicated that zinc supplementation significantly increased height (WMD: 0.9 cm, 95% CI: 0.27–1.52), weight (WMD: 0.51 kg, 95% CI: 0.06–0.97), and height-for-age Z-score (HAZ) (WMD: 0.07, 95% CI: 0.03–0.10). No significant association was found between dose or duration of intervention and anthropometric outcomes. Subgroup analyses suggested that factors such as study location, intervention duration, gender, and sample size contributed to heterogeneity.

The studies included in the meta-analysis employed a range of methodologies, with most using parallel designs and various dosages of zinc supplements (5–15 mg/d) over durations spanning 6–28 weeks. Sample sizes varied significantly, from as few as 46 to as many as 804 participants, leading to differences in statistical power and generalizability. While two studies were deemed high-quality based on the Cochrane risk of bias tool, others had notable limitations such as unclear allocation concealment, potential performance and detection biases, and reporting biases. The meta-analysis employed random effects models due to high heterogeneity among studies, which may stem from differences in geographical locations, gender distribution, and intervention durations. Although the studies consistently showed positive effects of zinc on growth, the variations in study designs, population characteristics, and quality highlight the need for more standardized and high-quality RCTs to confirm these findings comprehensively.

Higher versus lower protein intake in formula-fed term infants

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Cochrane Database Syst Rev 2023;11:CD013758

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Comments: Depending on the amount of protein they contain, formulas are categorized as low-protein (less than 1.8 g per 100 kcal), standard-protein, or high-protein (2.5 g or more per 100 kcal). The systematic review by Gonzalez-Garay et al. [4] evaluates the impact of high versus low protein intake in formula-fed term infants. The review included 11 randomized controlled trials involving 1,885 infants. The results show that there is very low-certainty evidence that feeding infants high-protein formula compared to standard-protein formula has little to no effect on underweight, stunting, wasting, overweight, or obesity. Similarly, there is low-certainty evidence that standard-protein formula compared to low-protein formula has minimal impact on these same outcomes. Additionally, the review found little evidence to suggest that protein content in formula significantly affects the occurrence of adverse events such as diarrhea, vomiting, or milk hypersensitivity. The authors conclude that further large-scale studies are needed to better understand the long-term benefits and risks of varying protein levels in infant formulas, as the current evidence is insufficient to draw definitive conclusions.

The studies included in this meta-analysis have several limitations: variability in study design and reporting, high dropout rates, and generally short study durations, with most lasting only about 4 months and only two extending to 5 years or more. Additionally, the number of participants varied widely, with some studies including as few as 20 infants, reducing statistical power. These factors contribute to the very low to low certainty of evidence, highlighting the need for further well-designed, large-scale, long-term research to draw more definitive conclusions about the effects of high versus low protein intake in formula-fed term infants.

Probiotic supplementation for promotion of growth in undernourished children: a systematic review and meta-analysis

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https://pubmed.ncbi.nlm.nih.gov/37779227/

Comments: This comprehensive review [5] evaluated the evidence related to probiotic supplementation on growth in undernourished children under 5 years of age. The authors evaluated results from nine randomized controlled trials with 5,295 children and duration of supplementation ranging from 1 to 12 months and were able to pool results from seven trials. Their random effects meta-analysis showed that probiotics may have little to no effect on weight-for-age (SMD: 0.05 standard deviation [SD], 95% CI: −0.04 to 0.13, n = 2,115 children; low-certainty evidence) and height-for-age (SMD: −0.04 SD, 95% CI: −0.14 to 0.07, n = 1,357 children; low-certainty evidence). They concluded that the studies so far were extremely heterogenous and while the effects showed little to no effect on growth, there was the continued need for larger, better controlled studies to assess the link between gut microbiota, probiotic supplementation, and growth.

This review specifically assessed effects on linear growth in comparison to others [14], which focused on weight gain and found some effects in studies of probiotics and

synbiotics. Clearly, growth is just one outcome of interest in studies of probiotic use to optimize child health and longer-term outcomes [15], areas that will receive a lot more attention in the years to come.

Ready-to-use therapeutic foods (RUTFs) based on local recipes are as efficacious and have a higher acceptability than a standard peanut-based RUTF: a randomized controlled trial in Indonesia

Rachmadewi A[1], Soekarjo DD[1], Bait BR[2], Suryantan J[2], Noor R[3], Rah JH[2], Wieringa FT[4,5]

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Nutrients 2023;15:3166

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https://pubmed.ncbi.nlm.nih.gov/37513584/

Comments: The study by Rachmadewi et al. [6] evaluated the efficacy and acceptability of locally produced ready-to-use therapeutic foods (RUTFs) in treating severe acute malnutrition (SAM) in Indonesian children compared to standard peanut-based RUTF. This well-designed randomized controlled trial involved 302 children aged 6–59 months who received one of the five RUTFs for 8 weeks. The results indicated no significant difference in weight gain across the different RUTF groups. However, the locally produced RUTFs, particularly those made from mung bean (MUN2) and peanuts (PEA), were more acceptable and consumed in higher quantities than the standard RUTF. The overall dropout rate was high (29.1%); however, children in the control group dropped out significantly earlier. The study concluded that locally produced RUTFs are as effective as standard RUTF and have higher acceptability, suggesting the need to develop local RUTFs to enhance community-based treatment of SAM in Indonesia.

This study has several limitations, including a high dropout rate of 29.1%, which may affect the reliability and generalizability of the findings. The intervention duration of 8 weeks might not be sufficient to observe long-term effects, and compliance issues, particularly with the standard and soy-based RUTFs, could impact the results. The study was geographically limited to a specific region of Indonesia, potentially affecting applicability to other areas. Additionally, the intensive guidance provided during the study is not reflective of standard program settings, which may have led to higher compliance and better outcomes than in real-world conditions. Variability in the nutritional content of the RUTFs and reliance on caregiver reports also introduce potential biases, necessitating further research in diverse settings with larger sample sizes and longer follow-up periods.

Bioactive glycans in a microbiome-directed food for children with malnutrition

Hibberd MC[1,2,3], Webber DM[1,2,3], Rodionov DA[4], Henrissat S[1,2,5], Chen RY[1,2], Zhou C[1,2], Lynn HM[1,2], Wang Y[1,2], Chang HW[1,2], Lee EM[1,2], Lelwala-Guruge J[1,2], Kazanov MD[6], Arzamasov AA[4], Leyn SA[4], Lombard V[5], Terrapon N[5], Henrissat B[7,8], Castillo JJ[9], Couture G[9], Bacalzo NP Jr[9], Chen Y[1,2,9], Lebrilla CB[9], Mostafa I[10], Das S[10], Mahfuz M[10], Barratt MJ[1,2,3], Osterman AL[4], Ahmed T[10], Gordon JI[1,2,3]

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Nature 2024;625(7993):157–165

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https://pubmed.ncbi.nlm.nih.gov/38093016/

A microbiota-directed complementary food intervention in 12-18-month-old Bangladeshi children improves linear growth

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EBioMedicine 2024;104:105166

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Comments: Bioactive glycans are complex carbohydrates that exert significant biological effects in the body, particularly by interacting with and modulating the gut microbiome. Found in certain dietary fibers and plant-based foods, bioactive glycans include mannans, pectins, inulin, fructooligosaccharides, and galactooligosaccharides. The current study by Hibberd et al. [7] investigates the role of bioactive glycans in a microbiome-directed complementary food (MDCF-2) and its effects on the gut microbiome and weight gain in malnourished children. The objective was to compare MDCF-2 with a conventional supplementary food (RUSF) in 12- to 18-month-old Bangladeshi children with moderate acute malnutrition. This randomized controlled study compared the effect of MDCF-2, which contains an abundance of bioactive glycans that are metabolized by the

gut microbiota to promote growth [16], with that of RUSF, which is calorically denser but not designed to alter the microbiome. The intervention lasted for 3 months, followed by a 1-month follow-up period. Key findings included an increased abundance of specific bacterial taxa like *Prevotella copri* and a total of 75 bacterial genomes positively associated with weight-for-length Z-score. MDCF-2 demonstrated superior weight gain, despite being less calorically dense, with a lesser effect on height Z-score. However, in a follow-up study by Mostafa et al. [8], describing 2 years of follow-up, children who had received MDCF-2 were significantly less stunted after 2 years than those who received RUSF.

This study is robust in its design, involving a randomized controlled trial, detailed microbial analysis, and comprehensive metabolic profiling. While the results show a strong association between MDCF-2 consumption, microbiome changes, and growth, it does not establish a direct causal link. The results of this study underscore the efficacy of MDCF-2 in addressing malnutrition through mechanisms beyond mere caloric intake, specifically through the modulation of the gut microbiome. Future studies will need to address the generalizability of these results, the optimal timing of intervention, the ideal glycan dosing, and other unresolved questions regarding the role of the microbiome in stunting and wasting.

Effects of L-carnitine supplementation on the rate of weight gain and biomarkers of environmental enteric dysfunction in children with severe acute malnutrition: a double-blind randomized controlled clinical trial

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J Nutr 2024;154:949–961

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Comments: L-carnitine is one of the key nutrients involved in mitochondrial function and is known for its role in fatty acid oxidation. It is also crucial in protecting cellular membranes, preventing fatty acid accumulation, modulating ketogenesis and gluconeogenesis, and eliminating toxic metabolites. Children with SAM suffer from both L-carnitine deficiency and mitochondrial dysfunction, resulting in increased oxidative stress and decreased ATP production. Previous research has suggested that increased ATP production, which can be influenced by L-carnitine, may correlate with improvements in the nutritional status of malnourished children.

The authors of this study [9] hypothesized that L-carnitine supplementation would improve biomarkers associated with environmental enteric dysfunction (EED) and enhance weight gain in children with severe acute malnutrition (SAM). To test this hypothesis, they conducted a prospective, double-blind, placebo-controlled, randomized clinical trial at Dhaka Hospital, Bangladesh. The trial included 98

children aged 9–24 months with SAM, who were randomly assigned to receive either L-carnitine syrup (100 mg/kg/d) or a placebo for 15 days, in addition to the standard of care.

The primary outcome, the rate of weight gain, was found to be similar between the L-carnitine and placebo groups (2.09 ± 2.23 vs. 2.07 ± 2.70; $p = 0.973$). This result remained consistent after adjusting for potential covariates. The average duration of hospital stay for children in both groups was approximately 4 days, with no significant difference between the treatment arms. There was no significant difference in EED biomarkers (myeloperoxidase, neopterin, alpha-1 antitrypsin) between the L-carnitine and placebo groups after the intervention. In conclusion, the study found that L-carnitine supplementation did not have a beneficial effect on weight gain or EED biomarkers in children with SAM.

Long-term outcomes after severe childhood malnutrition in adolescents in Malawi (LOSCM): a prospective observational cohort study

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Lancet Child Adolesc Health 2024;8:280–289

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https://pubmed.ncbi.nlm.nih.gov/38368896/

Comments: Long-term health risks in survivors of severe acute malnutrition (SAM) include persistent stunted growth, cognitive deficits, an increased risk cardiometabolic diseases and reduced muscle strength. However, there is a lack of longitudinal data on the prognosis of children who were treated for SAM during childhood. This study [10] aimed to assess long-term outcomes in adolescents in Malawi who were treated for SAM ($n = 168$), comparing them with siblings ($n = 123$) and community adolescents ($n = 89$) who were not exposed to SAM. It was a prospective observational cohort study that followed up these adolescents 15 years after their initial treatment. The participants were initially recruited as part of a previous study (ChroSAM) and were reevaluated for various health outcomes.

Adolescents who had been treated for SAM showed modest improvement in height-for-age Z-scores (HAZ) compared to their earlier measurements. However, their HAZ scores remained lower than those of both siblings and community adolescents. Previously malnourished adolescents also exhibited weaker handgrip

strength compared to community adolescents, although no significant difference was found when compared with siblings. There was little evidence of differences in metabolic health indicators, such as fasting glucose levels, blood pressure, and insulin sensitivity, between previously malnourished adolescents and their unexposed peers. The study did not find significant differences in cognitive function or mental health outcomes between previously malnourished adolescents and those who were not exposed to SAM.

The study's strengths include its prospective design, the long follow-up period of 15 years, and the use of a well-characterized cohort, which provides valuable insights into the long-term effects of SAM. However, the study is limited by healthy survivor bias, as many of the most vulnerable children did not survive to adolescence. Additionally, the sample size for some outcomes was small, and there was a lack of detailed data on diet and exercise.

While the study offers some optimism for ongoing recovery in height and physical strength deficits among survivors of severe childhood malnutrition, it underscores the need for continued follow-up and research to fully understand the long-term health implications and to optimize postmalnutrition interventions.

Gut microbiota in regulation of childhood bone growth

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Exp Physiol 2024;109:662–671

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Comments: This comprehensive review [11] provides a broad perspective and an up-to-date overview of the role of the gut microbiota in regulating childhood bone growth. It covers various topics related to the complex interplay between nutrition, the microbiome, and linear growth. The review primarily focuses on how the GH/IGF-I axis, a critical endocrine pathway for bone growth, is influenced by both nutritional status and the gut microbiota.

The review discusses the potential role of short-chain fatty acids, produced by the gut microbiota during fiber fermentation, in stimulating the GH/IGF-I axis to promote bone growth. However, the exact signaling pathways involved remain unclear, and further research is necessary to confirm this connection. The review also explores how chronic inflammation, often associated with gut microbiota dysbiosis, can suppress IGF-I production and impede bone growth. It suggests that the gut microbiota may help reduce inflammation, thereby supporting healthier growth.

Additionally, the review elaborates on the NOD2-mediated sensing pathway, through which the gut microbiota can influence bone growth. NOD2, a receptor in intestinal

epithelial cells, detects bacterial components and triggers IGF-I production [17], a process crucial for bone growth. This pathway suggests a direct link between microbial sensing and the endocrine regulation of growth.

The review also highlights ongoing clinical trials and research into microbiota-based therapies, such as probiotics, prebiotics, and microbiota-directed foods, which aim to improve gut microbiota composition and, consequently, enhance bone growth and overall health.

While the potential of gut microbiota in regulating growth is promising, the review underscores the challenges of translating these findings into effective treatments. Issues such as the maturation of a healthy microbiota, the effects of antibiotics, and the long-term impact of interventions still warrant further investigation.

Shigella and childhood stunting: evidence, gaps, and future research directions

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PLoS Negl Trop Dis 2023;17:e0011475

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Comments: This review [12] evaluated the relationship between early childhood infection with *Shigella* infections in early childhood and linear growth. The authors evaluated several recent longitudinal multicountry and single-site studies evaluating infection with various pathogens including *Shigella* and childhood growth. They summarized that *Shigella* was most commonly detected in toddlers and young children, with greater effects on linear growth among those under 12 months of age. They recommended that future studies should employ more *Shigella*-specific molecular assays and identify diarrheal etiologies using standardized diagnostics to better understand the relationship between symptomatic and asymptomatic *Shigella* infections, intestinal inflammation and linear growth in children, and potential interventions.

Such association of *Shigella* infections with impaired growth in children has been recognized for a long time [18] and a subject for dietary intervention studies [19], but needs more contemporary validation. Such a longitudinal multicountry study, Enterics for Global Health Shigella surveillance study, is currently underway [20] and should inform studies on rapid detection techniques, treatment, and vaccine development.

Childhood growth during recovery from acute illness in Africa and South Asia: a secondary analysis of the childhood acute illness and nutrition (CHAIN) prospective cohort

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EClinicalMedicine 2024;70:102530
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Comments: Although growth faltering is well-recognized during acute childhood illness, much of the information is from historical studies and there are limited recent data on growth in hospitalized children from low- and middle-income countries. In this multicountry study from the CHAIN network across South Asia and sub-Saharan Africa [13], the authors evaluated 2,472 children between 2 and 23 months who survived to 6 months postdischarge.

They documented that weight increased in most children postdischarge with comparatively greater weight gain among those with more severe types of wasting or those with nutritional edema. The greatest weight gain was early (the first 45 days postdischarge). They also identified that two-thirds of children who were underweight at discharge remained so at 6 months postdischarge, with associated factors such as age-inappropriate nutrition, adverse caregiver characteristics, small size at birth, severe or moderate anemia, and chronic conditions. Their findings underscored the importance of follow-up and addressing social determinants of ill health and household factors that often impair recovery and portend relapse.

These findings also underscore other findings by Khara et al. who pooled data from twelve cohorts [21] and underscored the importance of identifying early anthropometric criteria for identifying children at higher risk of mortality following nutrition rehabilitation.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 16–32 (DOI: 10.1159/000541846)

Stunting in Developing Countries

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Introduction

In 2022, 148.1 million children under 5 years were stunted (height or length for age more than two standard deviations below the World Health Organization [WHO] Child Growth Standards median) [1, 2]. Despite the progress that has been made globally, in reducing the rates of stunting from 33.0% in 2000 to 22.3% in 2022, many countries in Africa and South Asia are unlikely to meet the World Health Assembly target of reducing stunting by 40% among under 5 years (from 162 million in 2012) by 2025 [1]. As we approach 2025 and 2030, the window to address stunting is narrowing. Countries like Peru and Brazil dramatically reduced their rates of stunting, demonstrating the potential for accelerated progress when countries make bold investments and implement ambitious actions to scale coverage of interventions. It is now well recognized that childhood stunting often begins during fetal life, with intrauterine growth restriction due to maternal undernutrition accounting for over 20% of stunting [3, 4]. Additionally, the effects of climate variability, weather extremes, conflicts, and poor financing of health and nutrition programs in many developing countries, are likely to reverse any progress that has been made [5]. Therefore, it is imperative that continued interdisciplinary efforts are made to understand the mechanisms of childhood stunting in different contexts in developing countries, to develop more targeted approaches to address this, particularly in regions of the world where limited or no progress has been made to reduce the rates of stunting in early childhood.

An understanding of the contextual factors will allow for the right mix of direct and indirect nutrition interventions that are more likely to succeed [2].

In this chapter, we highlight the emerging evidence on the impact of climate change and weather patterns on childhood stunting across many developing countries. We draw attention to the potential mechanisms by which climate change and household indoor air pollution might lead to stunting. Cognizant of the in utero origins of stunting, we feature papers that evaluate the environmental factors to linear growth faltering from preconception through to the prenatal period. We also explore the impact of potential mitigators of these shocks (including cash transfer programs) on stunting. We then feature early work on the genetic and epigenetic influences on stunting through multiple mechanisms. Modifiable environmental factors that influence the expression of genetic factors involved in the regulation of height can be targeted through interventions to reduce stunting. In addition to their role in child growth, we highlight the need to explore their role in the cognitive and neurological development of children. While this work is preliminary, it holds immense potential to elucidate mechanisms of stunting in the future. In addition, we discuss the gaps in financing the proposed multisectoral approaches and recommendations that could potentially accelerate the reduction of stunting in early childhood in many developing countries. We also highlight the potential role of childcare centers in impoverished communities on ameliorating stunting in developing countries, in the absence of appropriate governance and policy frameworks.

Finally, we explore the potential role of machine learning in addressing childhood stunting. We highlight how machine learning models might improve prediction of stunting starting from birth. The early testing of machine learning in nutrition has focused on its ability to use large national or survey datasets to detect various forms of malnutrition. While precision medicine has shown the immense usefulness of machine learning tools in specific health areas, there is limited research on their role in clinical nutrition or personalized nutrition therapies. A recent scoping review showed that nutrition overall lagged behind other health disciplines in the adoption of machine learning approaches [6].

Key articles reviewed for this chapter

Dynamics of Linear Growth Faltering and Stunting

Early-childhood linear growth faltering in low- and middle-income countries
Benjamin-Chung J, Mertens A, Colford JM Jr, Hubbard AE, van der Laan MJ, Coyle J, Sofrygin O, Cai W, Nguyen A, Pokpongkiat NN, Djajadi S, Seth A, Jilek W, Jung E, Chung EO, Rosete S, Hejazi N, Malenica I, Li H, Hafen R, Subramoney V, Häggström J, Norman T, Brown KH, Christian P, Arnold BF, & the Ki Child Growth Consortium
Nature 2023;621(7979):550–557

Stunting in the first year of life: pathway analysis of a birth cohort
Mwangome M, Ngari M, Brals D, Bawhere P, Kabore P, McGrath M, Berkley JA
PLoS Glob Public Health 2024;4(2):e0002908

Short-term dynamics of linear growth among Peruvian infants in the first year of life in a population with linear growth faltering
Lee GO, McCormick BJJ, Yori PP, Paredes-Olortegui M, Caulfield LE, Kosek MN
Am J Hum Biol 2024;36:e24039

Effects of Planetary Health and Cooking-Related Pollution on Stunting

Peak timing of slowest growth velocity among young children coincides with highest ambient temperatures in Burkina Faso: a longitudinal study
Cliffer IR, Naumova EN, Masters WA, Perumal N, Garanet F, Rogers BL
Am J Clin Nutr 2024;119:393–405

Early life exposure to cold weather shocks and growth stunting: evidence from Tanzania
Hongoli JJ, Hahn Y
Health Econ 2023;32:2855–2879

Effects of cooking with liquefied petroleum gas or biomass on stunting in infants
Checkley W, Thompson LM, Sinharoy SS, Hossen S, Moulton LH, Chang HH, Waller L, Steenland K, Rosa G, Mukeshimana A, Ndagijimana F, McCracken JP, Díaz-Artiga A, Balakrishnan K, Garg SS, Thangavel G, Aravindalochanan V, Hartinger SM, Chiang M, Kirby MA, Papageorghiou AT, Ramakrishnan U, Williams KN, Nicolaou L, Johnson M, Pillarisetti A, Rosenthal J, Underhill LJ, Wang J, Jabbarzadeh S, Chen Y, Dávila-Román VG, Naeher LP, McCollum ED, Peel JL, Clasen TF, for the HAPIN Investigators
N Engl J Med 2024;390:44–54

Biomass smoke exposure and somatic growth among children: the RESPIRE and CRECER prospective cohort studies in rural Guatemala
Lu W, Jenny A, Romero C, Diaz-Artiga A, Kuster A, Canuz E, Pillarisetti A, McCracken JP, Huang W, Smith KR, Balmes J, Thompson LM
Environ Int 2024;183:108401

Interventions: Cash Transfer Programs

Impact of cash transfer programs on birth and child growth outcomes: systematic review
Lisboa CS, Guimarães NS, Ferreira AJF, Silva KBBD, Alves FJO, Rocha ADS, Ortelan N, Texeira CSS, Falcão IR, Silva NJ, Ribeiro-Silva RC, Barbosa D, Barreto ML
Cien Saude Cole 2023;28:2417–2432

Understanding the Genetic and Epigenetic Mechanisms and Influences on Stunting

Genetic variation in environmental enteropathy and stunting in Zambian children: a pilot genome wide association study using the H3Africa chip
Mweetwa MN, Haritunians T, Dube S, Chandwe K, Amadi B, Zyambo K, Liu TC, McGovern D, Kelly P
PLoS One 2023;18:e0291311

DNA methylation at the suppressor of cytokine signalling 3 (SOCS3) gene influences height in childhood
Issarapu P, Arumalla M, Elliott HR, Nongmaithem SS, Sankareswaran A, Betts M, Sajjadi S, Kessler NJ, Bayyana S, Mansuri SR, Derakhshan M, Krishnaveni GV, Shrestha S, Kumaran K, Di Gravio C, Sahariah SA, Sanderson E, Relton CL, Ward KA, Moore SE, Prentice AM, Lillycrop KA, Fall CHD, Silver MJ, Chandak GR, for the EMPHASIS Study Group
Nat Commun 2023;14:5200

Perspectives and Policy

Childcare centre attendance and health, growth, and development among children aged 0–3 years in low- and middle-income countries: a systematic review
Behbehani F, Kowalski AJ, Selam H, Dombrowski E, Black MM
J Glob Health 2024;14:04028

The Potential Role of Machine Learning in Understanding and Addressing Stunting

Machine learning algorithms for predicting stunting among under-five children in Papua New Guinea
Shen H, Zhao H, Jiang Y
Children (Basel) 2023;10:1638

Dynamics of Linear Growth Faltering and Stunting

Early-childhood linear growth faltering in low- and middle-income countries

Benjamin-Chung J[1,2,3], Mertens A[2], Colford JM Jr[2], Hubbard AE[2], van der Laan MJ[2], Coyle J[2], Sofrygin O[2], Cai W[2], Nguyen A[1,2], Pokpongkiat NN[2], Djajadi S[2], Seth A[2], Jilek W[2], Jung E[2], Chung EO[2], Rosete S[2], Hejazi N[2], Malenica I[2], Li H[2], Hafen R[4], Subramoney V[5], Häggström J[6], Norman T[7], Brown KH[8], Christian P[9], Arnold BF[10,11], & the Ki Child Growth Consortium

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Nature 2023;621(7979):550–557
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Comments: This collaborative project builds on the momentum around catch-up growth in recent years. The authors conducted a pooled analysis of longitudinal studies (32 cohorts of 52,640 children aged 0–24 months) from 14 low- and middle-income countries (LMICs) between 1987 and 2017. One key strength of this paper is their choice to use longitudinal studies, whose designs provide information on the timing of growth faltering and insights in defining critical windows required to deliver preventative interventions. The authors report that stunting incidence was highest between 0 and 3 months, and its onset at birth was a key predictor for linear growth faltering at 15 months or stunting relapse in the first year of life. Also, they highlight that stunting reversal was rare between 0 and 15 months, and children who reversed their stunting status frequently relapsed. These results highlight the need for preventive interventions during the critical period before birth, and in the first 6 months to reducing stunting. These interventions ought to be context specific and could

include maternal micronutrient and macronutrient supplementation, women education, reducing adolescent pregnancies, intermittent preventative treatment of malaria, and interventions on the small and vulnerable newborns. Further, they highlight the "*whole population phenomenon*" where both stunted and nonstunted children experience suboptimal growth patterns early in life in certain populations. Even among children who did not meet the criteria for stunting based on LAZ, mean LAZ steadily declined by over 0.5 Z-scores by 15 months. This highlights the need for countries to design programs that target specific populations and geographical locations to address specific gaps through identifying and implementing the right mix of nutrition-specific and nutrition-sensitive interventions. Overall increases in healthcare spending might also contribute to reducing linear growth faltering. Consistent with the 2016 Maternal and Child *Lancet* Series [3], this paper underscores the potential of life course interventions among women of childbearing age and a greater emphasis on children under 6 months to address the early onset of linear growth faltering. Within the first 1,000 days, they highlight the critical window during the prenatal period and early postnatal period, within which stunting might be prevented or reversed through upstream preventative interventions.

Stunting in the first year of life: pathway analysis of a birth cohort

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PLOS Glob Public Health 2024;4:e0002908

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https://pubmed.ncbi.nlm.nih.gov/38363746/

Comments: Mwangome et al. used a hypothetical framework analysis using data from a 2004 birth cohort of 1,017 infants from Burkina Faso to explore pathways to stunting at birth, 3, 6, and 12 months. The authors found that stunting was more prevalent at 3 months (23%) and 6 months (20%) compared to the birth period (7.4%). Stunting at 12 months was more likely to be attributed to stunting at 6 months (40%, 95% CI: 31%–49%) or 3 months (32%, 95% CI: 22%–41%) in comparison to birth (11%, 95% CI: 5%–16.0%), while stunting at birth was more likely to be linked with subsequent stunting in childhood. Consistent with the first paper in this chapter, these findings emphasize the need for life course and upstream interventions during the first 1,000 days, as these have the potential to alter the direct and indirect pathways to stunting among infants. While the association between these factors and stunting itself has been highlighted in previous studies, this paper underscores the complex relationships and interactions between these direct and indirect factors at specific periods in the first year. They show the linkages and pathways between the immediate (child and maternal factors), underlying (paternal and household

characteristics), and basic (community and societal) factors, highlighting critical pathways where interventions are likely to have an impact. Interventions should be designed to simultaneously address these multidomain factors and their complex relationships since siloed approaches have often failed to reduce stunting.

Short-term dynamics of linear growth among Peruvian infants in the first year of life in a population with linear growth faltering

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Am J Hum Biol 2024;36:e24039

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https://pubmed.ncbi.nlm.nih.gov/38189589/

Comments: Lee et al. examined the changes in growth patterns between stunted infants and those who are not stunted in an observational cohort study among 61 (28 boys and 33 girls) Peruvian children who experienced growth faltering in their first year of life. The authors did not find a difference in the timing or magnitude of saltations between children who were stunted ($n = 18$) or not stunted ($n = 43$) at 1 year, though stunted children had a greater variability in the duration of stasis and growth saltations (accelerations). On the other hand, there was some weak evidence that children who had greater declines in LAZ had longer durations between growth saltations (14.5 days vs. 13.4 days, $p = 0.05$), though there were no differences in the magnitude of saltations. The number of saltations were higher in the early infancy (382 and 310 at 0–3 months and 3–6 months respectively) compared to late infancy (183 at 9–12 months). While their sample size was small, and might have been underpowered to detect any differences, the study provides insights on the interplay between environmental exposures and biological regulators that drive the short-term nonlinear growth dynamics. The time lag (21 days) between exposure and outcome, like in other similar studies investigating short-term growth dynamics, requires a very robust power and analysis strategy to provide accurate insights on changes in growth patterns; hence, their results should be interpreted with some caution. Other researchers following up individual children have suggested that the growth saltatory processes might be a normal process of development, though stunted children might have longer duration of stasis, and the magnitude of saltation might vary. We recommend larger studies in future to improve the understanding of these dynamics of linear growth. It might be important to also explore whether these early life growth dynamics in infants differ among children stunted at older age groups through longitudinal studies.

Peak timing of slowest growth velocity among young children coincides with highest ambient temperatures in Burkina Faso: a longitudinal study

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Am J Clin Nutr 2024;119:393–405

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Comments: Cliffer et al. explored the influences of seasonal changes in temperature, precipitation, and vegetation cover on child growth in Sanmatenga province in Burkina Faso. Anthropometric data from 5,039 children in 199 villages were collected between August 2014 and December 2016 in this longitudinal study. While previous categorizations of seasonality have focused on the Gregorian calendar months, the authors adopted regression methods to model nutrition seasonality. This is a valuable approach, considering recent changes in seasons that are not consistent with known climate patterns. Overall, they found that the two peak temperature periods in April and October were highly synchronized with the respective weight and length velocities among the children. Length velocity was slowest 15 and 5 days after the first and second peak temperatures, respectively. On the other hand, weight velocity was slowest 13 and 11 days before the first and second peaks, respectively. These findings highlight some possible indirect relationships between seasonality and growth. Interestingly, the authors report that length velocity and LAZ declined overall, and did not follow the seasonal pattern, consistent with the "*whole population phenomenon*" reported in the first and second papers in this chapter. Weight and length velocities were not associated with rainfall peaks, and growth faltering did not peak in the rainy season when there was food insecurity and poor care practices for children. This contrasts other findings of lower weight velocities in rainy seasons. For instance, Nabwera et al. [7] in a 40-year retrospective cohort study in The Gambia found that reductions in weight velocity were more marked in the rainy season when infections were high, though these variations in the magnitude or size of seasonal growth reduced with time. The seasonal climate changes likely indirectly influence various immediate and underlying drivers of child growth. As these underlying mechanisms remain somewhat unclear, we call for a reenergized interest in this area, considering the recent climate shocks and weather extremes. Further studies could explore the potential of synchronizing environmental and climate sensitive interventions to optimize growth among children.

Early life exposure to cold weather shocks and growth stunting: evidence from Tanzania

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Health Econ 2023;32:2855–2879
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Comments: Cold weather shocks indirectly affect child growth through altering the disease environment, food insecurity, and agricultural productivity. In this paper, Hongoli and Hahn model the effects of early life and in utero exposure to cold weather on child growth among children under 5 years in Tanzania using nationally representative weather data collected between 2003 and 2015. They defined a cold weather shock as a temperature below one standard deviation of the long-term average of 15°C. They found that an increase in 10% points in the proportion of days with temperatures below the long-term average of 15°C was associated with an increase in the probability of mean stunting and severe stunting by 5.5% and 9.7%, respectively. One strength of their approach is the use of high-resolution daily weather variations from two data sources that are somewhat specific. Overall, in utero exposure to cold weather was associated with long-term growth outcomes and there was strong evidence of effects on stunting during the 2nd trimester, but not the 1st and 3rd trimesters. This reinforces evidence for investment in lifelong interventions, especially in the first 1,000 days, but with the potential of better outcomes with targeted approaches. Whereas some interventions in the past have been designed with considerations on seasonality, the extreme weather events currently present a unique challenge for LMICs where robust mitigation approaches are almost nonexistent. Climate-sensitive interventions could support populations that are most vulnerable to weather shocks. As this paper highlights, exposure to extreme cold weather adversely affects growth in early childhood, and approaches that address these are urgently needed.

Effects of cooking with liquefied petroleum gas or biomass on stunting in infants

Checkley W[1,2], Thompson LM[3], Sinharoy SS[4], Hossen S[1], Moulton LH[2], Chang HH[5], Waller L[5], Steenland K[6], Rosa G[7], Mukeshimana A[8], Ndagijimana F[8], McCracken JP[9,10], Díaz-Artiga A[10], Balakrishnan K[11], Garg SS[11], Thangavel G[11], Aravindalochanan V[11], Hartinger SM[12], Chiang M[13], Kirby MA[14], Papageorghiou AT[15], Ramakrishnan U[4], Williams KN[1], Nicolaou L[1], Johnson M[16], Pillarisetti A[17], Rosenthal J[18], Underhill LJ[19], Wang J[5], Jabbarzadeh S[5], Chen Y[5], Dávila-Román VG[19], Naeher LP[20], McCollum ED[1,2,21], Peel JL[22], Clasen TF[6], for the HAPIN Investigators

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Comments: In this multicountry, randomized controlled trial, the Household Air Pollution Intervention Network assessed the effects of replacing biomass cookstoves with liquified petroleum gas (LPG) cookstoves on stunting among 3,200 pregnant women (9–20 weeks gestation) in four LMICs, i.e., Guatemala, India, Peru, and Rwanda. Whereas the intervention reduced prenatal and postnatal 24-h personal exposures to fine particulate matter, there was no difference in LAZ between the intervention and control at 6 or 12 months. They found that the use of unventilated LPG cookstoves and behavioral messaging starting in pregnancy until infants were 12 months old did not reduce childhood stunting, despite large reductions in household air pollution. The prevalence of stunting at 1 year was higher in the intervention group (27.4%) than in the control group (25.2%). This may possibly be mediated by other underlying and basic drivers of undernutrition. For example, the cooking method may be a marker for socioeconomic status, poor nutrition, and education status, which were not addressed by the intervention. The findings emphasize the complexity of stunting; isolated interventions that only address one factor (in this case, exposure to household smoke or air pollutants) may have a limited potential to address stunting on its own, despite improvements in other health outcomes. There is thus a need to explore the effect of bundling clean energy interventions with other nutrition interventions and investigate their influence on stunting. Interest may be paid to cleaner energies, and more upstream interventions, during preconception.

Biomass smoke exposure and somatic growth among children: the RESPIRE and CRECER prospective cohort studies in rural Guatemala

Lu W[1], Jenny A[2], Romero C[3], Diaz-Artiga A[3], Kuster A[4], Canuz E[3], Pillarisetti A[1], McCracken JP[5], Huang W[6], Smith KR[1], Balmes J[1,7], Thompson LM[8]

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Environ Int 2024;183:108401

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Comments: Lu et al. in this prospective study investigated the relationship between cooking-related biomass smoke exposure and growth outcomes among children under 5 years in Guatemala. Data collected from the RESPIRE study (2002–2004), and its follow-up, the CRECER study (2006–2009), were merged to provide a robust analysis. The three study groups received the chimney stoves at different ages of the study children; at the start of RESPIRE (<6 months), at the end of RESPIRE (18–24 months), and finally at the end of CRECER (at 57 months). It is important to note that the study population had a high prevalence of stunting (90.4%) and 40.5% underweight, indicating a severe level of undernutrition. Children in households with wood-fueled chimney stoves had lower carbon monoxide (CO) exposure (ppm) than those from households with open wood fires. A 1 ppm higher average CO exposure was associated with a 0.21 lower HAZ (95% CI: 0.17–0.25), a 0.13 lower WAZ (95% CI: 0.10–0.17), and a 0.06 lower WAZ (95% CI: 0.02–0.10), and boys were more vulnerable to the effects of smoke exposure than girls. However, there was no difference in stunting and underweight based on availability of the stoves across the three study groups. Whereas some evidence of the relationship between average CO exposure, but not across the study groups, is suggested, we recommend larger studies that investigate the role of more clean energies on stunting in LMICs, and a more in-depth exploration of the causal mechanisms to further improve our understanding and highlight potential interventions.

Impact of cash transfer programs on birth and child growth outcomes: systematic review

Lisboa CS[1], Guimarães NS[2], Ferreira AJF[3], Silva KBBD[3], Alves FJO[3], Rocha ADS[3], Ortelan N[3], Texeira CSS[3], Falcão IR[3], Silva NJ[4], Ribeiro-Silva RC[2,3], Barbosa D[5], Barreto ML[2,3]

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Cien Saude Colet 2023;28:2417–2432

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Comments: This systematic review sought to investigate the impact of cash transfers (CTs) on health outcomes (birth weight, prematurity, and anthropometric indices) among children under 5 years. While primarily featuring (nine) studies from LMICs, the review includes two studies from high-income countries (the United States and Canada). This highlights the growing interest in CTs across low-, middle-, and high-income countries alike. Overall, conditional cash transfers (CCTs) were associated with a reduction in stunting, underweight, and wasting while unconditional cash transfers (UCTs) were associated with reduced low birth weight and preterm births. Only one of the three included UCTs had an impact on HAZ. Among the CTs, there were differences across geographical regions, based on durations of the studies, and the type of CTs. For example, longer CT programs (16 m to over 60 m) were more likely to have an impact on nutrition and birth outcomes, when implemented with other interventions. CCTs seemed to be more positively associated with nutrition outcomes compared to UCTs, which were associated with improved birth outcomes. Further, while there is some reasonable evidence on CCTs, there was a limited number of UCTs included in the review, which calls for a renewed interest in the later, particularly as this year's State of Food Security and Nutrition report calls for a rethinking on financing for nutrition interventions. Social protection mechanisms are being explored across both high-, middle-, and low-income countries for their potential to accelerate efforts to address income inequalities and eliminate poverty ahead of 2030 (SDG1). Whereas cash transfers in isolation have inconsistent impact on nutrition outcomes, they have the potential to improve stunting when implemented as part of multisectoral interventions such as health, nutrition, and education. Future studies could examine the underlying mechanisms and pathways with which the CTs interact with other societal, household, and individual factors to influence child growth.

Genetic variation in environmental enteropathy and stunting in Zambian children: a pilot genome wide association study using the H3Africa chip

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PLoS One 2023;18:e0291311

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Comments: In this exploratory study, Mweetwa et al. investigated the genetic contribution to stunting and environmental enteropathy (EE) using the H3Africa genotyping array. They explored whether genetic variants were different between 117 stunted children and 41 controls aged 0–18 months in Zambia. Children with stunting (cases) were enrolled into the study and given nutrition therapy. The authors define stunting in children whose LAZ had not responded to nutrition supplementation in 4–6 months, and whose LAZ remained below −2, while controls were children whose LAZ was greater or equal to −1 at recruitment. Genetic association was through logistic regression, with genome-wide levels of significance $p < 5 \times 10^{-8}$, while $p < 1 \times 10^{-3}$ was considered suggestive of an association. The key findings indicate that no SNP had a significant association with stunting or EE at a higher threshold of $p < 5 \times 10^{-8}$, while interesting associations are reported at lower thresholds of $p < 1 \times 10^{-3}$. They report that SNPs associated with stunting were in genomic regions known to modulate neuronal differentiation and fatty acid biosynthesis. They also highlight the links between SNPs and various biomarkers of enteropathy, including increased microbial translocation, intestinal inflammation, epithelial damage, celiac disease, and HLA genes. Genetic variations associated with stunting and EE possibly act through multiple pathways, including gene expression, glycosylation, nerve signaling, and sensing of the nutritional and microbiological environment. Their small sample size provides inconclusive evidence, hence does not sufficiently clarify the gene associations involved in the pathophysiology of stunting. Nevertheless, it highlights potential mechanisms of genetic contributions to stunting. These are novel areas that have the potential to elucidate mechanisms with which stunting and cognitive deficits develop. The role of genetic variation in malnutrition thus warrants further research to improve our understanding of the pathophysiology and possible interventions.

DNA methylation at the suppressor of cytokine signalling 3 (SOCS3) gene influences height in childhood

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Nat Commun 2023;14:5200

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https://pubmed.ncbi.nlm.nih.gov/37626025/

Comments: In this novel study, the EMPHASIS group used mendelian randomization analysis to explore the relative contributions of epigenetic factors on child height in four cohorts from LMICs (India and The Gambia), and an additional high-income country (HIC) cohort from the United Kingdom. They found a robust association between methylation (at the three CpGs in the second exon of the SOCS3 gene) and height in children in LMICs, and this was independent of genetic factors. A 1% increase in methylation was associated with an average 0.25 cm increase in height, though they found some variations between countries, with a greater effect size reported in India compared to The Gambia. While these variances might be explained by the smaller sample sizes and lower rates of stunting in The Gambia, they also highlight variances in environmental influences across geographical regions and the need for context-specific interventions. The observed association in the LMICs was replicated in the HIC cohort, but with a smaller (0.11 cm) increase in height for each 1% increase in methylation, again highlighting the variances in environmental exposures. Strong evidence of a causal relationship between SOCS3 and height, independent of genetics, is reported with a 1% increase in methylation associated with an 0.07 SD change in height (95% CI: 0.03–0.11; $p = 1.7 \times 10^{-3}$). Further, they reported that the offspring's SOCS3 gene was potentially influenced by maternal folate and socioeconomic status (SES), but not BMI status, pregnancy homocysteine, or vitamin B_{12} concentrations. This emphasizes the influences of maternal health and SES on the child's height, through epigenetics, and a need to explore the role of additional micronutrients. Overall, these findings provide strong evidence of genome-wide DNA methylation associations with height in children from the LMICs, providing new insights on the role of epigenetics on height variation. The effects of maternal factors during pregnancy on DNA methylation in their offspring have practical implications; interventions could scale up folate supplementation, and in addition to maternal and child factors, an interest in interventions that improve environmental factors such as SES might have some effects on linear growth.

Childcare centre attendance and health, growth, and development among children aged 0–3 years in low- and middle-income countries: a systematic review

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J Glob Health 2024;14:04028

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https://pubmed.ncbi.nlm.nih.gov/38385435/

Comments: This systematic review examines the associations between childcare attendance in LMICs and children's health, growth, and development. Twenty-two articles published between 2000 and 2021 from PsycINFO, Medline, Pubmed, and Cochrane electronic databases, including data from 36,927 children (aged 0–3 years), were reviewed. They found that childcare attendance was positively associated with nutrition, growth, and development but not with improved health outcomes. Specifically, childcare attendees had lower prevalence of stunting across two studies in South Africa and Brazil. Regarding child development, three of the four studies reported better development outcomes from children attending childcare centers when compared with their control groups. Only one study, with a relatively small sample size (n = 37) did not find any differences in development scores. Despite these potential benefits, the childcare centers raise serious health concerns. The review reported that attendees had an increased risk of infections, diarrhea, and obesity, as well as lower rates of physical activity and exclusive breastfeeding. Childcare centers will likely continue to play a major role in early childhood and nurturing, as more women participate in the work force or move to cities in LMICs. As the overall quality of evidence in this review was low, further studies could inform the designing of safer centers that include culturally and context-sensitive curriculum. Governments ought to urgently address the hygiene, sanitation, infections, and safety concerns in these childcare centers. Immediate actions could include formulating regulations and policies to govern establishment and operation (or standards) of childcare centers in LMICs.

Machine learning algorithms for predicting stunting among under-five children in Papua New Guinea

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Children (Basel) 2023;10:1638

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https://pubmed.ncbi.nlm.nih.gov/37892302/

Comments: There is growing interest in the potential applications of machine learning models in stunting. Shen et al., using data from 3,380 children (0–5 years) from the 2016–2018 Papua New Guinea Demographic Health Survey, sought to identify the most effective model in identifying stunting and predicting its associated risk factors from several machine learning algorithms. On testing different approaches, the authors report that one approach, the LASSO-XGBoost method, a combination of a machine learning model and feature selection method, provided the best prediction of stunting (AUC: 0.767, 95% CI: 0.714–0.819). Further, they report that the optimal model identified socioeconomic status, low birthweight, and living in the highlands as the most important factors in predicting stunting, consistent with other researchers. This paper highlights the potential of machine learning in addressing stunting through potentially establishing causal pathways. Specifically, machine learning could improve our understanding of contextual factors and could be leveraged to design population-specific or localized interventions. Optimizing the performance of machine learning algorithms in predicting the risk of malnutrition will require an understanding of the logic and decision-making processes of the models to ensure results are valid, accurate, and ethical. When available, large and high-quality data may be used to build models that explore the complex pathways that result into stunting. However, researchers and organizations ought to take precautions to address the data safety, privacy, and ethical concerns associated with machine learning use.

Conclusion

As women continue to engage in work and move to cities, childcare centers will play a key role in child nurturing in LMICs. The 2016 *Lancet* Early Childhood Development Series proposed pathways for implementation of early childhood development at scale [8, 9]. The series emphasizes a "nurturing care" approach for children aged 0–3 years through multisectoral interventions to enable children to access all essential health and nutrition services and achieve their developmental and cognitive development stages [8, 9].

Policymakers and governments ought to urgently design policies that address the challenges of these informal childcare centers. Policy actions could include establishing standards for the quality of child care, WASH standards, and the training and continuous development requirements for staff in the centers. In addition, to optimize the potential of machine learning in addressing stunting, further research could explore its use in designing specific nutrition therapies for patients with chronic diseases. Machine learning could also support the management of large community nutrition programs and assist community health workers to accurately diagnose complicated SAM cases, among other applications. Despite its potential, several scholars have written widely about data safety, security, transparency, and ethical concerns of machine learning, or the risk of exacerbating already existing health inequalities. Governments, researchers, and organizations ought to tackle these concerns while harnessing machine learning's potential in addressing stunting.

Conflict of Interest Statement

The authors report no conflict of interest

Funding Sources

Helen M. Nabwera is currently jointly funded by the UK Medical Research Council (MRC) and the UK Foreign, Commonwealth and Development Office (FCDO) under the MRC/FCDO Concordat agreement. This United Kingdom-funded award is part of the EDCTP2 program supported by the European Union.

Martha K. Mwangome is currently funded by the Wellcome Trust and the Bill and Melinda Gates Foundation. Emmanuel Okello, Joycelyn Kathembe, Janet Tapkigen, and Andrew M. Prentice received no funding.

Author Contributions

All the authors read and commented on the manuscript.

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 33–48 (DOI: 10.1159/000541849)

The Physiology and Mechanisms of Growth

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Introduction

A selection of articles published in the period from July 1, 2023, to June 30, 2024, addressing physiology and mechanisms of growth is presented in this chapter. We acknowledge the limitations of our selection process and the possibility of omitting important articles. We recommend that readers thoroughly examine the included articles to enhance their knowledge of the topic.

In this year's chapter, a substantial part was attributed to the discussion on the role of microbiota on both pubertal development and linear growth. There are complex interactions between the pubertal and growth axis at all levels from the central nervous system to the growth plate. It is known that start of puberty and rate of pubertal progression have important influence on linear growth and final height. In several selected articles, influence of sex hormones (both internal and used as medication) on bone and growth plate mechanisms of linear growth is discussed. Most articles suggest associations or possible interplay between growth, puberty, and modifying role of microbiota. However, exact mechanisms are not yet well determined. In the future, more data are needed on this topic to optimize microbiota composition in children with growth disorders.

More information was shared on important external modifiers of growth. Exact mechanisms by which inflammation (especially chronic) and medications (e.g., cisplatin) could affect growth in children were studied. The data suggest that pediatric endocrinologist should be intensively involved in planning of short- and long-term follow-up of children

with chronic conditions, such as juvenile idiopathic arthritis (including therapy with growth hormone), or even during planning of chemotherapy for cancer from the point of view of growth.

Additional data were shared on phenotype and the effect of growth hormone treatment in children with heterozygous pathologic variants in genes associated with bone dysplasia (e.g., IGF-1). At least short-term therapy seems to be beneficial for increased growth velocity.

Insulin is an important link between nutrition and linear growth. The role of insulin signaling through the insulin receptor on bone and growth hormone–IGF-1 axis was studied in subjects with different types of insulin receptor function defects.

Novel genes and signaling pathways involved in linear growth were identified, also by studying individuals with tall stature. Epigenetic mechanisms have in important role in growth and puberty. Using novel techniques to identify and interpret them and gaining a better understanding of the consequences of such alterations, we will be more able to correctly address therapy and provide genetic counseling for the families of children with growth disorders caused by such alterations.

Last but not least, an article on the possibilities of management of children with extreme tall stature is included. This, sometimes controversial, topic is becoming again more in the forefront of discussions in regard to treatment options for these individuals.

Key articles reviewed for this chapter

Gender-affirming hormone therapy preserves skeletal maturation in young mice via the gut microbiome
Pal S, Morgan X, Dar HY, Gacasan CA, Patil S, Stoica A, Hu YJ, Weitzmann MN, Jones RM, Pacifici R
J Clin Invest 2024;134:e175410

Exploring the mechanistic interplay between gut microbiota and precocious puberty: a narrative review
Yue M, Zhang L
Microorganisms 2024;12:323

Gut microbiota-metabolite interactions meditate the effect of dietary patterns on precocious puberty
Wang Y, Jin C, Li H, Liang X, Zhao C, Wu N, Yue M, Zhao L, Yu H, Wang Q, Ge Y, Huo M, Lv X, Zhang L, Zhao G, Gai Z
iScience 2024;27:109887

Natural sweetener glycyrrhizin protects against precocious puberty by modulating the gut microbiome
Nguyen NN, Lin CY, Tsai WL, Huang HY, Chen CM, Tung YT, Chen YC
Life Sci 2024;350:122789

Aspartame intake delayed puberty onset in female offspring rats and girls
Lin CY, Nguyen NN, Tsai WL, Hsieh RH, Wu HT, Chen YC
Mol Nutr Food Res 2024;68:e2300270

Children with idiopathic short stature have significantly different gut microbiota than their normal height siblings: a case-control study
Lazar L, Eshel A, Moadi L, Yackobovitch-Gavan M, Bar-Maisels M, Shtaif B, Nevo M, Phillip M, Turjeman S, Koren O, Gat-Yablonski G
Front Endocrinol (Lausanne) 2024;15:1343337

GH therapy in children with juvenile idiopathic arthritis: a four-decade review
Sassano G, La Bella S, Di Ludovico A, Breda L, Chiarelli F
Clin Pediatr Endocrinol 2024;33:1–11

Cisplatin triggers oxidative stress, apoptosis and pro-inflammatory responses by inhibiting the SIRT1-mediated Nrf2 pathway in chondrocytes
Hsieh PL, Tsai KL, Chou WC, Wu CH, Jou IM, Tu YK, Ma CH
Environ Toxicol 2023;38:2476–2486

Growth disorders caused by variants in epigenetic regulators: progress and prospects
Lui JC
Front Endocrinol (Lausanne) 2024;5:1327378

Gene expression signatures predict first-year response to somapacitan treatment in children with growth hormone deficiency
Garner T, Clayton P, Højby M, Murray P, Stevens A
J Clin Endocrinol Metab 2024;109:1214–1221

Identification of novel genes including NAV2 associated with isolated tall stature
Weiss B, Ott T, Vick P, Lui JC, Roeth R, Vogel S, Waldmüller S, Hoffmann S, Baron J, Wit JM, Rappold GA
Front Endocrinol (Lausanne) 2023;14:1258313

Safety and efficacy of bilateral epiphysiodesis surgery to reduce final height in extremely tall adolescents: a follow-up study
Aeppli TRJ, Benyi E, Wehtje H, Chrysis D, Sävendahl L
Horm Res Paediatr 2024 Feb 23. https://doi.org/10.1159/000538016. Epub ahead of print

IGF1 haploinsufficiency: phenotype and response to growth hormone treatment in 9 patients
Punt LD, van der Kaay DCM, van Setten PA, de Groote K, Kruijsen AR, Bocca G, de Munnik SA, Renes JS, de Bruin C, Losekoot M, van Duyvenvoorde HA, Wit JM, Joustra SD
Horm Res Paediatr 2024 Jun 28:1–11. https://doi.org/10.1159/000540053. Epub ahead of print

Insulin signaling through the insulin receptor increases linear growth through effects on bone and the GH–IGF-1 axis
Okawa MC, Tuska RM, Lightbourne M, Abel BS, Walter M, Dai Y, Cochran E, Brown RJ
J Clin Endocrinol Metab 2023;109:e96–e106

Gender-affirming hormone therapy preserves skeletal maturation in young mice via the gut microbiome

Pal S[1,2], Morgan X[3], Dar HY[1,2], Gacasan CA[2,4], Patil S[1,2], Stoica A[1,2], Hu YJ,[5] Weitzmann MN[1,2,6], Jones RM[2,4], Pacifici R[1,2,7]

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J Clin Invest 2024;134:e175410

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https://pubmed.ncbi.nlm.nih.gov/38530358/

Comments: Over the past decade, there has been a global increase in adolescents with gender dysphoria, leading to a higher number seeking treatment. Gender-affirming hormone therapy is frequently prescribed to transgender adolescents to alleviate gender dysphoria. However, the impact of such therapy on the developing skeleton remains unclear. Treatment may often also include puberty suppression, which can further complicate the situation. Since approximately 30%–40% of peak bone mass is accumulated during adolescence, manipulating normal puberty could affect peak bone mass. Current clinical studies on hormone therapy and bone mass in adolescents with gender dysphoria have yielded conflicting results. Recent research has highlighted the critical role of gut microbiota in regulating bone development. Additionally, a connection between sex steroids, puberty, and gut microbiota has been established. Despite these findings, the relationship between hormone therapy in adolescents with gender dysphoria, bone accrual, and gut microbiota interaction remains unknown.

In this experimental study, Pal et al. evaluated the impact of gender-affirming hormones in male and female mice that had undergone orchiectomy. The results indicated that estrogen supplementation in young male mice led to an improvement in trabecular bone structure by improvement bone formation. However, testosterone treatment in female mice did not produce similar improvements in trabecular structure. Moreover, the investigators found that gender-affirming hormone therapy altered the gut microbiome composition in both male and female mice. Notably, fecal microbiota transfers revealed that the gut microbiome shaped by hormone therapy regulated bone structure and turnover in male mice but not in female mice. Two *Bacteroides* species were identified as significant contributors to the bone effects observed in male mice. These species have the capacity to expand Treg populations in the gut. The experimental results also showed that gender-affirming hormone therapy increased intestinal Tregs and stimulated their migration to the bone marrow in male mice, but not in female mice. Pharmacological blockade of Treg expansion

prevented the bone anabolic effects of the hormone therapy. Thus, in male mice, gender-affirming hormones stimulated bone formation and improved trabecular structure by promoting Treg expansion mediated through the microbiome. In female mice, hormone therapy neither improved nor impaired trabecular structure. Further studies should explore the role of dietary interactions with the microbiome and hormone therapy and open up the possibility of a nutritional supplemental approach to mitigate bone loss in adolescents with gender dysphoria.

Exploring the mechanistic interplay between gut microbiota and precocious puberty: a narrative review

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Microorganisms 2024;12:323

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https://pubmed.ncbi.nlm.nih.gov/38399733/

Comments: Recently, there has been a global increase in the incidence of precocious puberty, particularly among girls, with approximately 90% of central precocious puberty cases having no clearly identifiable cause. The underlying reason for this global increase of precocious puberty remains unclear. Recent research suggests that the gut microbiota is involved in the process of sexual maturation during puberty, showing notable differences in composition before and after this crucial developmental stage. Although a link between precocious puberty and the gut microbiota has been suggested, the exact causality and underlying mechanisms remain unclear.

The authors conducted a narrative review aiming to systematically elucidate published literature that address the potential mechanisms underlying the complex relationship between the gut microbiota and precocious puberty. While not a systematic review, a structured and systematic search of the literature was performed. Key areas addressed include the impact of the gut microbiota on endocrine function, particularly its role in regulating hormones such as gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Additionally, the authors examined the complex interplay between the gut microbiome, metabolism, and obesity, given the established association between obesity and precocious puberty. The review also touched on how the microbiome's involvement in nutrient metabolism may influence the onset of precocious puberty. In addition, the microbiota's ability to produce neurotransmitters and neuroactive compounds (the gut-brain link) that could affect the central nervous system components involved in regulating puberty was also reviewed and discussed. Future research to identify

unexplored targets via the role of the gut microbiome in precocious puberty may lead to the development of noninvasive diagnostic methods and innovative therapeutic strategies, such as specific nutritional or probiotic therapies, for managing precocious puberty.

Gut microbiota-metabolite interactions meditate the effect of dietary patterns on precocious puberty

Wang Y[1,2], Jin C[3,4], Li H[1,2], Liang X[1,2], Zhao C[3,4], Wu N[3,4], Yue M[3,4], Zhao L[3,5,6], Yu H[1,2], Wang Q[1,2], Ge Y[1,2], Huo M[1,2], Lv X[1,2], Zhang L[1,2], Zhao G[3,4,7,8], Gai Z[1,2]

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iScience 2024;27:109887

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https://pubmed.ncbi.nlm.nih.gov/38784002/

Comments: In this experimental study, Wang et al. explored the interaction between gut microbiota and dietary pattern in 21 girls with central precocious puberty, 45 girls with peripheral precocious puberty, and 48 healthy controls. The investigators found that increased alpha diversity and abundance of short-chain fatty acid-producing bacteria led to elevated levels of luteinizing hormone and follicle-stimulating hormone, contributing to precocious puberty. The investigators also found that it may be possible to utilize specific microbiota as diagnostic value for precocious puberty. The *Prevotella* genus-controlled interaction factor, influenced by complex carbohydrate consumption, mediated a reduction in estradiol levels. Interactions between obesity-related bacteria and metabolites mediated the beneficial effect of seafood in reducing luteinizing hormone levels, reducing the risk of obesity-induced precocious puberty, and preventing progression from peripheral precocious to central precocious puberty. This study provides valuable insights into the complex interplay between diet, gut microbiota, and metabolites in the onset. The study should also be replicated in other countries with different dietary patterns. In addition, these results point to further research into dietary intervention as management of precocious puberty.

Natural sweetener glycyrrhizin protects against precocious puberty by modulating the gut microbiome

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Life Sci 2024;350:122789

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https://pubmed.ncbi.nlm.nih.gov/38848942/

Comments: Precocious puberty is the early onset of puberty, defined as breast development in girls under 8 and testicular enlargement in boys under 9. This condition can lead to adverse outcomes and has become more common, especially in girls, over the past 10–20 years. The most frequent cause is central precocious puberty, resulting from the premature activation of the hypothalamic-pituitary-gonadal axis, influenced by genetic and environmental factors involving the endocrine and central nervous systems. Recent research suggests a link between gut microbiota and puberty, indicating that precocious puberty may be a gut-brain disorder. Current diagnostic and treatment methods for central precocious puberty can be invasive, poorly tolerated, and expensive, highlighting the need for alternative strategies. Glycyrrhizin, a natural sweetener, has gained popularity for its health benefits. Although its impact on precocious puberty remains unexplored, there is emerging evidence that natural sweeteners might affect puberty.

Nguyen et al. aimed to explore the protective effects of glycyrrhizin against precocious puberty through both human observational and animal interventional studies. The human observational study utilized clinical data from the Taiwan Puberty Longitudinal Study, which has enrolled over 2,500 children from pediatric endocrinology outpatient clinics since 2018. In the animal study, female rats with danazol-induced precocious puberty were treated with glycyrrhizin in the form of monoammonium glycyrrhizinate. Researchers collected blood and fecal samples and conducted fecal microbiota transplantation to establish a causal relationship between glycyrrhizin and precocious puberty.

In the human studies, glycyrrhizin intake, assessed using a validated semiquantitative food frequency questionnaire, exhibited a protective effect against precocious puberty in children (OR: 0.60, 95% CI: 0.39–0.89, $p = 0.013$), driven primarily by its significance in girls. No significant effect was observed in boys. Differences in alpha and beta diversity of gut microbiota were identified between low and high glycyrrhizin consumers and nonconsumers. However, the significant relationship

between glycyrrhizin intake and precocious puberty was no longer statistically significant after adjusting for BMI Z-scores.

The effect of glycyrrhizin intake on precocious puberty in the human study was consistent with findings in rodents. These benefits were achieved through modulation of the gut microbiome, which functionally suppressed the hypothalamic-pituitary-gonadal axis. This includes inhibition of the GnRH expression. Fecal microbiota transplantation indicated that the causal relationship between glycyrrhizin intake and precocious puberty is mediated by alterations in the gut microbiome.

This study suggests that glycyrrhizin may protect against precocious puberty by altering the gut microbiome. These findings should be replicated by other researchers, and if consistent, randomized clinical trials will be necessary to test the safety and efficacy of glycyrrhizin in clinical practice.

Aspartame intake delayed puberty onset in female offspring rats and girls

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Mol Nutr Food Res 2024;68:e2300270

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Comments: Recent research has identified that dietary factors can influence the hypothalamic-pituitary-gonadal axis, thereby affecting pubertal onset and progression. The effects of nutrition may be mediated by alterations in the gut microbiota, which, in turn, can impact the brain through the gut-brain axis, with central neurotransmitters playing a role in the regulation of puberty. Nonnutritive sweeteners have been shown to influence pubertal development and the maturation of reproductive organs. This study investigates the effects of long-term aspartame consumption on puberty and gut microbiota in both animals and humans.

In the animal studies, aspartame-fed female offspring rats exhibited delayed vaginal opening, reduced serum estrogen levels, and elevated serum luteinizing hormone levels. Aspartame treatment (60 mg/kg) decreased the mRNA levels of gonadotropin-releasing hormone, Kiss1, and G protein-coupled receptor 54, which are critical for the release of GnRH from the hypothalamus. Additionally, it reduced the expression of gonadotropin-releasing hormone neurons in the hypothalamus. Aspartame treatment also resulted in significant differences in the relative bacterial abundance at the genus level (beta diversity strain) and decreased fecal short-chain fatty acid levels, with *Escherichia* and *Shigella* negatively correlated with several short-chain fatty acids. In the human studies involving 399 boys and 858 girls, high-dose aspartame consumption, as determined by a

validated food frequency questionnaire, was associated with a decreased risk of precocious puberty in girls. However, no differences in gut microbiota composition were observed between the groups.

These preliminary findings suggest that aspartame may reduce the risk of early-onset puberty in female offspring and girls. Specifically, in the animal study, aspartame-fed female offsprings (60 mg/kg) experienced delayed pubertal onset, which was linked to the dysregulation of the hypothalamic-pituitary-gonadal axis and alterations in gut microbiota composition. The investigators focused on the relationship between aspartame consumption and the risk of precocious puberty; however, further research is needed to explore the potential impact of aspartame on delayed puberty, which is more commonly observed in boys.

Children with idiopathic short stature have significantly different gut microbiota than their normal height siblings: a case-control study

Lazar L[1,2], Eshel A[3], Moadi L[3], Yackobovitch-Gavan M[1,2,4], Bar-Maisels M[2,5], Shtaif B[1,5], Nevo M[2], Phillip M[1,2,5], Turjeman S[3], Koren O[3], Gat-Yablonski G[1,2,5]

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Front Endocrinol (Lausanne) 2024;15:1343337

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https://pubmed.ncbi.nlm.nih.gov/38464968/

Comments: As demonstrated by previously presented articles, microbiota could have an important effect on the timing and possibly progression of puberty. Both could affect the pattern of growth and final height. In this case-control study, microbiota of prepubertal children with ISS and their siblings was studied. Significant differences in metabolomics and gut microbiota were identified.

Specifically, phylum Euryarchaeota was present exclusively in children with ISS. Within the ISS group, two subgroups were created. One with a similar gut microbiota composition to their normal height sibling and one with a different composition. In the latter group, genus *Methanobrevibacter* was found exclusively. These ISS children were significantly shorter than those from the first ISS subgroup. These findings suggest that the composition of GM may play a role in explaining disparities in linear growth in some of the ISS children. In addition, differences in the metabolomic profile between groups were determined. Bioinformatics analysis suggests a possible increase in genes encoding enzymes involved in the de novo biosynthesis of pyrimidines and purines, as well as flavin, thiamine, and other similar compounds in the ISS group remains unclear what clinical significance an increase in fecal levels of these compounds would have in children with ISS. The strength of the study lies in its design. The control of each ISS child with their normal-height sibling enabled reduction of the bias of confounding factors such as genetics, living environment, and dietary habits.

GH therapy in children with juvenile idiopathic arthritis: a four-decade review

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Clin Pediatr Endocrinol 2024;33:1–11

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https://pubmed.ncbi.nlm.nih.gov/38299178/

Comments: Linear growth is a complex process that can be significantly affected by chronic disease in children with growth potential. One of them is juvenile idiopathic arthritis (JIA), which is a chronic inflammatory joint disease of unknown etiology that begins before age 16 years and lasts for more than 6 weeks. Several subtypes exist and all are associated with growth failure, ranging from a slight decrease in height to severe short stature. Mechanisms leading to growth failure are linked to chronic inflammation, poor nutritional intake, increased catabolism, decreased energy expenditure, and therapy (most significantly by glucosteroids). The increasing use of biological drugs has significantly decreased the use of systemic glucocorticoids, severely restricting adverse effects such as growth failure and subsequently reducing the need for rhGH in patients with JIA.

In this review, authors discuss aforementioned causes on regulation, circulation, and action of GH in IGF-1. Special attention is dedicated to the actions at the level of the growth plate (IL-6, IL-1, TNF-alpha), where chondrocyte proliferation and differentiation are decreased, along with the silencing of growth hormone actions directly and IGF-1 actions indirectly. In addition to effective and safe treatment of JIA (including medications and nutrition), the role of GH treatment is discussed in detail, enabling us an excellent insight into the feasibility of the use of GH in promoting growth in JIA. Combination therapy with modulators of puberty in addition to GH is also discussed.

Altogether, as is discussed extensively in this review, in addition to effective and safe JIA treatment, GH treatment alone or with modulators of puberty can be effective to some effect. Optimal final height can however seldom be achieved.

Cisplatin triggers oxidative stress, apoptosis and pro-inflammatory responses by inhibiting the SIRT1-mediated Nrf2 pathway in chondrocytes

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Environ Toxicol 2023;38:2476–2486

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Comments: Due to the advancement of cancer therapies, most children with cancer can survive into adulthood. Accumulating evidence suggests that various cancer treatments or comedication for childhood malignancies cause chondrocyte apoptosis and growth plate disfunction. Several investigations have shown that chemotherapeutic agents affect the proliferative capacity of growth plate chondrocytes, leading to a decrease in growth rate. Cisplatin has been found to reduce chondrocyte proliferation in vitro and inhibit the height of the individual proliferating layer of the growth plate by inhibiting cell cycle progression. Cell molecular mechanisms underlying the influences of cisplatin on growth plate chondrocyte proliferation have been studied in this study.

SIRT1 is an important modulator of cartilage homeostasis acting via transactivation of collagen 2(α1) and recruitment of PGC-1α to the collagen 2(α1) promoter in chondrocytes. SIRT1 also has been shown to regulate cell survival of chondrocytes through blockage of apoptosis. SIRT1 has been implicated in the stimulation of longitudinal bone growth as well as growth plate chondrogenesis. Therefore, the study aimed to assess the cell viability and the expression of SIRT1 in chondrocytes following chemotherapy to better understand the cisplatin-impaired homeostasis of chondrocytes and the possible mechanism underlying the growth plate dysfunction of patients with childhood cancers treated with cisplatin. Moreover, we observed that cell viability was reduced in cisplatin-receiving cells, while this phenomenon was prevented when SIRT1 activator was coadded.

Altogether, it was determined that cisplatin suppresses SIRT1/PGC-1α signaling, leading to apoptosis and oxidative stress. These data suggest that possible protective adjunctive therapy might be needed when treatment with cisplatin is used in children with growth potential treated for cancer.

Growth disorders caused by variants in epigenetic regulators: progress and prospects

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Comments: It is well known that genetics has an important role in linear growth. Each year we report on novel genes involved in different pathways associated with growth and there are now more than 400 genes associated with skeletal dysplasia. However, there are still gaps in our knowledge in regard to both genetic and perhaps even bigger gaps in epigenetic causes. In part, this is due to the developments in the technology that enables accurate and reproducible results. The role of environment on the expression or genes is becoming more and more revealed. Since epigenetics is becoming more and more advanced, both for research and diagnostic purposes, the present review is an excellent possibility to familiarize oneself with the up-to-date knowledge on the topic.

Over the years, many targets that regulate gene expression via epigenetic mechanisms have been identified. Molecules involved in epigenetic regulation of DNA transcription in a posttranscription modulation can be categorized into several classes: histone acetylation, histone methylation, DNA methylation, chromatin remodeling, and noncoding RNA. In the review, each of the possible mechanisms is discussed in detail in relation to the influence on the certain stage in the endochondral ossification or senescence. Altogether epigenetic processes that influence growth are good candidates for drug development also in growth failure disorders. Compared to genetic mutations, epigenetic alternations have greater plasticity and are more likely to be reversible. Epigenetic drugs, or epidrugs, are nowadays best recognized in cancer biology. Some of the drugs have similar targets also in disorders of growth. Efficacy and especially short- and long-term safety, however, need to be addressed prior to their use in disorders of growth caused by epigenetic mechanism.

Gene expression signatures predict first-year response to somapacitan treatment in children with growth hormone deficiency

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J Clin Endocrinol Metab 2024;109:1214–1221

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Comments: There is a wide consensus that treatment of children with growth hormone deficiency by either daily or recently approved weekly growth hormone is effective. However, there are challenges in predicting growth response to GH therapy in individuals and the variability in treatment outcomes. Nowadays, the importance of personalized treatment approaches is emphasized.

In this interesting clinical research study, the focus was on predicting growth response in children with growth hormone deficiency undergoing treatment with once-weekly somapacitan or daily growth hormone therapy. It highlights the use of RNA-seq analysis and clinical variables to forecast response, the advantages of reducing treatment burden with somapacitan, and the importance of predictive models in guiding treatment decisions.

The study emphasizes the value of pretreatment blood transcriptome profiling in predicting therapy response. A common set of genes can predict the treatment response to both once-weekly somapacitan and conventional daily GH. This approach could potentially be developed into a clinically applicable pretreatment test to improve clinical management. The research emphasizes the importance of personalized medicine in optimizing treatment outcomes for children with GHD and highlights the variability in treatment outcomes, advocating for tailored treatment approaches.

Identification of novel genes including NAV2 associated with isolated tall stature

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Front Endocrinol (Lausanne) 2023;14:1258313
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Comments: Novel genes associated with linear growth can be identified both in population of individuals with short stature and those with tall stature. Variants in the same gene can result in either modified expression of the gene leading to decreased growth velocity and short final stature or increased growth velocity and tall final height. Identifications of these genes is important to identify signaling pathways important for linear growth. This enables further, more targeted research focusing on these pathways with the goal of identifying other potential target genes. This of course opens new possibilities for more targeted treatment of specific disorders of growth.

In the present study, a three-generation family with extreme tall stature was studied to identify potential genetic targets shared in the family. Using whole exome sequencing, six genes were identified as potential candidates. Using publicly available GWAS studies data, *NAV2* was one of the three potential genes associated with tall stature in the studied family cluster. Further, network analysis by ingenuity pathway analysis was carried out. To gain insight into the functional role of these candidate genes in bone growth, mRNA expression in murine growth plates was performed. *NAV2* was identified as the strongest gene associated with functional role in the growth plate. Finally, a variant in the NAV2 gene was also determined in an unrelated individual with tall stature.

Altogether *NAV2* can be considered a novel gene associated with both short and tall stature.

Safety and efficacy of bilateral epiphysiodesis surgery to reduce final height in extremely tall adolescents: a follow-up study

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Horm Res Paediatr 2024 Feb 23. https://doi.org/10.1159/000538016. Epub ahead of print
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Comments: In addition to studying mechanisms leading to short stature, studying those leading to tall stature can inform us equally in regard to the mechanisms of linear growth and final height. Better understanding this mechanism in relation to growth and conditions related to growth importantly affects our understanding of these conditions and leads us to better decision-making regarding diagnosis and treatment of children with both short and tall stature.

Perhaps less well known is the fact that individuals with tall and especially extremely tall stature (males >200 cm, females >186 cm) are at an increased risk for certain physical and psychological problems. Therefore, they present to pediatric endocrinologist to be considered for therapy. Treatment options for tall stature are however limited. Using high doses of sex hormones (estradiol and testosterone) that promote senescence at the growth plate and therefore decreases the time of linear growth has serious side effects and should be implemented very early in puberty to be effective. Somatostatin, counteracting GH secretion, is another proposed method that is at the moment not considered as the mainstay of treatment due to the lack of long-term efficacy and safety data.

In this study, another method affecting linear growth is considered. Efficacy and safety of bilateral epiphysiodesis around the knee in extremely tall girls were studied until final height was achieved. In this single-center study, 72 subjects were followed up from surgery (age 12.3 ± 0.2 years in girls and 13.7 ± 0.2 years in boys). Their height at surgery was already relatively high (175.7 cm in girls and 188 in boys). The final heights were 185.3 in girls and 199.9 in boys. The difference between predicted and final height was 3.6 in girls and 8.6 in boys. No serious complications were reported; however, prolonged postoperative pain was present in about 1/3 of participants in addition to other less frequent surgery-related complications.

Altogether surgical intervention at the level of growth plate was determined to have an important effect on the process of linear growth, which could be applied to discussions of the procedure in both tall and other children, as it does affect final height. Greater reductions in growth can be achieved when performed earlier and in boys.

IGF1 haploinsufficiency: phenotype and response to growth hormone treatment in 9 patients

Punt LD[1], van der Kaay DCM[2], van Setten PA[3], de Groote K[1], Kruijsen AR[1], Bocca G[4], de Munnik SA[5], Renes JS[6,7], de Bruin C[1], Losekoot M[8], van Duyvenvoorde HA[8], Wit JM[1], Joustra SD[1]

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Horm Res Paediatr 2024 Jun 28:1–11. https://doi.org/10.1159/000540053. Epub ahead of print

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https://pubmed.ncbi.nlm.nih.gov/38952118/

Comments: In the present manuscript, the authors described nine patients with heterozygous IGF-1 variants from six families and observed severe proportionate short stature (mean −3.8 SD), moderate microcephaly, early feeding difficulties, low serum IGF-1 values in combination with IGFBP-3 in the upper half of the reference range, sufficient stimulated GH peaks, and moderately low birth weight (−1.7 SDS) and length (−1.9 SDS).

IGF-1 haploinsufficiency is a rare phenomenon. Search of the literature reveals only few case reports of children with heterozygous IGF-1 variant and even fewer were treated with growth hormone. Case reports and retrospective case series are, therefore, important to the clinician who follows up patients with short stature. Even though there were differences in the respond to GH therapy, overall, there was a positive increment in height SDS and growth rate of the treated children. During therapy in most children, IGF-1 levels increased by 1 SDS but remained below 0 SDS in 50% of the children. It might be that GH dosing regimen of children with IGF-1 haploinsufficiency should be different from the dosing of children with SGA and ISS. It is reasonable to think that titration of GH dose should be based on IGF-1 levels with the aim of achieving IGF-1 level between 0 and 2 SDS during therapy.

Since the experience with IGF-1 haploinsufficiency is scarce, the clinical description of the new nine cases and their response to GH treatment might help clinicians to decide whom to screen for that mutation and how to treat them.

Insulin signaling through the insulin receptor increases linear growth through effects on bone and the GH–IGF-1 axis

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J Clin Endocrinol Metab 2023;109:e96–e106

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Comments: It is impossible to conduct prospective randomized controlled studies (which are the most valuable tools for the practice of evidence-based medicine) in rare diseases. In the present manuscript, the authors, in a very elegant way, used several medical situations created by "mistakes of nature" to try and better understand the mechanisms, whereby insulin receptor signaling influence growth. In their retrospective study, they chose to investigate the growth of children with congenital generalized lipodystrophy (CGL), which is associated with a severe pathway-selective insulin resistance, and children with nonselective insulin resistance, which is caused by genetic mutations of the gene for insulin receptor. They were able to collect information of 23 patients with congenital lipodystrophy, 13 patients with homozygous insulin receptor mutations, 17 patients with autosomal dominant mutations, and 8 patients with type B insulin resistance in the active period and during remission. Comparing the four groups, the similarities and the differences between them, they were able to better understand the direct effect of insulin through its receptor on children's growth and the indirect effect through the GH-IGF1 axis.

In our clinical life, we meet patients who come to see us with different gene mutations and medical conditions that affect their growth. Like in many other medical situations, "experiments of nature" can teach us more about normal physiology. Over the years, many "mistakes of nature" shed light on unknown mechanisms and led to elucidate different biological situations. It is, therefore, our obligation to stay alert to use those situations to expand our understanding of mechanisms of growth and possible ways of interventions.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 49–72 (DOI: 10.1159/000541850)

Obesity, Metabolic Syndrome, and Nutrition

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Introduction

Childhood obesity is a significant global health issue with serious implications for the well-being of children and society at large. It adversely affects both physical and mental health and often continues into adulthood, increasing the risk of morbidity and mortality. The multifaceted nature of childhood obesity arises from a complex interplay of genetic, environmental, socioeconomic, and behavioral factors.

Nutrition plays a significant role in both the prevention and management of childhood obesity. Despite substantial efforts, numerous challenges remain in addressing this issue and promoting healthy nutrition. These challenges include socioeconomic disparities in access to nutritious food, pervasive marketing of unhealthy foods to children, inadequate nutrition education, and cultural norms surrounding food and eating behaviors.

Early-life conditions significantly impact the physiology and metabolism of the unborn child, contributing to the early shaping of human health. Several studies reviewed in this chapter examine in utero exposures such as maternal weight, maternal gestational diabetes, maternal diet quality during pregnancy and postpartum, and maternal supplementation during pregnancy with folic acid, docosahexaenoic acid, and fish oil. These studies explore the associations between these factors and the subsequent development of childhood obesity and cardiometabolic risk in offspring.

Early-life nutrition also plays a significant role in lifelong health. Some studies evaluated breastfeeding as a preventive measure against obesity and examined the content of infant formula as a factor influencing childhood adiposity, insulin resistance, and cardiometabolic risk. Additionally, one study assessed the impact of the timing and quality of complementary food introduction in infancy on ectopic fat deposition in childhood.

Further studies investigated the impact of diet composition and mineral intake during childhood on adiposity. A healthy diet is essential for fostering healthy growth and preventing future diseases. The global increase in ultra-processed food consumption has contributed to rising obesity trends. Children with obesity are at higher risk of developing obesity-related comorbidities. A systematic review presented in this chapter reports on the impact of ultra-processed food intake on obesity and cardiometabolic comorbidities in children and adolescents.

In this year's edition of the yearbook chapter focused on the relationship between nutrition and obesity, we conducted a Medline search for articles dealing with the following topics: nutrition and obesity and nutrition and cardiometabolic comorbidities from infancy to childhood and young adulthood. We selected 14 notable articles from many meritorious manuscripts that offer some insight into these issues published in the past year between July 2023 and June 2024.

Key articles reviewed for this chapter

Maternal Diet during Pregnancy and Risk of Childhood Obesity

Relationships of pregnancy and postpartum diet quality with offspring birth weight and weight status through 12 months
Lipsky L, Cummings J, Siega-Riz AM, Nansel T
Obesity (Silver Spring) 2023;31:3008–3015

Maternal folic acid supplementation during pregnancy in association with childhood overweight or obesity
Hung CY, Lee HJ, Tsai ZT, Huang SJ, Huang HY, Tsai HJ, Yao TC
Obesity (Silver Spring) 2024;32:1179–1186

Effects of prenatal docosahexaenoic acid supplementation on offspring cardiometabolic health at 11 years differs by maternal single nucleotide polymorphism rs174602: follow-up of a randomized controlled trial in Mexico
Wimalasena ST, Ramírez-Silva CI, Gonzalez Casanova I, Stein AD, Sun YV, Rivera JA, Demmelmair H, Koletzko B, Ramakrishnan U
Am J Clin Nutr 2023;118:1123–1132

Fish oil supplementation during pregnancy, anthropometrics, and metabolic health at age ten: a randomized clinical trial
Vinding RK, Sevelsted A, Horner D, Vahman N, Lauritzen L, Hagen CP, Chawes B, Stokholm J, Bønnelykke K
Am J Clin Nutr 2024;119:960–968

Randomization to a provided higher-complex-carbohydrate versus conventional diet in gestational diabetes mellitus results in similar newborn adiposity
Hernandez TL, Farabi SS, Fosdick BK, Hirsch N, Dunn EZ, Rolloff K, Corbett JP, Haugen E, Marden T, Higgins J, Friedman JE, Barbour LA
Diabetes Care 2023;46:1931–1940

Associations among prenatal exposure to gestational diabetes mellitus, brain structure, and child adiposity markers
Luo S, Hsu E, Lawrence KE, Adise S, Pickering TA, Herting MM, Buchanan T, Page KA, Thompson PM
Obesity (Silver Spring) 2023;31:2699–2708

Nutrition during Infancy and Risk of Childhood Obesity

Maternal pre-pregnancy BMI, breastfeeding, and child BMI
Shipp GM, Wosu AC, Knapp EA, Sauder KA, Dabelea D, Perng W, Zhu Y, Ferrara A, Dunlop AL, Deoni S, Gern J, Porucznik C, Aris IM, Karagas MR, Sathyanarayana S, O'Connor TG, Carroll KN, Wright RJ, Hockett CW, Johnson CC, Meeker JD, Cordero J, Paneth N, Comstock SS, Kerver JM; program collaborators for Environmental influences on Child Health Outcomes
Pediatrics 2024;153:e2023061466

Low-protein infant formula enriched with alpha-lactalbumin during early infancy may reduce insulin resistance at 12 months: a follow-up of a randomized controlled trial
Tinghäll Nilsson U, Lönnerdal B, Hernell O, Kvistgaard AS, Jacobsen LN, Karlsland Åkeson P
Nutrients 2024;16:1026

Infant milk formula with large, milk phospholipid-coated lipid droplets enriched in dairy lipids affects body mass index trajectories and blood pressure at school age: follow-up of a randomized controlled trial
Abrahamse-Berkeveld M, Jespers SN, Khoo PC, Rigo V, Peeters SM, van Beek RH, Norbruis OF, Schoen S, Marintcheva-Petrova M, van der Beek EM, Stoelhorst GM, Vandenplas Y, Hokken-Koelega AC; Mercurius Study Group
Am J Clin Nutr 2024;119:87–99

Nutrition during Childhood and Risk of Childhood Obesity

Epigenome-wide meta-analysis reveals associations between dietary glycemic index and glycemic load and DNA methylation in children and adolescents of different body sizes
Ott R, Stein R, Hauta-Alus HH, Ronkainen J, Fernández-Barrés S, Spielau U, Kirsten H, Poulain T, Melton PE, Küpers LK, Azaryah H, Colombo M, Landgraf K, Tobi EW, O'Sullivan T, Huang RC, Campoy C, Winkler C, Vioque J, Vrijheid M, Kiess W, Körner A, Sebert S, Jarvelin MR, Ziegler AG, Hummel S
Diabetes Care 2023;46:2067–2075

Association between minerals intake and childhood obesity: a cross-sectional study of the NHANES database in 2007–2014
Wang L, Liu W, Bi S, Zhou L, Li L
PLoS ONE 2023;18:e0295765

Longitudinal associations between diet quality, sedentary behaviours and physical activity and risk of overweight and obesity in preschool children: the ToyBox-study
Miguel-Berges ML, Mouratidou T, Santaliestra-Pasias A, Androutsos O, Iotova V, Galcheva S, De Craemer M, Cardon G, Koletzko B, Kulaga Z, Manios Y, Moreno LA; on behalf of the ToyBox-study group
Pediatr Obes 2023;18:e13068

Nutrition and Risk of Obesity-Related Comorbidities

Associations of infant feeding practices with abdominal and hepatic fat measures in childhood in the longitudinal Healthy Start Study
Cohen CC, Harrall KK, Hu H, Glueck DH, Perng W, Shankar K, Dabelea D
Am J Clin Nutr 2024;119:560–568

The impact of ultra-processed foods on obesity and cardiometabolic comorbidities in children and adolescents: a systematic review
Petridi E, Karatzi K, Magriplis E, Charidemou E, Philippou E, Zampelas A
Nutr Rev 2024;82:913–928

Relationships of pregnancy and postpartum diet quality with offspring birth weight and weight status through 12 months

Lipsky L[1], Cummings J[1,2], Siega-Riz AM[3,4], Nansel T[1]

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Obesity (Silver Spring) 2023;31:3008–3015

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https://pubmed.ncbi.nlm.nih.gov/37731285/

Comments: Understanding influences on infant weight status is critical for preventing child obesity risk. Maternal pregnancy nutrition is an important factor on fetal growth. In fact, available data have documented lower odds for macrosomia and multiple indicators of lower neonatal adiposity and weight status (e.g., skinfolds, fat mass, and size-for-gestational-age) are associated with several condition including a lower maternal high-fat diet, higher protein diet, greater intake of fruit and pulses, healthier data-derived dietary patterns, and higher scores on a priori diet quality indices. However, still few data characterizing the relationship of pregnancy and postpartum diet quality with weight status throughout infancy are available. In this prospective, observational study, Lipsky et al. by evaluating data from the Pregnancy Eating Attributes Study (PEAS) (a prospective cohort study of women enrolled in early pregnancy and followed up through 12 months postpartum) were able to show that a higher maternal diet quality was associated with lower infant weight-for-length Z-scores and body mass index Z-scores throughout the first year of life. Associations were driven by the moderation components of the Healthy Eating Index (HEI), suggesting that maternal pregnant and postpartum intake of refined grains, added sugars, fatty acids, sodium, and saturated fat is more strongly associated with infant weight outcomes than intake of adequacy components (i.e., fruit, vegetables, whole grains, dairy, and protein foods). Higher pregnancy diet quality was associated with lower large for gestational age child at birth and lower infant age- and sex-specific body mass index Z-scores and weight-for-length Z-scores from birth through age 12 months. In infants who received any breast milk for at least 6 months, maternal postpartum diet quality was associated with lower age- and sex-specific BMI Z-scores and weight-for-length Z-scores from birth through age 12 months, whereas the estimated associations were closer to zero and not statistically significant in infants who were breastfed for fewer than 6 months. Therefore, taken together, these results stress the relevance of adopting strategies aimed to increase maternal adherence to the dietary guidelines for Americans during pregnancy and postpartum, which may lead to lower offspring weight status throughout infancy.

Maternal folic acid supplementation during pregnancy in association with childhood overweight or obesity

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Obesity (Silver Spring) 2024;32:1179–1186

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https://pubmed.ncbi.nlm.nih.gov/38572577/

Comments: Nutrition during pregnancy may influence susceptibility to obesity through epigenetic mechanisms, such as alterations in methylation levels that modify gene expression patterns. Folate intake during pregnancy, as well as the maternal methyltetrahydrofolate reductase (MTHFR) C677T genotype, affects the availability of methyl donors for methylation during gestation. This may, in turn, be associated with offspring body composition in childhood. At present, there is insufficient evidence on whether prenatal folic acid supplementation can have an effect on early childhood health.

A previous study [1] investigated the associations between maternal folic acid supplementation at 18 and 32 weeks of pregnancy, dietary folate intake at 32 weeks of pregnancy, and offspring body composition at age nine in a large cohort of UK children. This study did not find evidence supporting the hypothesis that intrauterine folate exposure influences childhood body composition. In contrast, a prospective birth cohort study from the United States [2] examined whether maternal folate concentrations significantly affect child metabolic health and whether sufficient maternal folate levels can mitigate the metabolic risks associated with pre-pregnancy obesity. This study found an L-shaped association between maternal plasma folate concentrations and child overweight or obesity in an urban low-income population, highlighting the benefits of sufficient folate concentrations, especially among obese mothers. However, maternal plasma folic acid concentrations in this study reflected both dietary intake and folic acid supplementation during pregnancy.

The current study provides further evidence that maternal folic acid supplementation during pregnancy is significantly associated with a decreased risk of childhood overweight, obesity, and body fat percentage, particularly after adjusting for relevant confounding factors. The findings suggest that the beneficial effects of maternal folic acid supplementation on reducing obesity risk may be more pronounced among children with obesity risk factors, such as lack of breastfeeding and low parental educational levels.

The study's strengths include a large population-based cohort and the use of body fat percentages as an objective marker of adiposity. However, limitations include the retrospective self-reporting of maternal folic acid supplementation, which may be subject to recall bias, and the lack of data on dietary folate intake and the dose and timing of folic acid supplementation during pregnancy.

Over the past few decades, folic acid supplementation during pregnancy has been recommended in many countries to prevent neonatal neural tube defects. This study illuminates additional beneficial effects of folic acid supplementation during pregnancy, suggesting potential benefits beyond neurodevelopment that may extend to obesity prevention.

Effects of prenatal docosahexaenoic acid supplementation on offspring cardiometabolic health at 11 years differs by maternal single nucleotide polymorphism rs174602: follow-up of a randomized controlled trial in Mexico

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Am J Clin Nutr 2023;118:1123–1132

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Comments: Docosahexaenoic acid (DHA) is an omega-3 long-chain polyunsaturated fatty acid (LC-PUFA) that plays a crucial role during the latter half of pregnancy, supporting optimal fetal tissue development, immune function, and DHA deposition in fetal tissues. Animal models and epidemiological studies indicate that variations in prenatal DHA supply may affect long-term cardiometabolic risk in offspring by influencing cell and organ development, gene expression, and neuroendocrine signaling pathways.

Observational studies in humans [3] have linked higher maternal omega-3 LC-PUFA status during pregnancy with reduced adiposity, dyslipidemia, and leptin levels in offspring during early to mid-childhood. Moreover, prenatal DHA supplementation appears particularly advantageous for mother-offspring pairs, especially among overweight or obese women. This supplementation enhances maternal insulin sensitivity, improves lipid profiles, and reduces placental inflammation, thereby potentially mitigating fetal overnutrition and adiposity [4]. Tissue LC-PUFA concentrations are determined by dietary intake of omega-6 and omega-3 LC-PUFAs and the endogenous conversion from dietary PUFA precursors. This conversion involves a series of desaturation and elongation steps, with the rate-limiting desaturase steps mediated by Δ-6 and Δ-5 desaturase enzymes encoded by the fatty acid desaturase (*FADS*) gene cluster (*FADS1*, *FADS2*, *FADS3*). Notably, the maternal *FADS2* SNP rs174602 has been shown to influence the impact of prenatal DHA supplementation on offspring birth weight [5] and metabolome at 3 months of age [6].

In the present study, prenatal DHA supplementation exhibited no overall effect on offspring cardiometabolic health at 11 years of age. However, outcomes varied based on maternal *FADS2* SNP rs174602 variants. Offspring of mothers who were

homozygous for the minor allele (TT) and received prenatal DHA supplementation had lower metabolic syndrome (MetS) scores compared to those in the placebo group. Conversely, offspring of mothers homozygous for the major allele (CC) who received DHA supplementation had higher MetS scores compared to those whose mothers received a placebo. These findings suggest that the effects of prenatal DHA supplementation on long-term cardiometabolic risk in children may be influenced by the mother's genotype. Individuals with genotypes associated with lower endogenous conversion to DHA might be at a higher risk of DHA deficiency and could benefit more from supplementation with preformed DHA.

The study's strengths include its double-blind randomized controlled trial (RCT) design, high compliance with the prenatal intervention, comprehensive characterization of mothers and children throughout the trial, long follow-up duration, and availability of genetic data. The study sample was representative of a population with low dietary intakes of preformed DHA, high dietary intakes of omega-6 fatty acids, and a high prevalence of alleles associated with lower conversion of precursor PUFAs into LC-PUFAs.

However, the study also has limitations. Dietary data were collected via a single 24-h recall, which may introduce recall bias. Additionally, the trial was not originally designed to assess offspring cardiometabolic health, leading to small sample sizes and potentially limited statistical power to detect differences by treatment group or genotype. While the study highlights the potential importance of maternal *FADS* genotype in guiding supplementation strategies, the role of offspring genotype remains uncertain. These findings highlight the importance of incorporating genetic analysis of *FADS* polymorphisms in DHA supplementation trials. Such analyses may ultimately help develop targeted supplementation recommendations early in life to improve cardiometabolic health in clinical settings.

Fish oil supplementation during pregnancy, anthropometrics, and metabolic health at age ten: a randomized clinical trial

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Am J Clin Nutr 2024;119:960–968

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Comments: Maternal obesity during pregnancy can lead to systemic inflammation and an exaggerated form of insulin resistance, particularly in the latter half of pregnancy. This condition results in an increased delivery of lipids and glucose to the fetus, which can

lead to higher birth weight and greater body fat in the offspring. The underlying mechanism involves alterations in gene expression mediated by epigenetic changes, potentially increasing the risk of metabolic dysfunction and diseases later in life.

Interventional strategies during pregnancy, particularly anti-inflammatory and insulin-sensitizing treatments, are being explored to mitigate these adverse outcomes. Notably, higher fish consumption during pregnancy, or increased levels of *n*-3 long-chain polyunsaturated fatty acids (LC-PUFAs) from fatty fish, have been associated with lower BMI and healthier metabolic profiles in children, as evidenced by both animal and observational human studies. Fish oil supplementation during pregnancy, which enhances insulin sensitivity [7], is proposed as a potential preventive measure against the development of greater adiposity and metabolic dysfunction in the offspring of overweight or obese mothers.

A previous study [8] examined the effects of fish oil supplementation during the latter half of pregnancy and lactation in overweight or obese mothers on infant body composition and metabolism. The study found that fish oil supplementation reduced maternal and infant triglyceride levels but did not influence maternal or infant insulin resistance or infant body composition. Another randomized controlled trial [9] evaluated the impact of fish oil supplementation from the 24th week of pregnancy on offspring BMI and body composition up to 6 years of age. The trial reported a higher BMI in offspring from birth to 6 years of age without increasing the risk of obesity at age six. The body composition at 6 years was characterized by proportional increases in lean, bone, and fat mass, suggesting a general growth-stimulating effect of *n*-3 LC-PUFA.

The current study extends the follow-up period to age 10 years for participants of the previous study, assessing their metabolic health. The findings suggest that children of mothers who received *n*-3 LC-PUFA supplementation had an increased BMI at age 10, a higher risk of being overweight, tendencies toward a higher fat percentage, and elevated metabolic syndrome score. These results indicate a potential shift in body composition toward a higher proportion of fat mass and a less favorable metabolic profile due to prenatal *n*-3 LC-PUFA supplementation.

The study limitations include the treatment initiation from mid-pregnancy rather than preconception or throughout the entire pregnancy, which may impact results. The study's strengths include a relatively large sample size and a long follow-up period of 10 years.

The findings raise concerns about the potential adverse health effects of *n*-3 LC-PUFA supplementation during pregnancy. Replication of these results in larger, independent randomized controlled trials is essential before making any changes to current recommendations for fish oil supplementation during pregnancy.

Randomization to a provided higher-complex-carbohydrate versus conventional diet in gestational diabetes mellitus results in similar newborn adiposity

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Diabetes Care 2023;46:1931–1940
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Comments: Preventive strategies aimed to tackle the problem of childhood obesity must be focused on all the modifiable risk factors not only related to child life but also associated to those factors related to pregnancy. Particularly, gestational diabetes mellitus represents an important modifiable risk factor. Gestational diabetes mellitus is defined as hyperglycemia first recognized during pregnancy. Gestational diabetes mellitus is related not only to perinatal morbidity but also to an increased risk of diabetes and cardiovascular disease in the mother in later life, and to childhood obesity in the offspring [10]. As pre-pregnancy body mass index has rapidly increased, the global gestational diabetes mellitus prevalence is estimated at 14%, with some high-risk populations exceeding 20% [10]. The United States has reported a 20% increase in gestational diabetes mellitus cases between 2016 and 2020 alone, with Asian, Native American, and Hispanic/Latina women disproportionately affected [11]. Therefore, studies evaluating preventive strategies related to the metabolic alteration related to gestational maternal diabetes are needed. Interestingly, in this controlled, prospective RCT study, authors investigated whether randomization to a higher complex carbohydrate (60%) and lower fat (25%) diet versus a conventional lower carbohydrate (40%) and higher fat (45%) diet in gestational diabetes results in lower newborn adiposity and improves maternal insulin resistance and 24-h glycemia. Authors have shown no between-diet differences in newborn adiposity, maternal 24-h glycemia, and insulin resistance. Thus, despite a 100-g carbohydrate difference, both diets achieved similar glycemic and newborn outcomes. Therefore, these data suggest that flexibility in dietary CHO is possible while limiting simple sugars, saturated fats, and excess calories, paving the way for expanded and personalized options for nutrition therapy in gestational maternal diabetes. Pregnancy is a window period, and occurrence of gestational diabetes mellitus during pregnancy represents an opportunity to reduce short- and long-term risk of adverse health outcomes in the mothers and their children. Offspring born to mothers diagnosed with gestational diabetes mellitus, as defined by the World Health Organization 2013 gestational diabetes mellitus criteria, had higher rates of abnormal glucose tolerance, higher rates of overweight or obesity, greater body mass index, higher blood pressure, lower oral disposition index, and a trend toward reduced β-cell function compared with those born to mothers without gestational diabetes mellitus. Medical nutrition therapy for gestational diabetes mellitus is an individualized nutrition plan developed between the pregnant person and a registered dietitian nutritionist (RDN) familiar with the management of gestational diabetes mellitus [12]. The food plan should provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote appropriate weight gain, according to the 2009 National Academy of Medicine recommendations [12]. However, so far

there is no definitive research that identifies a specific optimal calorie intake for women with gestational diabetes mellitus or suggests that their calorie needs are different from those of pregnant individuals without gestational diabetes mellitus [12]. Therefore, further studies exploring appropriate and novel diet approaches to gestational maternal diabetes are needed to guide public health prevention efforts in childhood obesity.

Associations among prenatal exposure to gestational diabetes mellitus, brain structure, and child adiposity markers

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Obesity (Silver Spring) 2023;31:2699–2708

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Comments: Offspring born to mothers diagnosed with gestational diabetes mellitus have an increased risk of higher adiposity measures (body mass index, waist-to-hip circumference, waist-to-height ratio) and increased risk of developing obesity later in life. Furthermore, the body mass index of offspring exposed to gestational diabetes mellitus is greater than that of their siblings who were not exposed to gestational diabetes mellitus [13], suggesting that the effect of prenatal gestational diabetes mellitus exposure on offspring body mass index is independent of shared genetics and environment. Therefore, different and still not completely elucidated mechanisms for increased obesity risk in gestational diabetes mellitus–exposed offspring need to be characterized. By evaluating anthropometric data in children aged 9–10 years old from the Adolescent Brain Cognitive Development (ABCD) study (a 10-year, large-scale, longitudinal study of pediatric brain and cognitive development in the United States), Shan Luo et al. were able to offer novel and interesting results examining the relationships between prenatal exposure to gestational diabetes mellitus and brain structural measures (i.e., cortical and subcortical volumes, cortical thickness, and surface area). Of note, authors were able to show that prenatal exposure to gestational diabetes mellitus was associated with lower global cortical and regional cortical gray matter volume in the entire study sample. Interestingly, similar results were confirmed also in a subset of the sample including siblings

discordant for gestational diabetes mellitus exposure. Finally, results also showed that the global cortical gray matter volume, in part, mediated relationships between prenatal gestational diabetes mellitus exposure and adiposity markers in children. Therefore, taken together, these results suggest that a low cortical gray matter volume may be a potential neural mechanism by which prenatal gestational diabetes mellitus exposure mediates obesity risk in offspring. Thus, it is important for clinicians to be aware of detrimental effects of diabetes during pregnancy on the developing brain in offspring. In gestational diabetes mellitus–exposed offspring, the mechanisms for the increase of significantly higher rates of abnormal glucose tolerance, higher rates of overweight or obesity, greater body mass index, higher blood pressure, lower oral disposition index, and a trend toward reduced β-cell function still need to be completely characterized. Therefore, additional studies are needed in order to completely understand the underlying mechanisms and suggest novel preventive and therapeutic approach in childhood obesity. In addition, future studies are needed to examine potential interventions that may mitigate adverse effects of prenatal gestational diabetes mellitus exposure on offspring brain development, thereby reducing obesity risk.

Nutrition during Infancy and Risk of Childhood Obesity

Maternal pre-pregnancy BMI, breastfeeding, and child BMI

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This article is also discussed in the chapter by Larnkjær and Mølgaard [this vol., pp. 140–155].

Comments: Childhood obesity has become a public health problem worldwide, thus imposing to take effective preventive and therapeutic measures in children to address the major risk factors related to fat accumulation. Relatively recent data have shown that the characterization of the major risk factors and the most appropriate time of intervention represent two of the major components of all preventive strategies. Particularly, some preventable risk factors need be characterized in peculiar times of the life due to their pivotal role in the risk of childhood obesity. In addition, infancy seems to be one of the most important periods influencing health later in life and may thus represent the best time to prevent obesity and its adverse consequences. A growing amount of evidence suggests that the first 1,000 days of life, encompassing the time from conception to the age of 24 months, is a key period for the development of later overweight and obesity. Several important risk factors have been identified during this period: excessive maternal weight before pregnancy, excessive maternal weight gain during pregnancy, maternal smoking during pregnancy, gestational diabetes, absence or short duration of breastfeeding, high protein intake, caesarean section, vitamin D_3 deficiency, high birth weight or excessive weight gain in the first year of life, low socioeconomic status, shortened daily sleep of the infant, and early (<4 months of age) introduction of solid foods. All these factors can co-occur and, through a cumulative effect, further increase the risk of obesity [14]. Among the modifiable risk factors related to childhood obesity in the first 1,000 days of life, breastfeeding has been shown by a large body of evidence to be a protective factor although still few data evaluating this relationship among women with obesity before and during pregnancy are still poor. Interestingly, in this study by Shipp et al., authors explored the associations between breastfeeding practices and child body mass index for age Z-score (BMIz), stratified by maternal body mass index. Particularly, authors were able to show a protective association between breastfeeding and childhood obesity regardless of maternal pre-pregnancy body mass index category. More importantly, across most breastfeeding exposures, the associations were stronger among children with mothers who had obesity at pre-pregnancy compared with those whose mothers were categorized as overweight at pre-pregnancy. Similar results were observed when comparing children of mothers with pre-pregnancy obesity to mothers with a healthy weight across all breastfeeding practices. Although, the WHO recommends exclusive breastfeeding until 6 months, with continued breastfeeding and appropriate complementary foods up to 2 years of age or beyond, some reports have shown that women with obesity are less likely to initiate breastfeeding and are more prone to early cessation compared with women of a healthy weight. Therefore, these aspects make it difficult to assess the associations between breastfeeding behavior and childhood obesity in this group. These results support the encouragement of all women, including women who are overweight or obese before conception, to breastfeed as a preventive measure against the

development of childhood obesity. Therefore, in order to progress in tackling the problem of childhood obesity, future studies and public health prevention efforts should continue focusing on addressing two highly prevalent problems that disproportionately affect marginalized populations resulting in adverse health outcomes: shortened duration of breastfeeding and maternal overweight and obesity.

Low-protein infant formula enriched with alpha-lactalbumin during early infancy may reduce insulin resistance at 12 months: a follow-up of a randomized controlled trial

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Nutrients 2024;16:1026

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Comments: Despite efforts to promote breastfeeding, various social factors and maternal illnesses often lead mothers to cease breastfeeding prematurely. Consequently, there is a demand for infant formulas that offer optimal nutritional composition essential for adequate infant growth and development. Ongoing research has facilitated the development of infant formulas that closely mimic human milk by incorporating diverse food ingredients to meet infants' nutritional needs and contribute to their development.

Certain studies have indicated that high protein intake during early life may be linked to obesity and an increased risk of metabolic diseases in later stages [15]. To address this, the protein composition of infant formulas has been adjusted in both quality and quantity, reducing protein intake and altering the whey/casein ratio. The development of infant formula containing bovine α-lactalbumin (a whey protein component) has enabled a reduction in the overall protein content of the formula.

Protein overload can result in elevated serum concentrations of branched-chain amino acids (BCAAs), leading to increased secretion of insulin and insulin-like growth factor 1 (IGF-1). Consequently, high protein intake during infancy may be associated with accelerated early weight gain, increased fat deposition, and the development of overweight and obesity [16]. Previous studies have reported higher serum insulin and IGF-1 levels in formula-fed (FF) infants compared to breastfed (BF) infants during the first half of infancy [17]. Thus, the higher protein content in infant formula compared to breast milk could contribute to the higher weight gain observed in FF infants.

Over the past decades, the protein concentration in infant formulas has been reduced, and protein quality has improved. Despite this, current infant formulas with reduced protein concentrations still contain higher protein levels than breast milk. Some infant formulas with protein content slightly below the EU regulatory lower limit, enriched with alpha-lactalbumin-enriched whey (α-lac-EW) or casein glycomacropeptide-reduced whey (CGMP-RW), have been developed.

The current double-blind, controlled, prospective intervention trial with follow-up evaluated the effects on growth, and metabolic and hormonal markers at 12 and

6 months postintervention, of feeding low-protein infant formulas with either α-lac-EW or CGMP-RW compared to standard infant formula or breast milk in early infancy. The study results indicated that growth, as well as serum insulin and C-peptide levels at follow-up at 12 months of age, was more similar to BF infants among those fed low-protein infant formula with either α-lac-EW or CGMP-RW during early infancy. This suggests that low protein intake, closer to that of BF infants, influences growth 6 months postintervention, potentially through reduced insulin resistance. It has been shown previously that although serum BCAAs (S-BCAAs) were higher in all formula groups compared to the BF group during the intervention, S-BCAAs were lower in the low-protein formula groups than in the standard formula group at 6 months [15]. Furthermore, at this age, weight gain and BMI were more similar in the low-protein formula groups and the BF group. Therefore, it is possible that BCAA concentrations influenced insulin concentration postintervention, resulting in lower weight gain between 6 and 12 months and lower BMI at 12 months in the low-protein formula groups compared to the standard formula group, aligning growth rates more closely with BF infants. In this study, serum insulin at 12 months, but not at 6 months, was associated with weight gain between 6 and 12 months, suggesting potential imprinting of insulin secretion by protein intake during the intervention period.

The study's strengths include the analysis of metabolic and hormonal markers (IGF-1, insulin, C-peptide, leptin) 6 months postintervention, which allows for a better evaluation of whether low-protein formula given during the first half of infancy influences growth and the metabolic profile 6 months postintervention. However, the study's limitations include the lack of data regarding body composition, which precludes evaluating the proportions between fat mass and fat-free mass.

The results demonstrated that feeding a modified low-protein infant formula early in life resulted in growth patterns 6 months postintervention that were more similar to those of BF infants compared to feeding a standard formula with higher protein concentration. Hence, further reducing formula protein concentration by modifying protein quality may be a viable strategy for the early prevention of childhood overweight and obesity. Longer follow-up of the study population will be necessary to evaluate whether these findings persist later in childhood.

Infant milk formula with large, milk phospholipid-coated lipid droplets enriched in dairy lipids affects body mass index trajectories and blood pressure at school age: follow-up of a randomized controlled trial

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Am J Clin Nutr 2024;119:87–99
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This article is also discussed in the chapter by Larnkjær and Mølgaard [this vol., pp. 140–155].

Comments: Lipids are essential for healthy infant growth and development. Compared to formula feeding, human milk feeding is associated with different growth and adiposity patterns during infancy and may offer protection against childhood overweight and adverse metabolic health outcomes. One contributing factor could be the distinct differences in the supramolecular structure of lipid droplets. Human milk features large fat globules enveloped by a trilayered phospholipid membrane, while infant milk formula (IMF) contains small lipid droplets primarily coated by proteins.

Recently, a concept IMF was developed to more closely mimic the structure and composition of human milk fat globules. A previous study [18] evaluated whether a concept IMF with large, milk phospholipid-coated lipid droplets is equivalent to standard IMF regarding growth adequacy and safety in healthy, term infants. The findings indicated that the concept IMF supports adequate growth and was well tolerated and safe for use in healthy infants.

Additionally, a multicenter, randomized controlled trial [19] was conducted to assess the nutritional adequacy and safety of a concept IMF with large, milk phospholipid-coated lipid droplets containing dairy lipids. This trial demonstrated that the concept IMF, provided during the first months of age, was safe and well tolerated, with equivalent daily weight gain, daily length gain, and daily head circumference gain from baseline to 4 months of age compared to a control IMF with conventional, small lipid droplets containing vegetable oils.

The present research reports the results of the follow-up period of the previous study [19], focusing on later BMI outcomes until 5 years of age and blood pressure at school age as potential biomarkers for a healthier metabolic trajectory. The findings revealed that compared to the control IMF group, the concept IMF group had consistently lower mean BMI values during follow-up, particularly if the mother had overweight or obesity, with the most pronounced difference observed at 1 year of age, with mean values approaching those of the breastfed group. The control group had higher mean BMI values compared to the breastfed group during the follow-up from 1 to 5 years of age. At 5 years of age, the concept group exhibited lower diastolic and arterial blood pressure compared to the control group.

The study's strengths include its randomized design, multicountry setting, and prospective long-term follow-up with a breastfed infant group included as a reference. However, limitations include the relatively small number of patients in each group during the follow-up period and the lack of data on other foods consumed during the postintervention period, which may have influenced the children's anthropometric status during follow-up.

Future longitudinal, larger clinical studies are necessary to confirm the potential impact of this concept IMF on body composition and metabolic health outcomes.

Epigenome-wide meta-analysis reveals associations between dietary glycemic index and glycemic load and DNA methylation in children and adolescents of different body sizes

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Diabetes Care 2023;46:2067–2075
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Comments: The glycemic index (GI) and glycemic load (GL) are measures for assessing the rate at which the body converts carbohydrates into glucose, thereby indicating the glycemic impact of carbohydrate-containing foods. Previous research, including a meta-

analysis and cohort studies [20], suggests a significant association between high GI or high GL and an increased risk of cardiovascular disease (CVD) events. These events encompass diabetes, metabolic syndrome (MS), coronary heart disease (CHD), stroke, and stroke mortality in the general population. The risk of CVD outcomes appears to be stratified by sex, obesity status, and preexisting CVD conditions. High GI is associated with a higher propensity for CVD risk factors and mortality in healthy individuals, whereas high GL is linked to an elevated risk of severe heart diseases, including CVD or all-cause mortality, particularly in at-risk populations. Consequently, dietary interventions aimed at lowering both GI and GL are recommended for preventing CVD outcomes across all populations.

DNA methylation (DNAm) is a pivotal epigenetic mechanism regulating gene activity. Increasing evidence suggests that dietary factors can influence DNAm, thereby contributing to the long-term health effects of diet. The current study conducted meta-analyses of epigenome-wide association studies (EWAS) to investigate the relationship between dietary GI and GL and blood DNAm in children and adolescents. Researchers identified 537 associations between dietary GI and GL and blood DNAm, predominantly in children and adolescents with overweight or obesity.

The study's strengths include the derivation of GI and GL values across six cohorts and the use of data from similar age groups to evaluate the functional properties of DNAm sites in blood and adipose tissue. However, the study's limitations include a low sample size, particularly in the BMI-stratified analysis. Additionally, heterogeneity arising from various dietary sources across the cohorts may have influenced the GI and GL scores, and misreporting of food consumption could have affected the associations.

Although further investigation is needed to ascertain the functional importance of the identified CpGs, multiple CpGs appear to play regulatory roles in the expression of genes involved in metabolic impairment and obesity development. High-GI and/or high-GL diets may influence epigenetic gene regulation, promoting metabolic derangements in young individuals with increased BMI. Further analyses with larger sample sizes are required to support these observations and explore the causality and functionality of the identified CpG-gene relationships.

Association between minerals intake and childhood obesity: a cross-sectional study of the NHANES database in 2007–2014

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PLoS ONE 2023;18:e0295765

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Comments: The number of children with obesity has increased ten-fold during the last decades worldwide. Epidemiological data have documented a significant shift in its prevalence for boys and girls, moving from 5 and 6 million in 1975 to 50 and 74 million in 2016, respectively. In addition, prediction models have also shown alarming data suggesting that, by the end of 2050, the 25% of all children under 16 years will be

affected by obesity [21]. Obesity in children affects multiple organs in the body and is associated with both significant morbidity and ultimately with an increased risk of chronic diseases and premature mortality. Treatment guidelines currently focus on intervention with lifestyle and behavioral modifications, with pharmacotherapy and surgery reserved for patients who are refractory to such treatment. However, these approaches still need to be perfected. Particularly, most dietary measures on weight control focused on reducing the intake of macronutrients such as carbohydrates and fats. However, recent reports have also focused on a potentially relevant role of other diet components, such as minerals on obesity according to their oxidant or antioxidant functions and effects on insulin and glucose metabolism [22]. Interestingly in the study by Wang et al., authors have explored the association between minerals and obesity and body mass index in a very large group of children with different ages. In this cross-sectional study by using data of 10,450 children aged 2–17 years old extracted from the NHANES database in 2007–2014, authors were able to present robust results on the role of minerals dietary content. In fact, they reported a relevant association between dietary intakes of nine common minerals and childhood obesity and body mass index. Particularly, authors have shown that higher levels of dietary Fe and Zn intakes were associated with lower odds of childhood obesity. Oppositely, higher levels of dietary Cu and Na intakes seemed to be associated with higher odds of obesity. Dietary intakes of Ca, Na, and K were positively linked to the children's body mass index, whereas dietary Fe and Zn consumptions shared negative associations with body mass index. These relationships were also found in children with different age. Although the study has some relevant limitation regarding the retrospective design of the protocol as well as the information used for evaluating the dietary intake, this study clearly suggests that it is necessary to develop individualization recommendations of minerals intake for children with high risk of obesity in different age in the future. In addition, this study may provide some references for further studies exploring the causal associations and may further help the prevention and management of childhood obesity. Therefore, further prospective cohort studies focusing on the long-term effects of dietary minerals intake on childhood obesity are still needed in order to provide relevant information on the effects of not only macronutrients but also common minerals on childhood obesity and body mass index.

Longitudinal associations between diet quality, sedentary behaviours and physical activity and risk of overweight and obesity in preschool children: the ToyBox-study

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Pediatr Obes 2023;18:e13068
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Comments: To manage the growing public health crisis caused by the increasing rates of childhood obesity across the globe, effective and well-researched treatment options are essential. Particularly, all approaches must be started as early as possible. In fact, it is widely recommended that obesity prevention strategies focus on early childhood, as children with excess weight in adolescence are more likely to have obesity as adults. In addition, interventions focused on late childhood and adolescence are less effective given that lifestyle behaviors, such as eating and activity, are formed and established during the early years of life [23]. Moreover, it is important that childhood obesity is tackled early so that it can be managed before the onset of complications. At present, the management of childhood obesity focuses on lifestyle interventions and the importance of appropriate caloric intake. Lifestyle interventions have been shown to work in some patients, but the general increasing trend of this problem shows that it is not sufficient. The causes of these unsuccessful approaches are complex and multifactorial. In addition, they are mainly related to the fact that obesity in childhood is a multifactorial disease, resulting by the tight interaction between individual, sociocultural, community, and other factors, and follows a social gradient. Regarding lifestyle factors, evidence points to the synergetic effect of multiple lifestyle behaviors related to diet, physical activity, and sedentary behaviors, collectively referred to as energy balance–related behaviors (EBRBs), associated with increased risk of overweight and obesity. In the study by Miguel-Berges et al., authors examined the cross-sectional and longitudinal associations between diet, screen time (ST), and step recommendations and risk of overweight and obesity in European preschoolers participating in the ToyBox-study, a cluster-randomized controlled trial aiming to prevent obesity in preschool children conducted in six European countries. Particularly, authors found that adherence to EBRB recommendations was associated with decreased odds of having overweight/obesity. In fact, authors have reported that in European preschool children, the proportion of participants having a low Diet Quality Index score, not adhering to both step and ST recommendations, was very high, and it was associated with a high probability of developing overweight and obesity. The findings of this study strongly indicate that public health obesity prevention efforts should apply an integrated approach to physical activity and dietary intake from early childhood. Therefore, more effective and well-researched treatment options are essential and still need to be completely characterized. The development of effective obesity prevention interventions is even more relevant in the post–COVID-19 era as scientific evidence from young population groups indicates changes in dietary-lifestyle behaviors accompanied by a reduction in physical activity levels and lower energy expenditure that negatively affect body composition and

early metabolic alteration [24, 25]. Therefore, preschool children and their parents should try to increase family time spent at activities promoting physical activity and to minimize the time spent on ST or being sedentary, in order to maximize the effects of all types of preventive strategies in childhood obesity. Particularly, available literature in early years of life is scarce and further studies conducted in children are needed to perfect the available approaches.

Nutrition and Risk of Obesity-Related Comorbidities

Associations of infant feeding practices with abdominal and hepatic fat measures in childhood in the longitudinal Healthy Start Study

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Am J Clin Nutr 2024;119:560–568

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This article is also discussed in the chapter by Larnkjær and Mølgaard [this vol., pp. 140–155].

Comments: Nutritional exposures during the perinatal period, such as infant feeding practices, have been shown to exert long-lasting effects on offspring health, including an increased susceptibility to obesity and related metabolic disorders. Research indicates that greater abdominal fat deposition, particularly visceral fat, and hepatic fat accumulation are significant risk factors for insulin resistance and other cardiometabolic conditions in youth, independent of total adiposity [26].

Previous studies have suggested associations between dietary factors in infancy and the accrual of abdominal subcutaneous and visceral fat early in life [27]. However, whether these associations persist into later childhood remains unclear. A recent study found that a combination of early complementary feeding and a shorter duration of breastfeeding (≤4 months) was linked to elevated adiposity and cardiometabolic markers in children [28].

This study investigated the associations between infant feeding practices and abdominal fat and hepatic fat trajectories in childhood within the Healthy Start Study, a prospective prebirth cohort in Colorado. Abdominal subcutaneous (SAT) and visceral adipose tissue (VAT) areas, along with hepatic fat percentage, were assessed via magnetic resonance imaging (MRI) in early and middle childhood (median ages 5 and 9 years, respectively). The results demonstrated that the timing and quality of complementary foods introduced during infancy and toddlerhood were associated with distinct trajectories for abdominal SAT, VAT, and hepatic fat deposition in childhood. Specifically, early introduction of complementary foods by 4 months was associated with accelerated rates of change in abdominal SAT and VAT from early to middle childhood. A similar pattern was observed for the early introduction of soda,

where children introduced to soda by 18 months exhibited faster rates of change in SAT, VAT, and hepatic fat, leading to higher levels of these outcomes by middle childhood.

Recent meta-analyses have reported a protective effect of human milk consumption in infancy on later obesity risk [29]. A systematic review, including six cohorts with sibling-pair analyses and one randomized controlled trial of a breastfeeding promotion intervention [30], suggested moderate evidence that consuming human milk, as compared to never consuming it, was associated with a lower risk of overweight and obesity at age 2 years and older, particularly if the duration of human milk consumption exceeded 6 months. However, evidence was insufficient to determine the relationship between the duration of any human milk consumption and overweight or obesity at age of 2 years and older. Notably, the current study found no associations between the duration of any human milk consumption and childhood abdominal or hepatic fat trajectories.

The strengths of this study include its relatively large, prospective design involving mother-child dyads who have undergone extensive assessments since pregnancy, with adjustments made for key confounding variables. Additionally, the use of MRI to evaluate abdominal adiposity (SAT and VAT) enhances the robustness of the findings. However, limitations include the fact that only a subgroup of children from the larger cohort underwent abdominal MRI assessments in childhood. Furthermore, the assessment of infant feeding practices relied on self-reported data, which may be subject to recall bias or social desirability bias, particularly among parents of infants with overweight or obesity. Additionally, there was a lack of detailed information on the frequency or dosage of soda and other complementary foods introduced during infancy, which could further influence the strength of the associations observed.

The clinical implications of these findings underscore the importance of educating parents about the timing and quality of complementary foods and beverages introduced during infancy and toddlerhood. Recommendations should also emphasize delaying the introduction of soda during this critical developmental period.

The impact of ultra-processed foods on obesity and cardiometabolic comorbidities in children and adolescents: a systematic review

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Nutr Rev 2024;82:913–928

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Comments: Diet represents one of the keystones of all the preventive and therapeutic approaches in childhood obesity. Particularly, the quality of the dietary pattern is defined not only according to its content in specific nutrients or food items but also by other important factors such as its content in processed foods. Over the last few years, a complex and alarming change in daily diet worldwide has been documented [31, 32]. In fact, in several

countries, traditional foods and freshly prepared dishes and meals have been displaced by ultra-processed foods. Therefore, these changes have determined an alarming shift from healthier diet such as mediterranean diet toward modern diet with ultra-processed foods, characterized by high energy density, sugar, sodium, saturated fats, and trans fats and low fiber and micronutrient content. Therefore, a complete characterization on the adiposity and cardiometabolic risk related to ultra-processed foods consumption in children is important to properly face the alarming data on childhood obesity. In particular, in this scoping systematic review of observational studies, authors attempted to gather all existing knowledge regarding the association between the consumption of ultra-processed foods with obesity and cardiometabolic risk factors among children and adolescents. Particularly, by reporting data obtained from 17 observational studies available, authors have documented that the majority of the studies showed a positive association either in the risk of obesity or in cardiometabolic comorbidities, although the type and quantity of processed foods consumed have not been evaluated. Therefore, this systematic review confirms similar data report in adult subjects [33, 34] and raises concerns for future health regarding modern diet regimes and ultra-processed foods consumption. These modern diets are characterized by a high consumption of many foods that have undergone some degree of processing. Particularly, ultra-processed foods are manufactured using several ingredients, contain little or no whole food, follow a series of processes, and are combined with a sophisticated use of additives to increase their shelf-life and their palatability. These characteristics let the ultra-processed foods that are ready-to-consume or ready-to-heat and thus require little or no culinary preparation, which makes them easily accessible and convenient. However, although more convenient, these foods have been clearly associated to health problems both in adults and children including cardiometabolic risk factors, such as excess body weight, hypertension, increased total cholesterol and low-density lipoprotein cholesterol, and metabolic syndrome, thus with increased morbidity and mortality in the general population. Therefore, as consumption of ultra-processed foods may directly increase weight and cardiometabolic risk factors during childhood, and since childhood dietary habits may also track to adulthood, more longitudinal studies are essential to further investigate these findings, identify facilitating factors and potential barriers for this dietary behavior in children and adolescents, and thus use this information to promote effective policies for reducing intake. The continuous increasing consumption of the ultra-processed foods reported worldwide and particularly changes in dietary habit of different countries need to be further investigated in order to explore the role of specific types of ultra-processed foods on cardiometabolic conditions and identify the daily intake levels that increase risk in order to shape appropriate public health policies.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

Both authors have read and commented on the reviewed manuscripts.

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 73–85 (DOI: 10.1159/000541851)

Epigenetics, Nutrition, and Growth

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Introduction

Epigenetics is the study of modifying and controlling gene expression without a change in the DNA sequence. One widely studied epigenetic mechanism is DNA methylation, which represents the attachment of methyl groups to cytosine followed by guanine, referred to as CpG sites, thereby forming 5-methylcytosine. DNA methylation modulates gene expression by inhibiting the binding of transcription factors, and through proteins involved in gene repression. Another common epigenetic mechanism is modification of histones, which are structural proteins in the cell nucleus around which DHA is wrapped, providing the structure of chromosomes. Histones can be modified by adding or removing methyl or acetyl groups, or by phosphorylation. These chemical changes modify the chromatin structure and the binding of effector molecules and thereby affect gene expression. Early life periods including embryonic, fetal, and infant development are particularly sensitive time windows for epigenetic modifications of our genome when the human epigenome shows a high degree of plasticity and is particularly susceptible to external exposures, including metabolic and nutritional cues. For this chapter, the US National Library of Medicine (PubMed) was searched with the search terms "(epigenetic*) AND ((nutrit*) OR (growth))" and the filter "humans" for the time period from July 1, 2023, to June 30, 2024. The hits were hand searched by the author, and the publications included here were subjectively selected based on perceived interest and relation to human nutrition and growth.

Key articles reviewed for this chapter

Sex-based differences in placental DNA methylation profiles related to gestational age: an NIH ECHO meta-analysis
Bulka CM, Everson TM, Burt AA, Marsit CJ, Karagas MR, Boyle KE, Niemiec S, Kechris K, Davidson EJ, Yang IV, Feinberg JI, Volk HE, Ladd-Acosta C, Breton CV, O'Shea TM, Fry RC; on behalf of program collaborators for Environmental influences on Child Health Outcomes
Epigenetics 2023;18:2179726

Epigenetic phenotype of plasma cell-free DNA in the prediction of early-onset preeclampsia
He W, Zhang Y, Wu K, Wang Y, Zhao X, Lv L, Ren C, Lu J, Yang J, Yin A, Liu G
J Obstet Gynaecol 2023;43:2282100

Prenatal maternal stress is associated with site-specific and age acceleration changes in maternal and newborn DNA methylation
Quinn EB, Hsiao CJ, Maisha FM, Mulligan CJ
Epigenetics 2023;18:2222473

Early-to-mid pregnancy sleep and circadian markers in relation to birth outcomes: an epigenetics pilot study
Jansen EC, Zhang KP, Dolinoy DC, Burgess HJ, O'Brien LM, Langen E, Unwala N, Ehlinger J, Mulcahy MC, Goodrich JM
Chronobiol Int 2023;40:1224–1234

Placental accelerated aging in antenatal depression
Saeed H, Wu J, Tesfaye M, Grantz KL, Tekola-Ayele F
Am J Obstet Gynecol MFM 2024;6:101237

Epigenome wide association study in peripheral blood of pregnant women identifies potential metabolic pathways related to gestational diabetes
Linares-Pineda TM, Peña-Montero N, Gutiérrez-Repiso C, Lima-Rubio F, Sánchez-Pozo A, Tinahones FJ, Molina-Vega M, Picón-César MJ, Morcillo S
Epigenetics 2023;18:2211369

A meta-analysis of epigenome-wide association studies on pregnancy vitamin B12 concentrations and offspring DNA methylation
Monasso GS, Hoang TT, Mancano G, Fernández-Barrés S, Dou J, Jaddoe VWV, Page CM, Johnson L, Bustamante M, Bakulski KM, Håberg SE, Ueland PM, Battram T, Merid SK, Melén E, Caramaschi D, Küpers LK, Sunyer J, Nystad W, Heil SG, Schmidt RJ, Vrijheid M, Sharp GC, London SJ, Felix JF
Epigenetics 2023;18:2202835

Animal and plant protein intake during infancy and childhood DNA methylation: a meta-analysis in the NutriPROGRAM consortium
El Sharkawy M, Felix JF, Grote V, Voortman T, Jaddoe VWV, Koletzko B, Küpers LK
Epigenetics 2024;19:2299045

Assessment of aberrant DNA methylation two years after paediatric critical illness: a pre-planned secondary analysis of the international PEPaNIC trial
Coppens G, Vanhorebeek I, Verlinden I, Derese I, Wouters PJ, Joosten KF, Verbruggen SC, Güiza F, Van den Berghe G
Epigenetics 2023;18:2146966

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

A predictive tool based on DNA methylation data for personalized weight loss through different dietary strategies: a pilot study
García-Álvarez NC, Riezu-Boj JI, Martínez JA, García-Calzón S, Milagro FI
Nutrients 2023;15:5023

The effect of polyphenols on DNA methylation-assessed biological age attenuation: the DIRECT PLUS randomized controlled trial
Yaskolka Meir A, Keller M, Hoffmann A, Rinott E, Tsaban G, Kaplan A, Zelicha H, Hagemann T, Ceglarek U, Isermann B, Shelef I, Blüher M, Stumvoll M, Li J, Haange SB, Engelmann B, Rolle-Kampczyk U, von Bergen M, Hu FB, Stampfer MJ, Kovacs P, Liang L, Shai I
BMC Med 2023;21:364

Sex-based differences in placental DNA methylation profiles related to gestational age: an NIH ECHO meta-analysis

Bulka CM[1,2], Everson TM[3], Burt AA[3], Marsit CJ[3], Karagas MR[4], Boyle KE[5,6], Niemiec S[6], Kechris K[6,7], Davidson EJ[8], Yang IV[6,8], Feinberg JI[9], Volk HE[9], Ladd-Acosta C[10], Breton CV[11], O'Shea TM[12], Fry RC[1,13,14]; on behalf of program collaborators for Environmental influences on Child Health Outcomes

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Comments: **Evidence** has accumulated to show that already prenatal development of male and female organisms differs in many aspects. Bulka and coworkers from Chapel Hill, NC, USA, and several other US academic centers explored potential epigenetic changes in placental tissues that may be related to sex-specific differences in fetal development. They performed a meta-analysis of sex-specific associations between gestational age and placental DNA methylation. They included data from 355 female and 419 male infants born at gestational ages 23–42 weeks from four cohorts that are part of the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) Program. The authors identified 407 cytosine-guanine dinucleotides (CpGs) in females and 794 in males where placental methylation levels were associated with gestational age. Some 55 CpGs in females and 826 in males remained significant after adjustment for cell type. The authors determined that these hits were enriched for biological processes critical to the immune system in females and transmembrane transport in males. The results indicate that associations of placental DNA methylation with gestational age are largely explained by differences in placental cellular composition in females, whereas gestational age is directly associated with numerous alterations in methylation levels in males.

Epigenetic phenotype of plasma cell-free DNA in the prediction of early-onset preeclampsia

He W[1,2], Zhang Y[3,4,5], Wu K[3], Wang Y[2], Zhao X[2], Lv L[2], Ren C[2], Lu J[2], Yang J[2], Yin A[2], Liu G[6]

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J Obstet Gynaecol 2023;43:2282100

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Comments: He et al. from Guangzhou and Beijing, China, aimed at characterizing methylation haplotypes and nucleosome positioning patterns of placental DNA and plasma cell–free DNA of pregnant women with early-onset preeclampsia. They performed a case-control study in 135 pregnant women in whom placental villous parenchyma samples were obtained at delivery and venous blood at 12–15 weeks of gestation, and 50 nonpregnant women who provided venous blood samples. Whole genome bisulphite sequencing (WGBS) and methylation capture bisulphite sequencing (MCBS) were performed from extracted genomic DNA. The authors found different DNA methylation and nucleosome positioning patterns between women with early-onset or without preeclampsia. Preeclampsia-specific hypermethylated sites were found predominantly in the promotor regions and particularly enriched in *CTCF* on the X chromosome. Overall, some 2,379 preeclampsia-specific methylation haplotypes were found across the genome. A receiver operating characteristic (ROC) curve analysis found the area under the ROC curve (AUC) to be 0.938 (95% CI: 0.877, 1.000) with maximum AUC in a generalized linear model cutoff of 0.341, with a

sensitivity of 95.6% and a specificity of 89.7%. The data show that pregnant women with early-onset preeclampsia differ in DNA methylation and nucleosome positioning patterns in placental and plasma DNA.

Prenatal maternal stress is associated with site-specific and age acceleration changes in maternal and newborn DNA methylation

Quinn EB[1,2], Hsiao CJ[1,2,3], Maisha FM[1,2,4,5], Mulligan CJ[1,2]

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Epigenetics 2023;18:2222473

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Comments: Quinn et al. from Gainesville, FL, USA, and Goma, Democratic Republic of Congo, studied possible mechanisms through which prenatal maternal stress can adversely affect child. They studied 155 mother-newborn dyads in the Democratic Republic of Congo using four measures of maternal stress including general trauma, sexual trauma, war trauma, and chronic stress. Differentially methylated positions (DMPs) in DNA extracts from venous blood were associated with general trauma, sexual trauma, and war trauma in both mothers and neonates, whereas there were no associations with chronic stress. Sexual trauma was also positively associated with epigenetic age acceleration across several epigenetic clocks in mothers. In newborn infants, epigenetic age acceleration was positively associated with maternal general trauma and war trauma. The top DMPs were not enriched for enrichment of DNase I hypersensitive sites (DHS) in mothers, but in newborns, the top DMPs associated with war trauma were enriched for DHS in embryonic and fetal cell types. One of the top DMPs associated with war trauma in newborns predicted birth weight. Thus, the findings indicate that maternal stress is associated with site-specific changes in DNA methylation and epigenetic age acceleration in both mothers and neonates, which could represent a mechanism by which prenatal maternal stress exposure induces a negative impact on child health.

Early-to-mid pregnancy sleep and circadian markers in relation to birth outcomes: an epigenetics pilot study

Jansen EC[1], Zhang KP[1], Dolinoy DC[2], Burgess HJ[3], O'Brien LM[4], Langen E[5], Unwala N[6], Ehlinger J[6], Mulcahy MC[1], Goodrich JM[6]

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Comments: Jansen et al. from Ann Arbor, MI, USA, studied possible epigenetic mechanisms underpinning the relation between maternal sleep during pregnancy and birth outcomes. They studied 96 women who donated at least one blood sample during early-to-mid pregnancy, at a mean gestational age of 14.2 weeks. Further data were collected though a questionnaire and from medical charts. DNA methylation at multiple CpG sites within *BMAL1*, *PER1*, and *MTNR1B* genes was quantified by pyrosequencing from extracted leukocyte DNA. Higher DNA methylation of a CpG site in *PER1* was found associated with smaller log-transformed head circumference, and higher methylation of *MTNR1B* averaged across sites was associated with lower log-transformed birth weight. Also longer sleep duration was associated with higher birth weight. Thus, while reported sleep patterns were associated with birth weight, there was no indication of a mediating effect of DNA methylation.

Placental accelerated aging in antenatal depression

Saeed H[1,2], Wu J[3], Tesfaye M[4,5], Grantz KL[3], Tekola-Ayele F[3]

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Am J Obstet Gynecol MFM 2024;6:101237

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Comments: Saeed and coworkers from Bethesda, MD, USA, and Addis Adaba, Ethiopia, studied whether prenatal depression is associated with placental epigenetic age acceleration. Placental DNA methylation was measured from placenta samples of 301 women from diverse race and ethnic groups who completed the Edinburgh Postnatal Depression Scale up to six times across the three pregnancy trimesters. Depressive symptoms, defined as an Edinburgh Postnatal Depression Scale score of ≥10, were present in

10.3%, 16%, and 16.4% of women in the first, second, and third trimesters, respectively. Women with depressive symptoms in the second trimester showed a 0.41 weeks higher placental age acceleration than women without depressive symptoms. Sustained first- and second-trimester depressive symptoms were associated with 0.72 weeks higher placental age acceleration than no depressive symptom in these two trimesters. The association between second-trimester depressive symptoms and higher placental epigenetic age acceleration was stronger in pregnancies with male fetuses but was not significant in pregnancies with female fetuses. It is tempting to speculate that the observed association of depression in the second pregnancy trimester with increased placental age acceleration may reflect enhanced placental dysfunction and thereby lead to the observed pregnancy complications that have been found associated with prenatal depression.

Epigenome wide association study in peripheral blood of pregnant women identifies potential metabolic pathways related to gestational diabetes

Linares-Pineda TM[1,2,3], Peña-Montero N[1,2], Gutiérrez-Repiso C[1,2,4], Lima-Rubio F[1,2], Sánchez-Pozo A[3], Tinahones FJ[1,2,4,5], Molina-Vega M[1,2], Picón-César MJ[1,2], Morcillo S[1,2,4]

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Epigenetics 2023;18:2211369
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Comments: Linares-Pineda and coworkers from Malaga, Granada, and Madrid, Spain, aimed to characterize possible epigenetic mechanisms underlying gestational diabetes mellitus (GDM). They studied 16 pregnant women with and 16 without GDM and measured methylation of DNA extracted from peripheral blood obtained at 26–28 weeks of gestation. Some 1,141 differentially methylated positions (DMPs) were found, of which 714 were annotated in genes. The authors identified that 23 genes significantly related to carbohydrate metabolism and 27 DMPs correlated with biochemical variables such as fasting glucose and glucose levels at various time points of an oral glucose tolerance test, HOMAIR, HbA1c, and cholesterol at different visits during pregnancy and postpartum. The results provide indications that differentiated methylation patterns between pregnant women with and without GDM might determine altered metabolic responses, which should be replicated and explored in further studies.

A meta-analysis of epigenome-wide association studies on pregnancy vitamin B12 concentrations and offspring DNA methylation

Monasso GS[1,2], Hoang TT[3], Mancano G[4,5], Fernández-Barrés S[6,7,8], Dou J[9], Jaddoe VWV[1,2], Page CM[10,11], Johnson L[4,12], Bustamante M[6,7,8], Bakulski KM[9], Håberg SE[10], Ueland PM[13], Battram T[4], Merid SK[14,15], Melén E[14,15,16], Caramaschi D[17], Küpers LK[1,2,18], Sunyer J[6,8,19], Nystad W[20], Heil SG[21], Schmidt RJ[22,23], Vrijheid M[6,7,8], Sharp GC[4,5], London SJ[3], Felix JF[1,2]

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Epigenetics 2023;18:2202835

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Comments: Monasso et al. from Rotterdam, The Netherlands, and numerous collaborators from the Pregnancy and Childhood Epigenetics *(PACE) consortium studied whether fetal* DNA methylation changes might explain the known associations of blood vitamin B_{12} concentrations during pregnancy with offspring health. They performed a meta-analysis of associations of epigenome-wide cord blood DNA methylation with vitamin B_{12} concentrations in maternal blood during pregnancy (n = 2,420) or in cord blood (n = 1,029). The results indicate that maternal and newborn vitamin B_{12} concentrations were significantly associated with DNA methylation at 109 and 7 CpGs, respectively. In a subgroup of 482 children followed up at the ages of 4–10 years, persistent associations with peripheral blood cell DNA methylation were found for 40.7% of CpGs associated with maternal vitamin B_{12} and for 57.1% of CpGs associated with newborn vitamin B_{12}. Some 4.6% of CpGs identified in the maternal meta-analyses were previously associated with either birth weight or gestational age, and 14.3% of the CpGs identified in the newborn meta-analysis. Some 14.3% and 28.6 of CpGs identified in the neonatal meta-analysis were associated with childhood cognitive skills and nonverbal IQ, respectively. Among the 109 CpGs associated with maternal vitamin B_{12}, 18.3% were associated with nearby gene expression. In conclusion, this study with an impressively large sample size demonstrates maternal and newborn vitamin B_{12} concentrations to predict DNA methylation at multiple CpGs in offspring blood, which were linked to relevant child health outcomes including birth weight, gestational age, and later cognitive development.

Animal and plant protein intake during infancy and childhood DNA methylation: a meta-analysis in the NutriPROGRAM consortium

El Sharkawy M[1,2], Felix JF[3,4], Grote V[1], Voortman T[5], Jaddoe VWV[3,4], Koletzko B[1], Küpers LK[3,4]

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Epigenetics 2024;19:2299045

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Comments: EL Sharkawy and colleagues from Munich, Germany, and Rotterdam, The Netherlands, explored whether DNA methylation might be an underlying mechanism for the effect of higher animal protein intake in early childhood on increasing later childhood obesity risk, compared to lesser effects of plant protein intake. In children participating in the European Childhood Obesity Project trial (CHOP) and in the Dutch Generation R cohort study, animal and plant protein intakes in infancy were associated with peripheral blood DNA methylation in early (2–6 years, $N = 579$) and late (7–12 years, $N = 604$) childhood. Study-specific linear regression models adjusted for relevant confounders were performed and then meta-analyzed with a fixed effects model, including also sex-stratified meta-analyses. The results show no association of infant animal protein intake with DNA methylation in early childhood, but a significant positive association with late-childhood DNA methylation at two CpGs (cg21300373 and cg10633363). Infant plant protein intake was associated with early-childhood DNA methylation at one site (cg25973293). There was no overlap between the findings from the animal and plant protein analyses. Sex-specific DNA methylation associations were shown for both animal and plant protein intake. The authors did not find enriched functional pathways at either time point using CpGs associated with animal and plant protein. However, the identified cg21300373 was mapped to the transcription start site of *MARCHF1*, which was previously associated with adiposity in adults, and cg10633363 was mapped to the transcription start site of *HOXB9* associated with epigenetic aging of liver tissue that is accelerated with obesity. The observed associations of early protein intake with DNA methylation in late childhood indicate potential mediating epigenetic pathways between infant protein intake and health outcomes that require further investigation.

Assessment of aberrant DNA methylation two years after paediatric critical illness: a pre-planned secondary analysis of the international PEPaNIC trial

Coppens G[1], Vanhorebeek I[1], Verlinden I[1], Derese I[1], Wouters PJ[1], Joosten KF[2], Verbruggen SC[2], Güiza F[1], Van den Berghe G[1]

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Epigenetics 2023;18:2146966

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https://pubmed.ncbi.nlm.nih.gov/36384393/

Comments: Coppens and colleagues from Leuven, Belgium, and Rotterdam, The Netherlands, assessed DNA methylation in buccal mucosa 2 years after intensive care treatment in a large sample of 820 children who had previously participated in the PEPaNIC trial children. In this trial, pediatric intensive care patients had been randomized to earlier or later initiation of parenteral nutrition. Also 392 matched healthy children were studied. The results indicate significantly different DNA methylation at 4,047 CpG sites (2,186 genes) and 494 DNA regions (468 genes) in former intensive care patients, compared with healthy children. Most CpG sites (90.3%) in the patient group were hypomethylated, with an average absolute 2% effect size, while there was no consistent effect of the time of initiation of parenteral nutrition. Functional annotation using the KEGG pathway database related 41.2% of the differentially methylated KEGG pathways to physical or neurocognitive development, 32.8% to critical illness and intensive medical care, and 26.0% to disorders prior to intensive care admission. Thus, at 2 years after intensive care treatment for critical illness, methylation of CpG sites and DNA regions from buccal-mucosal DNA differed between healthy and previously sick children, with an association to pathways related to physical and neurocognitive development. However, the randomly assigned different parenteral nutrition strategies showed no significant effects on DNA methylation.

Differential methylation pattern in pubertal girls associated with biochemical premature adrenarche

Ponce D[1], Rodríguez F[1], Miranda JP[2,3], Binder AM[4,5], Santos JL[2], Michels KB,[4] Cutler GB[6] Jr, Pereira A[7], Iñiguez G[1], Mericq V[1]

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Epigenetics 2023;18:2200366

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https://pubmed.ncbi.nlm.nih.gov/37053179/

Comments: Ponce et al. from Santiago, Chile, and different sites in the United States explored whether premature adrenarche in girls before the age of 8 years, defined by elevated serum dehydroepiandrosterone sulfate (DHEAS), is related to different methylation profiles in puberty. The studied sample included 86 healthy girls in whom anthropometric measurements and DHEAS levels were determined from the age of 7 years onward. Girls were classified into low DHEAS (LD) (<42 μg/dL) and high DHEAS (HD) (≥42 μg/dL) groups. At Tanner stages 2 and 4, DNA methylation from peripheral blood buffy coat was assessed. The results indicate a differential methylation pattern between pubertal girls with and without biochemical premature adrenarche. A set of DNA methylation markers identified by the LASSO method distinguished between HD and LD girls, irrespective of Tanner stages. A subset of these markers was significantly associated with insulin levels, HOMA-IR, and glycemia. In conclusion, the results of this study support the hypothesis that premature adrenarche alters DNA methylation, which is associated with modifying glucose metabolism.

A predictive tool based on DNA methylation data for personalized weight loss through different dietary strategies: a pilot study

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Nutrients 2023;15:5023

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Comments: Garcia-Alvarez and collaborators from Pamplona and Madrid, Spain, aimed to explore whether the variation in weight loss during obesity treatment could be predicted by epigenetic differences. A large number of 306 overweight or obese people were randomly assigned to lifestyle interventions with hypocaloric diets for 4 months, either with moderately high protein (MHP) or with low fat (LF). Methylation of DNA extracted from white blood cells obtained at study start was assessed. Among the methylation sites significantly associated with percentage BMI loss, the authors constructed two weighted methylation subscores for each diet, with 15 CpGs used for the MHP diet and 11 CpGs for the LF diet. A prediction model was designed for percentage BMI loss with the interaction between diet and total score. This model predicted which diet achieved the highest percentage of BMI loss in 75 of the 306 participants, i.e., 37.3% of the total study population. The potential predictive value of DNA methylation analysis on the response to hypocaloric diets should be replicated and tested in further studies in other patient populations.

The effect of polyphenols on DNA methylation-assessed biological age attenuation: the DIRECT PLUS randomized controlled trial

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BMC Med 2023;21:364

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https://pubmed.ncbi.nlm.nih.gov/37743489/

Comments: Meir et al. from different academic institutions in Israel, Germany, and the United States explored the hypothesis that diets rich in polyphenols, such as found in green tea, might attenuate biological aging indicated by epigenetic DNA methylation. A total 256 participants aged 51.3 ± 10.6 years with abdominal obesity or dyslipidemia were studied before and after an 18-month randomized controlled trial in which they were assigned either to healthy dietary guidelines, a Mediterranean (MED) diet, and a polyphenol-rich, low-red/processed meat Green-MED diet. The adherence to the Green-MED diet was assessed by a questionnaire and urine polyphenol measurements. Biological aging was assessed by different epigenetic clocks based on blood DNA methylation. The subjects' chronological age correlated with all methylation age clocks. A greater Green-MED diet adherence was associated with a lower increase over the 18 months of the intervention and corresponded with elevated urine polyphenols. Participants assigned to either of the MED-style diets had about 9 months favorable difference between the observed and expected methylation at the end of the intervention. Thus, the study indicates that Mediterranean diets and increased polyphenol intakes have the potential to attenuate the advancement of biological aging indicated by epigenetic DNA methylation.

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.

Funding Sources

This work has been financially supported in part by the European Joint Programming Initiative Projects NutriPROGRAM and BiomarKids, and by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF; 01EA1904 and 01EA2203A) and as part of the German Center for Child and Adolescent Health (DZKJ; 01GL2406A). The author is the Else Kröner-Seniorprofessor of Paediatrics at Ludwig-Maximilians University of Munich, financially supported by Else Kröner-Fresenius Foundation, Bad Homburg, Germany, LMU Medical Faculty, and LMU University Hospitals, Munich, Germany.

Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 86–103 (DOI: 10.1159/000541856)

Nutrition and Growth in Preterm and Term Infants

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Introduction

This year, we selected several clinical studies, which all included relatively large numbers of preterm infants, and as such may potentially have a large impact in the field of neonatology [1–6]. For the term infants, we selected four studies on breastfeeding [21, 26–28], two studies on complementary feeding [32, 35], two studies on infant feeding [37, 38], and one study on food allergy [41].

Each of these studies will be assessed in more detail underneath

Key articles reviewed for this chapter

Preterm Infants

Nutritional support for moderate-to-late-preterm infants - a randomized trial
Alexander T, Asadi S, Meyer M, Harding JE, Jiang Y, Alsweiler JM, Muelbert M, Bloomfield FH for the DIAMOND Trial Group
N Engl J Med 2024;390:1493–1504

Neurodevelopmental outcomes of extremely preterm infants fed donor milk or preterm infant formula: a randomized clinical trial
Colaizy TT, Poindexter BB, McDonald SA, Bell EF, Carlo WA, Carlson SJ, DeMauro SB, Kennedy KA, Nelin LD, Sánchez PJ, Vohr BR, Johnson KJ, Herron DE, Das A, Crawford MM, Walsh MC, Higgins RD,

Stoll BJ and the MILK Trial Investigators; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network
JAMA 2024;331:582–591

Does extremely early expression of colostrum after very preterm birth improve mother's own milk quantity? A cohort study
Levene I, Quigley MA, Fewtrell M, O'Brien F
Arch Dis Child Fetal Neonatal Ed 2024;109:475–480

Effect of human milk-based fortification in extremely preterm infants fed exclusively with breast milk: a randomised controlled trial
Jensen GB, Domellöf M, Ahlsson F, Elfvin A, Navér L, Abrahamsson T
EClinicalMedicine 2024;68:102375

Breast milk enema and meconium evacuation among preterm infants: a randomized clinical trial
Zheng L, Gai L, Wu Y, Kong C, Sun F, Gao J, Yuan W, Liu M, Jiang H, Tuo N, Yang F
JAMA Netw Open 2024;7:e247145

Timing of red blood cell transfusions and occurrence of necrotizing enterocolitis: a secondary analysis of a randomized clinical trial
Salas AA, Gunn E, Carlo WA, Bell EF, Das A, Josephson CD, Patel RM, Tan S, Kirpalani H for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network
JAMA Netw Open 2024;7:e249643

Term Infants

Breastfeeding

90 versus 60 min of early-skin-to-skin contact on exclusive breastfeeding rate in healthy infants' ≥35 weeks: a randomized controlled trial
Kumawat SR, Vyas H, Mohan R, Sasidharan R, Yadav B, Gupta N
Acta Paediatr 2024;113:199–205

Relaxation therapy and human milk feeding outcomes. A systematic review and meta-analysis
Levene I, Mohd Shuki NH, O'Brien F, Quigley MA, Fewtrell M
JAMA Pediatr 2024;178:567–576

Breastfeeding or breast milk for procedural pain in neonates (Review)
Shah PS, Torgalkar R, Shah VS
Cochrane Database Syst Rev 2023;8:CD004950

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;118:468–475

Complimentary Feeding

Complementary feeding approaches and risk of choking: a systematic review
Correia L, Sousa AR, Capitão C, Pedro AR
J Pediatr Gastroenterol Nutr 2024;79:934–942

Feeding practices and dietary diversity in the first year of life: PreventADALL, a Scandinavian randomized controlled trial and birth cohort study
Saunders CM, Rehbinder EM, Carlsen KCL, Jonassen CM, LeBlanc M, Nordlund B, Skjerven HO, Söderhäll C, Vettukattil R, Carlsen MH
J Nutr 2023;153:2463–2471

Infant Feeding

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

Higher versus lower protein intake in formula-fed term infants (Review)
Gonzalez-Garay AG, Serralde-Zúñiga AE, Medina Vera I, Velasco Hidalgo L, Alonso Ocaña MV
Cochrane Database Syst Rev 2023;11:CD013758

Food Allergy

Effect of maternal egg intake during the early neonatal period and risk of infant egg allergy at 12 months among breastfeeding mothers. A randomized clinical trial
Nagakura KI, Sato S, Shinahara W, Kido H, Fujita H, Yanai T, Akiyama N, Futamura M, Koga H, Fujiwara M, Kaneko H, Taniguchi H, Makita E, Takahashi K, Yanagida N, Ebisawa M, Urashima M
JAMA Netw Open 2023;6:e2322318

Preterm Infants

Nutritional support for moderate-to-late-preterm infants – a randomized trial

Alexander T[1,2], Asadi S[1], Meyer M[2], Harding JE[1], Jiang Y[3], Alsweiler JM[4,5], Muelbert M[1], Bloomfield FH[1] for the DIAMOND Trial Group

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Neurodevelopmental outcomes of extremely preterm infants fed donor milk or preterm infant formula: a randomized clinical trial

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JAMA 2024;331:582–591
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Does extremely early expression of colostrum after very preterm birth improve mother's own milk quantity? A cohort study

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Effect of human milk-based fortification in extremely preterm infants fed exclusively with breast milk: a randomised controlled trial

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EClinicalMedicine 2024;68:102375
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Breast milk enema and meconium evacuation among preterm infants: a randomized clinical trial

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JAMA Netw Open 2024;7:e247145
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Timing of red blood cell transfusions and occurrence of necrotizing enterocolitis: a secondary analysis of a randomized clinical trial

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Comments: Researchers in New Zealand published one of the largest trials on neonatal nutrition this year, which was called the DIAMAND trial [1]. They conducted a multicenter randomized controlled trial (RCT) in 532 moderate-to-late preterm infants, who had intravenous access for clinical reasons and whose mothers intended to breastfeed. Infants were included within 24 h after birth after which three different interventions were tested simultaneously but independently with a factorial design. This efficient approach implied that infants were randomized for each of the three different interventions separately: to receive either intravenous amino acids (with or without glucose) or glucose solely, to receive a milk supplement (usually formula, rarely donor milk) in case of insufficient mother's own milk or not, and into exposure to taste and smell of milk during tube feeding or not. Authors assessed the time to full enteral feeding and body composition at 4 months corrected age as the primary outcomes. Overall, no differences in primary or secondary outcomes were observed. In each of the randomization groups, time to full enteral feeding was less than 6 days on average and growth was similar, both during initial hospitalization and in the months thereafter. Contrary to the hypothesis, the smelling and tasting of milk did not aid in achieving full enteral feeding, nor in reaching full oral intakes. It is not known whether this is due to the more mature study group, or whether there is a true absence of effect in line with prior data [7]. In fact, a very recent update on the Cochrane review on this topic did not really show any significant advantages either [8]. However, letting infants smell and taste milk during tube feeding is a simple and cheap intervention, without known harm, and may empower parents' bonding to their child. In addition, although there are similarities, it should be regarded separately from oropharyngeal colostrum application, which is thought to have a direct stimulation of

the mucosa-associated lymphoid tissue [9, 10]. Another message from the multicenter RCT was that there was no negative effect of supplementing insufficient mother's own milk availability with formula feeding on the final breastfeeding rates at the time of discharge. However, one must note that the trial was performed in neonatal nurseries in which there was dedicated lactation support for mothers who intended to breastfeed. Also, the provision of parenteral amino acids next to or instead of glucose did not seem to impact any of the outcomes. It appears that most of the included infants in the parenteral amino acid group did not receive all components of parenteral nutrition, such as lipids, electrolytes, vitamins, and trace elements. We have learned in the recent decade that in order to benefit from parenteral nutrition, provision and attention must be paid to all nutrients [11].

The best available evidence so far on the use and effects of donor human milk for preterm infants in comparison to preterm formula was published last year. This multicenter double-blind RCT, called the MILK trial, was conducted in the United States [2]. We regard it as the best evidence not only because of its size (483 preterm infants) and inclusion of high-risk infants (median gestational age was 26 weeks) but also because of the inclusion criterium that infants were only allowed to enter the trial if their mothers did not express any milk at all or only a limited amount. Prior studies were flawed by the fact that many infants in both the allocated formula and donor human milk groups received high volumes of mother's own milk, and only small and varying portions of donor human milk, thereby diluting any potential effects. Nonetheless, also in the current MILK trial, no differences were detected in the primary outcome, as the Bayley cognitive score at corrected age 2 years was similar in both groups. This is despite the fact that rates of necrotizing enterocolitis had halved from 9.0% to 4.2%. The protective effect on NEC supports most earlier evidence that donor human milk is the best alternative in case of insufficient mother's own milk [10, 12]. Nonetheless, clinicians should always empower and support mothers to express human milk, as infants benefit most from mother's own milk.

More research in this area is relatively rare, but researchers from the United Kingdom explored last year how the amount of mother's own milk for preterm infants can be increased [3]. From an existing database coming from an RCT, they assessed the relationship between time of first attempt to express milk after having given birth of a very preterm infant and the quantity of expressed milk at various time points thereafter. Detailed data on maternal and neonatal background and clinical variables, as well as time to first milk expression attempt after birth, number of daily expressions, and yielded milk volumes in the weeks after, were collected and analyzed. The cohort consisted of 132 women who had delivered at a mean gestational age of 27.8 weeks. About 20% had their first attempt of expression within 2 h postpartum, but the median time of the entire group was 6 h after birth. While addressing several potential confounding factors that could affect time to milk expression, it was shown that expressing within 6 h was associated with a significantly higher milk yield in the weeks after, than starting first expression later than 6 h after preterm birth. In addition, more frequent expressions during the first 3 weeks after birth were much more effective in terms of milk yield per expression, provided the first expression after birth was started within 6 h. This suggests they could potentially express less frequently at a certain point because of established milk flow. Additional analyses also assessed whether very early expression, i.e., within 2 h after birth, was more effective than first attempt between 2 and 6 h. This could however not be clearly shown, although this may also be due to a lack of statistical power because of low numbers.

Because human milk is most beneficial for preterm infants, there is continuing interest in whether infants could also benefit from fortifiers derived from condensed donor human milk instead of traditional bovine milk–derived multinutrient fortifiers. More high-quality data on this topic were published last year as well by Swedish investigators who published their N-forte trial [4]. In this multicenter RCT, all infants received mother's own milk supplemented with donor human milk, but the type of fortifier was randomized, either a human milk or a bovine milk–derived fortifier. In total, 228 preterm infants with a gestational age of less than 28 weeks received one of the two interventions until they reached a postmenstrual age of 34 weeks, after which all infants received the bovine fortifier. The primary outcome was a composite of the incidence of necrotizing enterocolitis, culture-proven sepsis, or mortality. However, the incidence of this outcome was nearly identical and reached approximately 35% in both groups. Also, if the composite outcome was split into separate individual outcomes, there were no differences, nor in any of the other secondary outcomes. This study is thus in line with the prior OptiMom study [13], which is the only similar study on this topic where the only difference in the control and intervention groups is the type of fortifier. Also in this trial, which was a bit smaller in size, there were no advantages apparent of a human milk–derived fortifier, except for a tendency in lower incidence of retinopathy of prematurity. However, in the current N-forte trial, there was no such reduction seen for this outcome. Thus, our conclusion on these data is that a strict human milk diet is not preferred to a human milk diet combined with a bovine milk–based human milk fortifier.

While, as discussed, human milk helps improve feeding tolerance in comparison to formula feeding, a proportion of infants have more feeding difficulties during the first few days of life. This may be related to delayed meconium passage, which can be especially troublesome in intrauterine growth–restricted preterm infants. The practice of enemas or rectal suppositories has, however, been sparsely studied. At present, (diluted) glycerin or saline is used most frequently. The latest meta-analysis on the effects of the use of enemas was published in 2016 and did not show clearly positive results [14]. Practically, no new RCTs have been published after, although the use of enemas in case of delayed meconium passage in combination with feeding intolerance is widespread in most neonatal intensive care units. Therefore, new RCTs are very welcome, such as recently conducted by researchers in China [5]. In total, 286 preterm infants born <30 weeks' gestation were randomized after parental consent, to receive enemas with either saline or human milk (5 mL/kg). Enemas were given prophylactically twice a day from the third day of life onward, regardless of any meconium passage at that time or feeding (in)tolerance, until meconium was entirely passed. Results from the trial showed that the median time to achieve complete meconium evacuation was reduced with about 2 days in the breast milk enema group, but still took significant period of time in the intervention group (median 11.4 days). Also, the time to reach full enteral feeding was reduced by about 6 days, but still took 30 days, which reflects the slow increase in enteral feeding practice throughout China. The duration of parenteral nutrition was similarly reduced (30.5 vs. 35.8 days). Thus, although there were some statistical and clinical advantages apparent after repetitive breast milk enema, the question arises whether precious human milk, especially colostrum, should be given rectally in a routine fashion. The paper does not provide information on the effects on human milk availability

for enteral nutrition, but the daily volume of 10 mL/kg is not negligible, so this must have had impact, especially in the first week. Moreover, generalizability may be poor to, for example, Europe and the Americas as many NICUs in those parts of the world will accomplish much faster enteral feeding advancement rates. In conclusion, human milk may be used as enema but only when there is a surplus of human milk available. Especially the use of colostrum should be reserved solely as enteral nutrition, allowing the many immunomodulatory effects that otherwise might be lost. In the next few years, we hope more data will appear from another study on the use of (prophylactic) enemas with glycerin that is currently being conducted in 440 preterm infants in China [15].

One of the fearful complications that may occur after preterm birth is necrotizing enterocolitis (NEC). Much research is therefore being done on NEC prevention. For example, there is still continuing debate whether NEC occurs more frequently in the days after a blood transfusion is given. A systematic review on this topic, which could only identify observational studies with very high heterogeneity in study designs and outcome reporting, produced mixed results, but failed to show a higher incidence of transfusion-associated NEC (TANEC) [16]. However, more recently, another systematic review with a different approach did identify a higher risk of NEC after transfusion [17]. Others have merely speculated whether a supposed higher incidence of NEC after a transfusion is merely an association with the occurrence of anemia. From prior studies and systematic reviews, however, there are no indications that liberal versus restrictive transfusion thresholds result in differing NEC rates [18], although these studies do not answer whether a more severe anemia may induce NEC. Nonetheless, in several institutions, enteral feeds are temporarily paused for approximately 12 h around transfusion trying to prevent TANEC, while in other units, this policy is not adhered to. High-quality research on this topic is very sparce, although there is a systematic review available [19]. Pooled results from 7 non-RCTs (n = 7,492) showed that withholding feeds during transfusion significantly reduced the incidence of TANEC. The four largest studies that were included, however, are only available as conference papers, presented >10 years ago by now. The validity of the data may thus be questioned. Consequently, more high-quality data on this topic are warranted. Last year, US authors published a post hoc secondary analysis of 1,690 preterm infants born with a birth weight of <1,000 g, who had participated in the transfusion of prematures (TOP) RCT [6]. The authors identified 4,947 hazard periods, defined as the 72 h posttransfusion period and 5,813 control periods of nonexposure during hospitalization. In total, there were 133 cases of NEC, but the frequency of NEC did not differ significantly between posttransfusion hazard periods and control periods. Thus, this study suggests that red blood cell transfusions are not temporally associated with a higher risk of NEC among extremely preterm infants. Unfortunately, however, no information is available on feeding practices around the moment of transfusion. Although it seems unlikely that all enteral nutrition was stopped in all participating centers and thereby preventing TANEC, this effect cannot be excluded based on their available data. Within about 2 years' time, though, results will appear from the very large WHEAT trial (n = 4,333), which is an ongoing multicenter RCT, conducted in the United Kingdom and Canada, investigating whether withholding enteral feeds during and after a transfusion in preterm infants will reduce the risk of NEC (NCT05213806). Likely, results will be discussed in this yearbook after these are published.

Term Infants

Breastfeeding

90 versus 60 min of early-skin-to-skin contact on exclusive breastfeeding rate in healthy infants' ≥35 weeks: a randomized controlled trial

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Relaxation therapy and human milk feeding outcomes. A systematic review and meta-analysis

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Breastfeeding or breast milk for procedural pain in neonates (Review)

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Cochrane Database Syst Rev 2023;8:CD004950
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Metabolizable energy content of breastmilk supports normal growth in exclusively breastfed Icelandic infants to age 6 months

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Comments: There are many reasons for the low rates of breastfeeding worldwide. Among these, the practice of routine mother-infant separation diverges from evolutionary history, where neonatal survival depended on close and virtually continuous maternal-infant skin-to-skin contact (SSC). SSC means the placing of the naked baby prone on the mother's bare chest or abdomen in direct contact at birth. A Cochrane review from 2016 concluded that women practicing SSC were more likely to breastfeed at 1–4 months postbirth (RR: 1.24, 95% CI: 1.07–1.43) and had higher exclusive breastfeeding rates up to the age of 6 months [20]. Early SSC for 60 min is endorsed by official bodies such as UNICEF and WHO, as well as many pediatric societies worldwide. However, very little is known on the optimal duration of early SSC. Kumawat et al. conducted an open-label, randomized study at a tertiary care center in India [21]. All healthy singleton infants ≥35 weeks of gestation born by vaginal delivery were eligible for inclusion in the study. The infants were assessed for eligibility at 5 min of life and enrolled once exclusion criteria (mainly need for immediate neonatal care) were ruled out. Early SSC was given for 90 min in the intervention group (n = 99) and 60 min in the control group (n = 99). The infants in the 90-min group were more likely to be exclusively breastfed at 60 ± 12 h than those in the 60-min control group, 75.8% versus 52.5% (RR: 1.44, 95% CI: 1.15–1.79, $p < 0.01$). The breastfeeding behavior of infants at 60 ± 12 h using the modified infant breastfeeding assessment tool (BAT) score [22] was significantly better in the 90-min group as compared to the control group. The proportion of infants on exclusive breastfeeding at 6, 10, and 14 weeks of age was also significantly higher in the 90-min SSC group compared to the control group: 73.2% versus 52.6%, 73.1% versus 52.1%, and 69.1% versus 50.0% (RR, 95% CI: 1.39 [1.11–1.74], 1.36 [1.08–1.07], and 1.38 [1.08–1.75], respectively). These results agree with two previous, retrospective, non-randomized studies that suggested a dose-response relationship between duration of SSC and breastfeeding [23, 24]. Despite methodological limitations, this study shows that increasing the duration of early SSC induced a dose-response benefit on exclusive breastfeeding rates and breastfeeding behavior, which were sustained until 14 weeks of age. There is a need to confirm these data in other settings, including high-income countries.

Relaxation therapy is made up of a variety of techniques, including progressive muscle relaxation, meditation, mindfulness, guided visualization, and breathing exercises. Music is equivalent to formal relaxation techniques in some settings. The common goal for relaxation therapies is to induce a relaxation response characterized by reduced heart rate, respiratory rate, and blood pressure and is associated with a perception of calm and well-being. Relaxation therapy was identified by a Cochrane review as a promising technique to improve lactation outcomes [25]. Relaxation therapy could influence lactation via the hormones controlling milk production and release (oxytocin and prolactin) through complex connections with stress hormones. The systematic review and meta-analysis from Levene et al. aimed at assessing whether relaxation interventions improve lactation and well-being [26]. Predefined exclusion criteria were manual interventions (e.g., massage) and cognitive behavioral

therapy. Interventions were music, guided relaxation, mindfulness, and breathing exercises/muscle relaxation. Of the 16 included studies, there were a total of 1,871 participants. There was moderate-certainty evidence that relaxation was associated with an increase in milk quantity of 0.73 SDs, a medium effect size. There was moderate-certainty evidence of an increase in infant weight, measured as the change in SD score (SDS; MD, Z-score change = 0.51; 95% CI, 0.30–0.72; $p < 0.001$; 3 studies, 226 participants). There was moderate-certainty evidence of a slight reduction in maternal stress and maternal anxiety. The key limitation of this study was the quality of available RCTs in this area. Levene et al. concluded that relaxation interventions can be proposed to lactating parents who would like to increase well-being, improve milk supply, or increase infant weight gain. Of note, the lack of harmful effects related to relaxation interventions and their high acceptability to the general population are further reasons for confidence in this recommendation. Relaxation interventions are easily available for dissemination, particularly the simplest forms using calming music.

Cumulative pain in the neonate is associated with morbidities, including adverse neurodevelopmental outcomes. Despite recommendations, neonatal pain continues to be inconsistently assessed and inadequately managed. Breastfeeding may provide pain relief for newborn babies undergoing painful procedures. Medication for pain relief is commonly given for major painful procedures, but may not be given for minor painful procedures such as blood sampling (by heel prick or taking a sample from a vein). The main objective of this Cochrane review [27] (first published in 2006 and updated in 2012) was to evaluate the effectiveness of breastfeeding or supplemental breast milk (expressed breast milk given via feeding tube or by placing breast milk in baby's mouth) in reducing procedural pain in neonates. Studies included were RCTs comparing breastfeeding or supplemental breast milk with no treatment/other measures in both term and preterm infants. The studies had to report on either physiological markers of pain or validated pain scores. Of the 66 included studies, 36 evaluated breastfeeding, 29 evaluated supplemental breast milk and one study compared them against each other. The procedures conducted in the studies were: heel lance ($n = 39$), venipuncture ($n = 11$), intramuscular vaccination ($n = 9$), eye examination for retinopathy of prematurity ($n = 4$), suctioning ($n = 4$) and adhesive tape removal as procedure ($n = 1$). Overall, the included studies were at low risk of bias except for masking of intervention and outcome assessment, where around one third of studies were at high risk of bias. This review concluded that there is moderate/low-certainty evidence to suggest that breastfeeding or supplemental breast milk may reduce pain in neonates undergoing minor painful procedures compared to no intervention/positioning/holding or placebo or nonpharmacological interventions. In addition, there is low-certainty evidence to suggest that moderate concentration (20%–33%) glucose/sucrose may be as efficient in reducing pain as breastfeeding. The effectiveness of breast milk for painful procedures should be studied in the preterm population, as there are currently a limited number of studies in this population.

WHO recommends exclusive breastfeeding (EBF) for a duration of 6 months. However, globally only ~40% of infants are EBF until 6 months of age, with a lower prevalence in most high-income countries. One reason for these low rates may be the perception of insufficient milk supply by breastfeeding mothers; in addition, there is still controversy as to whether EBF for 6 months can adequately meet infant energy requirements to support optimal growth and development. The aim of the study by Thoridsdottir et al. was to determine whether breast milk energy content is sufficient

to support growth during EBF until 6 months [28]. A total of 27 EBF infants were studied with doubly labeled water at the age of 5.6 months to measure breast milk intake, energy intake, body composition, and the metabolizable energy (ME) content of their mother's breast milk over the following week. Z-scores were calculated for anthropometry using WHO child growth charts and for fat-free mass (FFM) and fat mass (FM) using UK reference data. Anthropometric Z-scores from birth indicated normal weight and length growth patterns. At ~6 months, the mean ± standard deviation (SD) FFM Z-score was 0.22 ± 1.07, and the FM Z-score was 0.78 ± 0.70. Mean ± SD intake of breast milk was 983 ± 170 g per day and of energy, 75.9 ± 14.3 kcal/kg per day. The mean ME content of breast milk was 0.62 kcal/g. Compared with UK reference data, the sample showed normal FFM but elevated FM, indicating no constraint of fat-free tissue accretion in the first 6 months but higher concentrations of fat deposition. However, high body fat content in EBF infants is transient and is not associated with long-term health outcomes such as obesity or other non-communicable disease. Mothers were positive toward breastfeeding, on paid maternity leave (planned mean 10 months), and 56% of them had received specialized breastfeeding support. This study demonstrates that when mothers are motivated and supported without economic restraints, breast milk intake and the energy supplied by breast milk to EBF infants at 6 months of age can support normal growth patterns. These data further support the recommendation for EBF until the age of 6 months.

Complementary Feeding

Complementary feeding approaches and risk of choking: a systematic review

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J Pediatr Gastroenterol Nutr 2024;79:934–942

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https://pubmed.ncbi.nlm.nih.gov/38937992/

Feeding practices and dietary diversity in the first year of life: PreventADALL, a Scandinavian randomized controlled trial and birth cohort study

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Comments: Complementary feeding, the introduction of foods other than breast milk or infant formula, is an important step for the growth, development, and socialization of the infant. There are two main complementary feeding (CF) approaches: traditional spoon-feeding (TSF) and baby-led weaning (BLW). BLW can be used for infants from 6 months of age, born at term without health problems or neurodevelopmental abnormalities, able to remain seated on their own, vertically maintained to the back of the chair if necessary, so that they can catch the foods on the table [29]. The infant sits with the family at mealtimes and is not left alone with the food. Pureed foods and spoons commonly used to start TSF are not accepted. The child is offered the same food as the whole family, chooses the types of foods they want, and regulates the amounts ingested according to their appetite. Homemade foods are encouraged rather than processed baby foods. BLW appeared in the United Kingdom in the early 2000s with a boom following the 2008 publication of the book of Gill Rapley, who is considered a pioneer of this technique [30]. Many parents and healthcare professionals have concerns about the risk of choking and insufficient nutritional intake, mainly in energy and iron associated with BLW. In order to minimize these risks, an adaptation of the BLW called the "modified BLW" was proposed by a team from the University of Dunedin in New Zealand and assessed through a 2-year RCT of 206 healthy infants, the "Baby-Led Introduction to SolidS" – BLISS [31]. Parents benefit from additional advice and the delivery of documents on high-choking risk foods (e.g., raw apple, raw carrot, and whole grapes). The systematic review from Correia et al. aims at assessing the impact of the CF approach adopted by caregivers on infants' risk of choking [32]. Seven of the 165 studies initially identified were included. Recall bias may be present in all included studies. No study reported statistically significant differences in the risk of choking between babies following BLW, BLISS, and TSF. The risk of choking does not seem to be associated with the CF approach. Instead, it may be related to the familiarity of the baby with each texture and the parent's understanding of the information on how to minimize the risk of choking. The main limitation of this systematic review is the heterogeneity of exposures and outcomes due to different comparison groups and different definitions for choking risk, BLW, BLISS, and TSF approaches. These methodological differences in these studies did not allow to perform a meta-analysis.

There is an ongoing debate on the optimal age of introduction of complementary foods in young infants. Many European countries advocate the introduction of complementary feeding from 4 months onward as opposed to 6 months for WHO and the American Academy of Pediatrics [33]. This controversy may have an impact on the duration of exclusive breastfeeding and potentially on infants' health outcomes. In addition, it is now recognized that early introduction of allergenic foods before the age of 6 months may prevent food allergy [34]. Very few data are available on the impact of early food introduction

on feeding practices later in infancy. The aim of the study from Saunders et al. performed in Norway and Sweden was to assess infant feeding practices in the first year of life and to determine if early interventional food introduction influences breastfeeding and dietary diversity [35]. Dietary intake was assessed in infants from the population-based clinical trial Preventing Atopic Dermatitis and ALLergies (PreventADALL) in children. A total of 2,397 infants were cluster-randomized at birth into four different groups: (1) control, (2) skin intervention, (3) introduction to 4 allergenic foods between 3 and 4 months of age: peanut, cow milk, wheat, and egg, as small tastings until 6 months, and (4) combined skin and food interventions. Dietary data were available from at least one of the 3-, 6-, 9-, and 12-month questionnaires in 2,059 infants. In this study, groups 1 and 2 constitute the no food intervention group, whereas groups 3 and 4 constitute the food intervention group. At 3, 6, 9, and 12 months, 95%, 88%, 67%, and 51% were breastfed, respectively, and breastfeeding duration was not affected by the food intervention. In the no food intervention group, mean age of complementary food introduction was 18.3 weeks, whereas infants randomly assigned to the food intervention were introduced complementary foods from 12 weeks of age. An original finding of the study was that the dietary diversity score was 1.39 units (CI: 1.16, 1.62) higher at 9 months ($p < 0.001$) and 0.7 units (CI: 0.5, 0.9) higher at 12 months ($p < 0.001$) in the food intervention group compared to the no food intervention group. These data from two high-income countries with a long history of breastfeeding promotion policies show that introducing small amounts of complementary foods from about 3 months of age increased dietary diversity at 9 and 12 months but not at the expense of breastfeeding rates or breastfeeding duration. Further studies performed in different settings, e.g., low- and middle-income countries, are warranted before changing the recommendations on the age of introduction of complementary foods and thereby the duration of exclusive breastfeeding.

Infant Feeding

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

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Pediatr Res 2023;94:878–891

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https://pubmed.ncbi.nlm.nih.gov/36941339/

Higher versus lower protein intake in formula-fed term infants (Review)

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Cochrane Database Syst Rev 2023;11:CD013758

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Comments:

The role of nutritional programing in infancy on later growth has been widely debated over the last 2 decades. One hot topic is the optimal protein intake during early infancy, with several publications suggesting that high dietary protein intake in the first year of life may influence later growth and body composition. Conversely, the low protein content of breast milk may play a role in the association between breastfeeding and a lower risk of overweight and obesity later in life. The so-called "early protein hypothesis" suggests that higher protein intake in the first year(s) of life enhances adipogenic activity as a result of increased levels of insulin-like growth factor 1 and insulin [36]. Two recent publications aimed at reviewing the available literature related to this issue. Milani et al. performed a systematic review to assess the impact on growth during the first year of life based on infant formula composition providing different amounts of protein in healthy term infants [37]. A meta-analysis compared weight and length gain at 120 days from high- (>2.0 g/100 kcal) and low-protein (≤2.0 g/100 kcal) content formulas. Twelve papers (n = 2,275) were included and five of them (n = 677) contributed to the meta-analysis. Most studies compared a high-protein formula, a low-protein formula, and breastfeeding. The weighted mean difference at 120 days was very low, not only for weight gain, −0.02 g per day (95% CI: −1.41, 1.45), but also for length gain, 0.004 cm/month (95% CI: −0.26, 0.27). Therefore, the available evidence does not support the assumption that high- versus low-protein content formulas during exclusive milk feeding lead to different growth outcomes in the first year of life.

A Cochrane review aimed at evaluating the benefits and harms of higher protein intake versus lower protein intake in healthy, formula-fed term infants [38]. RCTs of healthy infants fed infant formula for at least three consecutive months at any time from birth were included. High protein content was defined as 2.5 g or more per 100 kcal, and low protein content as less than 1.8 g/100 kcal (for exclusive formula feeding) or less than 1.7 g/100 kcal (for complementary formula feeding).

Eleven RCTs (1,185 infants) conducted in high-income countries were included. The longest follow-up was 11 years. Feeding healthy term infants high-protein formula compared to standard-protein formula has little or no effect on underweight, stunting, and wasting in the first year of life. No effect on the occurrence of overweight or obesity was observed at 5 years of follow-up. Feeding healthy term infants standard-protein formula compared to low-protein formula has little or no effect on underweight, stunting, and wasting in the first year of life. No studies reported overweight, obesity, or all-cause mortality. The findings of six ongoing studies and two studies awaiting classification studies may change the conclusions of this review.

Effect of maternal egg intake during the early neonatal period and risk of infant egg allergy at 12 months among breastfeeding mothers. A randomized clinical trial

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JAMA Netw Open 2023;6:e2322318

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Comments: The prevalence of food allergy is increasing worldwide, estimated at approximately 10% in children [39]. Of note, hen's egg represents one of the main causes for food allergy. Thus, preventing egg allergy (EA) is important for children. Egg introduction in infants from age 3–6 months is associated with a lower risk of immunoglobulin E-mediated EA [40]. However, whether the risk of EA in infants at age 12 months is affected by maternal intake of eggs at birth is unknown. To gain more knowledge on this issue, Nagakura et al. performed a multicenter RCT in Japan [41]. Newborns with at least one of two parents having allergic disease were included, whereas newborns whose mothers had EA or were unable to consume breast milk after the age of 2 days were excluded. Newborns were randomized to a maternal egg consumption (MEC) group, where mothers consumed one whole egg daily during the first 5 days of life, or to a maternal egg elimination (MEE) group, where mothers eliminated eggs from their diet during the same period. The primary outcome was EA at age 12 months. A total of 380 newborns were included, of whom 367 could be followed up for 12 months. On days 3 and 4 after delivery, the proportions of newborns with ovalbumin and ovomucoid detection in breast milk were significantly higher in the MEC group than in the MEE group. However, at age 12 months, the MEC and MEE groups did not differ significantly in the prevalence of EA (9.3% vs. 7.6%) or sensitization to egg white (62.8% vs. 58.7%). In this RCT, the development of EA and sensitization to egg white was unaffected by MEC during the early neonatal period. No adverse effects were observed with either intervention.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 104–126 (DOI: 10.1159/000541852)

Cognition

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Introduction

Maternal and early-life nutrition, especially during critical periods such as preconception, pregnancy, infancy, and early childhood, significantly contribute to anatomic and functional brain development. The interplay between dietary patterns and specific micronutrient intake with cognitive outcomes has been a growing focus of research. This chapter presents a selection of recent studies published between July 1, 2023, and June 30, 2024, focusing on the relationship between nutrition and cognitive function across these sensitive phases.

The literature search was performed on the PubMed database using combinations of the following keywords: "cognitive function," "cognitive outcomes," "neurodevelopment," "brain growth," "cognitive performance," "diet," "dietary pattern," "food intake," "nutrients," "micronutrients," "vitamin," "iron," "fatty acids," "microbiome," "obesity," "pregnancy," "gestation," "infancy," "childhood," "infants," "children," and "offspring."

The selected original articles, including randomized controlled trials (RCTs), observational studies, and reviews, are grouped into two principal areas: "dietary patterns" and "micronutrients," each one further divided into two main categories: "pregnancy" and "infants/children." Indeed, while in previous, years we used to subdivide the chapter on cognition and growth by classes of age (intrauterine stage, infancy and lactation, early childhood, adolescents) for any single nutrient, this year, due to the rapid increase of interest in dietary patterns, closely connected to the widespread concept of sustainability, we have chosen to emphasize this topic. Micronutrients, on the other hand, represent an area of malnutrition closely connected to brain development and function, particularly in low-resource settings.

This chapter provides a comprehensive overview of these studies, mainly representing examples of the current evolution of the research in the field, offering valuable insights for supporting cognitive outcomes through targeted nutritional interventions.

Key articles reviewed for this chapter

Dietary Patterns

Pregnancy

Maternal obesity, gestational diabetes mellitus, and diet in association with neurodevelopment of 2-year-old children
Saros L, Lind A, Setänen S, Tertti K, Koivuniemi E, Ahtola A, Haataja L, Shivappa N, Hébert JR, Vahlberg T, Laitinen K
Pediatr Res 2023;94:280–289

Pre-pregnancy maternal obesity and infant neurodevelopmental outcomes in Latino infants
Babaei M, Machle CJ, Mokhtari P, Ottino González J, Schmidt KA, Alderete TL, Adise S, Peterson BS, Goran MI
Obesity (Silver Spring) 2024;32:979–988

Association between dietary patterns during pregnancy and children's neurodevelopment: a birth cohort study
Ouyang J, Cai W, Wu P, Tong J, Gao G, Yan S, Tao F, Huang K
Nutrients 2024;16:1530

How maternal nutritional and mental health affects child health during pregnancy: a narrative review
Naaz A, Muneshwar KN
Cureus 2023;15:e48763

Effect of a mediterranean diet or mindfulness-based stress reduction during pregnancy on child neurodevelopment. A prespecified analysis of the IMPACT BCN randomized clinical trial
Crovetto F, Nakaki A, Arranz A, Borras R, Vellvé K, Paules C, Boutet ML, Castro-Barquero S, Freitas T, Casas R, Martín-Asuero A, Oller Guzmán T, Morilla I, Martínez-Àran A, Camacho A, Pasqual M, Izquierdo Renau M, Pozo ÓJ, Gomez-Gomez A, Estruch R, Vieta E, Crispi F, Gratacós E
JAMA Netw Open 2023;6:e2330255

Investigation of the effects of maternal nutrition during pregnancy on cognitive functions of toddlers: a systematic review
Jalali Chimeh F, Aghaie E, Ghavi S, Fatahnia R
Int J Prev Med 2024;15:15

Maternal fermented food intake and infant neurodevelopment: the Japan Environment and Children's Study
Tanaka T, Matsumura K, Tsuchida A, Hamazaki K, Kasamatsu H, Hirai H, Kusabiraki S, Hiraiwa A, Miya K, Adachi Y, Inadera H; Japan Environment and Children's Study (JCES) Group
Asia Pac J Clin Nutr 2024;33:66–82

Association between daily breakfast habit during pregnancy and neurodevelopment in 3-year-old offspring: the Japan Environment and Children's Study
Imaizumi K, Murata T, Isogami H, Fukuda T, Kyozuka H, Yasuda S, Yamaguchi A, Sato A, Ogata Y, Shinoki K, Hosoya M, Yasumura S, Hashimoto K, Fujimori K, Nishigori H; Japan Environment and Children's Study (JECS) Group
Sci Rep 2024;14:6337

Infants

Breastfeeding and neurodevelopment in infants with prenatal alcohol exposure
Schaffer KE, Chambers CD, Garfein RS, Wertelecki W, Bandoli G
Pediatr Res 2024;95:819–826

The association between duration of breastfeeding and brain development trajectory of brain development from childhood to young adulthood: an 8-year longitudinal study
Grevet LT, Teixeira DS, Pan PM, Jackowski AP, Zugman A, Miguel EC, Rohde LA, Salum GA
Eur Child Adolesc Psychiatry 2024;33:1863–1873

Potential epigenetic effects of human milk on infants' neurodevelopment
Gialeli G, Panagopoulou O, Liosis G, Siahanidou T
Nutrients 2023;15:3614

Junk food use and neurodevelopmental and growth outcomes in low-resource settings
Chiwila MK, Krebs NF, Manasyan A, Chomba E, Mwenechanya M, Mazariegos M, Sami N, Pasha O, Tshefu A, Lokangaka A, Goldenberg RL, Bose CL, Koso-Thomas M, Goco N, Do BT, McClure EM, Hambidge KM, Westcott JE, Carlo WA
Front Public Health 2024;12:1308685

Micronutrients

Pregnancy

Vitamin D status in pregnancy and childhood associates with intelligence quotient at age 7 years: an Odense child cohort study
Cantio E, Bilenberg N, Nørgaard SM, Beck IH, Möller S, Cantio C, Jensen TK, Mortensen NB, Rasmussen A, Christesen HBT
Aust N Z J Psychiatry 2023;57:1062–1072

Prenatal iron supplementation adjusted to maternal iron stores reduces behavioral problems in 4-year-old children
Iglesias-Vázquez L, Canals J, Hernández-Martínez C, Voltas N, Arija V
Matern Child Nutr 2024;20:e13595

Prenatal vitamin B_{12} status and cognitive functioning in children at 4 years of age: the ECLIPSES Study
Cruz-Rodríguez J, Canals-Sans J, Hernández-Martínez C, Voltas-Moreso N, Arija V
Matern Child Nutr 2024;20:e13580

Prenatal vitamin B_{12} and children's brain development and cognitive, language and motor outcomes: a scoping review
Jembere F, Dewey D
Children (Basel) 2024;11:558

Intake of eggs, choline, lutein, zeaxanthin, and DHA during pregnancy and their relationship to fetal neurodevelopment
Christifano DN, Chollet-Hinton L, Hoyer D, Schmidt A, Gustafson KM
Nutr Neurosci 2023;26:749–755

Vitamin D is associated with visual memory in young northern adolescents
Bailey KRF, Pettersen JA
Nutr Neurosci 2024;27:392–403

Microbiome function and neurodevelopment in Black infants: vitamin B_{12} emerges as a key factor
Oliphant K, Cruz Ayala W, Ilyumzhinova R, Mbayiwa K, Sroka A, Xie B, Andrews B, Keenan K, Claud EC
Gut Microbes 2024;16:2298697

Impact of a nutrient formulation on longitudinal myelination, cognition, and behavior from birth to 2 years: a randomized clinical trial
Schneider N, Hartweg M, O'Regan J, Beauchemin J, Redman L, Hsia DS, Steiner P, Carmichael O, D'Sa V, Deoni S
Nutrients 2023;15:4439

A combination of phospholipids and long-chain polyunsaturated fatty acids supports neurodevelopmental outcomes in infants
Ren Q, Zhu X, Pan J, Li K, Zhou Y, Lyu Y, Xie Q, Xu Y
Front Nutr 2024;11:1358651

Effectiveness of intermittent iron and high-dose vitamin A supplementation on cognitive development of school children in southern Ethiopia: a randomized placebo-controlled trial
Gutema BT, Levecke B, Sorrie MB, Megersa ND, Zewdie TH, Yesera GE, De Henauw S, Abubakar A, Abbeddou S
Am J Clin Nutr 2024;119:470–484

The effect of iron-fortified lentils on blood and cognitive status among adolescent girls in Bangladesh
Barnett AL, Wenger MJ, Yunus FM, Jalal C, DellaValle DM
Nutrients 2023;15:5001

Milk–cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomised controlled trial in India
Upadhyay RP, Taneja S, Strand TA, Hysing M, Koshy B, Bhandari N, Bahl R
Br J Nutr 2023;130:868–877

Maternal obesity, gestational diabetes mellitus, and diet in association with neurodevelopment of 2-year-old children

Saros L[1], Lind A[2,3,4], Setänen S[5], Tertti K[6], Koivuniemi E[1], Ahtola A[7,8], Haataja L[9], Shivappa N[10,11], Hébert JR[10,11], Vahlberg T[12], Laitinen K[1,13]

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Pediatr Res 2023;94:280–289

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https://pubmed.ncbi.nlm.nih.gov/36596942/

Dietary pattern: Fish consumption, overall dietary quality

Setting: Finland

Association/effect: Yes

Study: Cohort study

Treatment/methods: Neurodevelopment was investigated using the Bayley Scales of Infant and Toddler Development, Third Edition, and the Hammersmith Infant Neurological Examination. Dietary quality and fish consumption were assessed using questionnaires and food diaries.

Age-related associations: At 2 years of age, gestational diabetes mellitus and higher maternal adiposity negatively affect neurodevelopment, while better diet quality and higher fish consumption were beneficial.

Pre-pregnancy maternal obesity and infant neurodevelopmental outcomes in Latino infants

Babaei M[1], Machle CJ[1,2], Mokhtari P[1], Ottino González J[1], Schmidt KA[1], Alderete TL[3], Adise S[1], Peterson BS[1], Goran MI[1]

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Obesity (Silver Spring) 2024;32:979–988

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https://pubmed.ncbi.nlm.nih.gov/38600046/

Dietary pattern: Pre-pregnancy maternal obesity, infant diet quality
Setting: Low-income countries (Latino population)
Association/effect: Yes
Study: Cohort study
Treatment/methods: Maternal pre-pregnancy BMI and infant diet quality were assessed, and neurodevelopment at 24 months measured, using the Bayley Scales of Infant Development.
Age-related associations: At 24 month of age, maternal obesity negatively affects infant neurodevelopment, with diet quality playing a mediating role.

Association between dietary patterns during pregnancy and children's neurodevelopment: a birth cohort study

Ouyang J[1,2,3,4], Cai W[1,2,3,4], Wu P[1,2,3,4], Tong J[1,2,3,4], Gao G[1,5], Yan S[1,5], Tao F[1,2,3,4], Huang K[1,2,3,4]

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Nutrients 2024;16:1530
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https://pubmed.ncbi.nlm.nih.gov/38794768/

Dietary pattern: Protein- and micronutrient-rich dietary patterns, low-iron dietary patterns
Setting: China
Association/effect: Yes
Study: Birth cohort study
Treatment/methods: Maternal dietary patterns during pregnancy were assessed using food frequency questionnaires. Neurodevelopment in children at 36 months was measured with the Ages and Stages Questionnaire, Third Edition.
Age-related associations: At 36 months of age, high-quality diet was beneficial, whereas low-iron diet was detrimental, to neurodevelopment.

How maternal nutritional and mental health affects child health during pregnancy: a narrative review

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Cureus 2023;15:e48763
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Dietary pattern: Diet rich in macronutrients and micronutrients (iron, omega-3 fatty acids)
Setting: Not specific to one location, global perspective
Association/effect: Yes
Study: Narrative review
Treatment/methods: Review of literature on maternal nutrition and mental health during pregnancy and their impact on child development
Age-related associations: Unbalanced diets of mother during pregnancy, leading to deficiencies of micronutrient (e.g., folic acid, iron, iodine) intake, besides substance abuse and maternal mental illnesses, negatively affect brain development throughout childhood and adolescence.

Effect of a mediterranean diet or mindfulness-based stress reduction during pregnancy on child neurodevelopment. A prespecified analysis of the IMPACT BCN randomized clinical trial

Crovetto F[1,2], Nakaki A[1,3], Arranz A[1], Borras R[4,5], Vellvé K[1], Paules C[1], Boutet ML[1], Castro-Barquero S[1,6,7], Freitas T[1,6,7], Casas R[6,7], Martín-Asuero A[8], Oller Guzmán T[8], Morilla I[9], Martínez-Àran A[9], Camacho A[1], Pasqual M[1], Izquierdo Renau M[2,10], Pozo ÓJ[11], Gomez-Gomez A[11], Estruch R[6,7], Vieta E[9], Crispi F[1,3,12], Gratacós E[1,2,12]

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Dietary pattern: Mediterranean diet, mindfulness-based stress reduction (MBSR)
Setting: Spain
Association/effect: Yes
Study: Randomized clinical trial (IMPACT BCN)
Treatment/methods: Participants received a Mediterranean diet intervention, MBSR, or usual care. Neurodevelopment at 2 years was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition
Age-related associations: At 2 years of age, there were improvements in neurodevelopment in both intervention groups.

Investigation of the effects of maternal nutrition during pregnancy on cognitive functions of toddlers: a systematic review

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Int J Prev Med 2024;15:15

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https://pubmed.ncbi.nlm.nih.gov/38715696/

Dietary pattern: Supplemented diet (iron, fatty acids, vitamins B and D, folic acid)
Setting: Mostly well-developed countries
Association/effect: Partial
Study: Systematic review
Treatment/methods: Review of studies on the impact of maternal nutrition during pregnancy on cognitive function in toddlers (1–3 years old)
Age-related associations: Between one and 3 years of age, a supplement during pregnancy of iron, vitamins B and D, and folic acid improved the cognitive functions of toddlers. On the other hand, taking supplements containing iodine and zinc had no significant effect on the development of cognitive functions. Diets containing seafood had a beneficial effect on the cognitive functions of children.

Maternal fermented food intake and infant neurodevelopment: the Japan Environment and Children's Study

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Asia Pac J Clin Nutr 2024;33:66–82

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https://pubmed.ncbi.nlm.nih.gov/38494689/

Dietary pattern: Fermented foods (miso soup, fermented soybeans, cheese, yogurt)
Setting: Japan
Association/effect: Yes
Study: Prospective cohort study

Treatment/methods: Maternal intake of fermented foods during pregnancy was assessed using a semiquantitative FFQ. Neurodevelopment in infants at 1 year of age was measured with the Ages and Stages Questionnaires.
Age-related associations: At 1 year of age, associations with psychomotor development in children have been found.

Association between daily breakfast habit during pregnancy and neurodevelopment in 3-year-old offspring: the Japan Environment and Children's Study

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Dietary pattern: Daily breakfast consumption
Setting: Japan
Association/effect: Yes
Study: Prospective cohort study
Treatment/methods: Maternal breakfast habits during pregnancy were analyzed in relation to offspring neurodevelopment at 3 years using the 3rd edition of Ages and Stages Questionnaire.
Age-related associations: At 3 years of age, consistent breakfast consumption during pregnancy shows positive effects on child neurodevelopment.

Comments: The selected articles emphasize a critical role of maternal nutrition and metabolic health during pregnancy in shaping neurodevelopmental trajectories in the offspring. Several studies highlight specific dietary patterns and food groups that contribute to improve cognitive, language, and motor skills. Evidence suggests that maternal consumption of fermented foods, a Mediterranean diet, and high-quality proteins during gestation may positively influence neurodevelopmental outcomes, particularly in communication, motor, and problem-solving abilities. Furthermore, higher fish consumption and consistent breakfast habits during pregnancy also appear to contribute positively to language and social-emotional skills in early childhood. On the other hand, maternal obesity, gestational diabetes mellitus, and poor dietary quality are associated with delayed neurodevelopment, including cognitive and language impairments. The findings emphasize the importance of holistic dietary interventions and weight management strategies both before and

during pregnancy, especially in populations at higher risk for adverse neurodevelopmental outcomes, such as low-income or overweight/obese mothers. Additionally, the potential mediatory role of infant diet quality in the relationship between maternal obesity and neurodevelopment suggests that early dietary interventions in infants could mitigate some negative effects. Overall, these studies highlight the need for comprehensive nutritional and lifestyle guidance for pregnant women to contribute to child neurodevelopmental outcomes across various domains. A more integrated approach to the whole macro- and micronutrient intake considering both quantity and frequency of consumption, mostly connected to the composition of geolocalized dietary patterns, is now overcoming the single-nutrient strategy to achieve long-term health and well-being in mothers and offspring.

Infants

Breastfeeding and neurodevelopment in infants with prenatal alcohol exposure

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Pediatr Res 2024;95:819–826

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Dietary pattern: Breastfeeding
Setting: Ukraine
Association/effect: Yes
Study: Prospective cohort study
Treatment/methods: 385 infants from a prospective cohort in pregnancy on mothers with PAE were assessed for neurodevelopment using the Bayley Scales of Infant Development II (BSID-II) at 6 and 12 months. Linear regression with interaction terms and stratification by PAE group analyzed the impact of breastfeeding.
Age-related associations: At 6 and 12 months, respectively, infants with high PAE who were breastfed for at least 4 months showed higher BSID-II scores, while those with moderate PAE had poorer outcomes at 12 months with extended breastfeeding. These observations indicate meaningful interactions between PAE and breastfeeding.

The association between duration of breastfeeding and brain development trajectory of brain development from childhood to young adulthood: an 8-year longitudinal study

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https://pubmed.ncbi.nlm.nih.gov/37650992/

Dietary pattern: Breastfeeding

Setting: Brazil

Association/effect: Yes

Study: 8-year longitudinal study

Treatment/methods: The study included 670 children with 1,326 MRI scans over 8 years. Breastfeeding duration was assessed through parental questionnaires, and brain measures were analyzed using generalized additive models.

Age-related associations: During the transition from childhood to young adulthood, longer breastfeeding was positively associated with cortical thickness and brain volume, suggesting beneficial effects on brain development.

Potential epigenetic effects of human milk on infants' neurodevelopment

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https://pubmed.ncbi.nlm.nih.gov/37630804/

Dietary pattern: Human milk

Setting: Global perspective

Association/effect: Yes

Study: Narrative review

Treatment/methods: The review analyzed existing literature on the bioactive components of human milk (miRNAs and long noncoding RNAs, stem cells, and microbiome) and their potential epigenetic effects on neurodevelopment

Age-related associations: In infancy, bioactive components of human milk may have neurodevelopmental impact in both full-term and preterm infants, although precise mechanisms remain unclear.

Junk food use and neurodevelopmental and growth outcomes in low-resource settings

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Front Public Health 2024;12:1308685

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Dietary pattern: Junk food

Setting: Low-income countries (Democratic Republic of the Congo, Guatemala, Pakistan, Zambia)

Association/effect: No significant effects

Study: Secondary analysis of a randomized controlled trial

Treatment/methods: The study assessed junk food consumption and its association with neurodevelopment and growth using the Bayley Scales of Infant Development II and other measures at 18 months.

Age-related associations: At 18 months, despite high consumption rates of junk food at a low age, no adverse associations with neurodevelopmental or growth outcomes were observed over the study period.

Comments: Breastfeeding (here intended as dietary pattern) confirms positive effects mitigating even the negative effects of prenatal alcohol exposure. It is associated with increased cortical thickness and brain volume into young adulthood when continued for a longer period (1 year or more) after birth, compared to shorter durations or not breastfeeding at all. The epigenetic effects of breast milk, through its bioactive components, suggest a potential influence on gene expression and brain development. Breastfeeding remains the gold reference for growth and development, wherever the setting. In the case, mothers do not breastfeed, formulas enriched with phospholipids and long-chain polyunsaturated fatty acids (LCPUFAs) have demonstrated positive effects on cognitive and motor development.

The study selected for the category of junk food consumption in low-resource settings is just an example of an ongoing debate. The authors of this multinational study found no direct link between low-quality diet and adverse neurodevelopmental outcomes while highlighting the impact of environmental factors. The need to improve energy needs in poor settings could explain the last finding, making this dietary pattern more affordable for most families. Accordingly, we may derive that the effects ultra-processed foods in general (inclusive of junk foods) require contextualization according to the setting before drawing conclusions.

Micronutrients

Pregnancy

Vitamin D status in pregnancy and childhood associates with intelligence quotient at age 7 years: an Odense child cohort study

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Aust N Z J Psychiatry 2023;57:1062–1072

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Nutrient: Vitamin D
Setting: Denmark
Association/effect: Yes
Study: Cohort study
Treatment/methods: The study investigates the association between serum 25-hydroxyvitamin D concentrations measured at four time points (early pregnancy, late pregnancy, cord blood, and at age 7) and intelligence quotient (IQ) at the age of 7 years in 1,404 mother-child pairs. The Wechsler Intelligence Scale for Children, 5th edition, was used for IQ assessment. Adjustments were made for maternal education, pre-pregnancy BMI, gestational age, sex, and head circumference. Subanalyses were stratified by sex.
Age-related associations: At the age of 7 years, lower serum 25-hydroxyvitamin D levels (<50 nmol/L) in boys during early pregnancy and cord blood, and in girls, were associated with a 2–4 point lower full-scale IQ.

Prenatal iron supplementation adjusted to maternal iron stores reduces behavioral problems in 4-year-old children

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Matern Child Nutr 2024;20:e13595

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Nutrient: Iron

Setting: Spain

Association/effect: Yes

Study: Randomized controlled trial

Treatment/methods: The study explored the impact of prenatal iron supplementation adjusted to maternal iron stores on behavioral problems in 4-year-old children. Pregnant women were randomized to receive different iron doses based on hemoglobin (Hb) levels before the 12th gestational week and serum ferritin (SF) levels. Behavioral problems were assessed using the Child Behavior Checklist and Teacher's Report Form and executive functioning with the Behavior Rating Inventory of Executive Function, Preschool Version.

Age-related associations: At 4 years, high iron doses (80 mg/d) improved behavior in children whose mothers had low iron stores (SF <15 μg/L), but worsened behavior in those whose mothers had normal-high iron stores. Low doses (20 mg/d) improved behavior in children of mothers with SF >65 μg/L.

Prenatal vitamin B_{12} status and cognitive functioning in children at 4 years of age: the ECLIPSES Study

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Matern Child Nutr 2024;20:e13580

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Nutrient: Vitamin B_{12}
Setting: Spain
Association/effect: Yes
Study: Longitudinal prospective study
Treatment/methods: The study examined the association between maternal vitamin B_{12} levels during the first and third trimesters of pregnancy and cognitive functioning in children at age 4. Cognitive functioning was measured using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) and Neuropsychological Assessment of Development (NEPSY-II). The analysis was adjusted for sociodemographic, nutritional, and psychological factors.
Age-related associations: At 4 years of age, higher maternal vitamin B_{12} levels in the first trimester were associated with better working memory scores, with significant differences observed between tertiles of maternal vitamin B_{12} levels.

Prenatal vitamin B_{12} and children's brain development and cognitive, language and motor outcomes: a scoping review

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Nutrient: Vitamin B_{12}
Setting: Not specific of one location, global perspective
Association/effect: Inconclusive
Study: Scoping review of 19 human epidemiological studies
Treatment/methods: This review assessed the current knowledge on the association between maternal vitamin B_{12} status during pregnancy and children's brain development or cognitive or motor development. Studies included were based on measures of vitamin B_{12} status, dietary intake, supplementation, or deficiency and assessed outcomes related to brain development and neurodevelopment in children under 18 years of age.
Age-related associations: The evidence of an association between maternal vitamin B_{12} during pregnancy and children's neurodevelopmental outcomes is inconclusive, highlighting the need for further longitudinal research.

Intake of eggs, choline, lutein, zeaxanthin, and DHA during pregnancy and their relationship to fetal neurodevelopment

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Nutr Neurosci 2023;26:749–755

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Nutrients: Eggs and other nutrient-dense food sources such as seafood and leafy greens (choline, lutein, zeaxanthin, DHA)

Setting: United States

Association/effect: Yes

Study: Cohort study

Treatment/methods: The study evaluated the relationship between maternal intake of eggs, choline, lutein, zeaxanthin, and DHA during pregnancy and fetal neurodevelopment in 202 pregnant women. Fetal neurodevelopment was assessed using fetal biomagnetometry, a noninvasive manner to study the longitudinal development of the human fetus through magnetic fields. The autonomic and brain maturation indices were calculated at 32 and 36 weeks of gestation, respectively

Age-related associations: At 32 and 36 weeks of gestation, the maternal intake of eggs and interactions between choline, lutein, zeaxanthin, and DHA were associated with improved fetal autonomic and brain maturation indices.

Comments: The selected articles highlight the need for more homogeneous and well-planned studies on the role of micronutrients, and related foods, intake during pregnancy in shaping cognitive and behavioral outcomes of infants (even before delivery) and children. The Odense Child Cohort study highlighted that low serum 25-hydroxyvitamin D levels during pregnancy and childhood were linked to a lower IQ at age 7, particularly in boys during early pregnancy and cord blood, and in girls at age 7, suggesting the critical role of maintaining adequate vitamin D levels during pregnancy and childhood. Similarly, the randomized controlled trial from Spain demonstrated that prenatal iron supplementation tailored to maternal iron stores could improve behavioral outcomes in children at age 4, while excessive iron supplementations in mothers with normal or high stores might have adverse effects. This finding confirms previous observations on the opportunity to supplement iron to all pregnant mothers, irrespective of maternal iron stores. The ECLIPSES study also found that higher maternal vitamin B_{12} levels in the first trimester were associated with better cognitive outcomes, specifically in working memory at age 4. However, a scoping review on vitamin B_{12} and children's neurodevelopmental outcomes

showed inconclusive evidence. Lastly, a study from the United States showed that maternal intake of eggs, choline, lutein, zeaxanthin, and DHA positively influenced fetal neurodevelopment, highlighting the importance of a diet balanced in functional nutrients and foods during pregnancy. Besides the heterogeneity of study designs, differences in study settings, local lifestyle, and the family background are confounders quite difficult to quantify, so limiting the power of final assertions.

Infants/children

Vitamin D is associated with visual memory in young northern adolescents

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Nutrient: Vitamin D
Setting: Canada
Association/effect: Yes
Study: Cross-sectional study
Treatment/methods: Visual memory was assessed using the Rey-Osterrieth Complex Figure Task (ROCF). Blood levels of 25(OH)D were measured with blood spot tests at home. Multiple regression analyses included age and sex as covariates.
Age-related associations: In prepubertal and pubertal age, the association was stronger in older adolescents (11–13 years) compared to younger ones (9–10 years), with significant correlations observed for visual memory and working memory in the older group.

Microbiome function and neurodevelopment in Black infants: vitamin B_{12} emerges as a key factor

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Nutrient: Vitamin B_{12}
Setting: Low-income population in a city of United States (Black infants in South Side of Chicago)
Association/effect: Yes
Study: Secondary analysis of a randomized controlled trial
Treatment/methods: Microbiome composition and function were analyzed through 16S rRNA gene sequencing, shotgun metagenomics, and targeted metabolomics of fecal samples. Neurodevelopment was assessed using developmental testing and maternal reports.
Age-related associations: In male Black infants of 7 months of age (range: 3–16 months), living in urban, low-income neighborhoods, vitamin B_{12} biosynthesis emerged as a key microbiome function showing positive associations with all measured developmental skills (i.e., cognition, language, motor, surgency, effortful control, and observed stress regulation).

Impact of a nutrient formulation on longitudinal myelination, cognition, and behavior from birth to 2 years: a randomized clinical trial

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Nutrient: A selected blend of nutrients including DHA, ARA, iron, folic acid, vitamin B_{12}, and an alpha-lactalbumin–enriched whey protein concentrate
Setting: United States
Association/effect: Yes
Study: Randomized controlled trial
Treatment/methods: Infants received a nutritional intervention for 12 months. Myelination was assessed via MRI, and neurodevelopment and behavior were evaluated using Bayley-III, ASQ, IBQ-R, TBAQ, and BISQ.
Age-related associations: Across various time points from 6 to 24 months, the intervention showed positive effects on brain development and sleep patterns, indicating the critical importance of early nutritional interventions during infancy.

A combination of phospholipids and long-chain polyunsaturated fatty acids supports neurodevelopmental outcomes in infants

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Front Nutr 2024;11:1358651

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https://pubmed.ncbi.nlm.nih.gov/38938667/

Nutrient: Phospholipids (PLs) and long-chain polyunsaturated fatty acids (LCPUFAs)
Setting: China
Association/effect: Yes
Study: Randomized double-blind controlled trial
Treatment/methods: 300 infants were randomly assigned to either a formula with PLs and LCPUFAs or a control formula. Neurodevelopmental outcomes were assessed using various developmental scales at 365 days (1 year) of age.
Age-related associations: At 1 year of age, an investigational formula with PLs and LCPUFAs led to higher cognitive, language, and motor scores, suggesting potential benefits for neurodevelopment during the first year of life.

Effectiveness of intermittent iron and high-dose vitamin A supplementation on cognitive development of school children in southern Ethiopia: a randomized placebo-controlled trial

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Am J Clin Nutr 2024;119:470–484

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https://pubmed.ncbi.nlm.nih.gov/37952928/

Nutrient: Iron and vitamin A
Setting: Low-income country (southern Ethiopia)
Association/effect: Partial
Study: Randomized controlled trial

Treatment/methods: Children were assigned to four groups receiving either iron, vitamin A, both, or placebos once weekly for 11 months. Cognitive development was assessed using Raven's Colored Progressive Matrices, digit span, Tower of London, and visual search tasks.
Age-related associations: In children 7–10 years of age, once-weekly intermittent iron supplementation did not have any positive or negative effect on the child's cognitive development outcomes. Conversely, vitamin A supplementation improved the child's working memory.

The effect of iron-fortified lentils on blood and cognitive status among adolescent girls in Bangladesh

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Nutrients 2023;15:5001
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Nutrient: Iron (fortified lentils)
Setting: Low-income country (Bangladesh)
Association/effect: Yes
Study: Randomized double-blind controlled trial
Treatment/methods: Adolescent and young girls received iron-fortified lentils for 4 months, with cognitive performance assessed using five cognitive tasks. Iron status was measured at baseline and endline.
Age-related associations: In adolescent girls aged 10–17 years, higher levels of cognitive performance were observed in those at risk of developing iron deficiency.

Milk-cereal mix supplementation during infancy and impact on neurodevelopmental outcomes at 12 and 24 months of age: a randomised controlled trial in India

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Br J Nutr 2023;130:868–877
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Nutrient: Protein and micronutrient (milk-cereal mix supplementation)
Setting: Transition country (India)
Association/effect: Partial
Study: Randomized controlled trial
Treatment/methods: Infants were randomized to receive two types of milk-cereal mixes (modest or high protein) or no supplementation, with neurodevelopmental outcomes assessed at 12 and 24 months of age, respectively.
Age-related associations: At 12 months, improvements in motor function and temperament were observed, but no significant differences were found at 24 months, suggesting a short-term benefit from modest protein supplementation during infancy.

Comments: Recent research has indagated the impact of specific micronutrients, such as vitamins and iron, on cognitive and neurodevelopmental outcomes during infancy and childhood, particularly in vulnerable populations. A cross-sectional study from Canada identified a positive association between vitamin D levels and visual memory, with stronger effects observed in older adolescents, suggesting age-dependent benefits of vitamin D on cognitive functions. Similarly, research on Black infants from low-income families in Chicago linked vitamin B_{12} to enhanced cognitive and language development, underscoring the significance of early-life micronutrient interventions in supporting neurodevelopmental outcomes. In addition to single nutrients, multinutrient interventions are being investigated. A randomized controlled trial in the United States demonstrated that a blend of DHA, ARA, iron, folic acid, vitamin B_{12}, and alpha-lactalbumin-enriched whey protein concentrate positively impacted myelination, gray matter volume, and sleep patterns in infants from birth to 2 years, supporting the critical role of comprehensive nutritional interventions during infancy. The effects of supplementation may differ depending on context and population. For instance, in a study from southern Ethiopia, vitamin A supplementation improved cognitive function, particularly working memory, in school children, while iron supplementation did not yield positive results. This nuanced view underscores the importance of considering both nutrient-specific effects and environmental factors in designing interventions. Iron, in particular, remains a focal point in addressing cognitive development in developing settings. A study in Bangladesh found that iron-fortified lentils improved cognitive performance among adolescent girls, reinforcing the need to address iron deficiency during critical developmental periods. Finally, a randomized trial in India explored the effects of milk-cereal mix supplementation, finding modest improvements in motor function and temperament with moderate protein supplementation during infancy, though no long-term benefits were observed from high protein supplementation. These findings emphasize the importance of targeted, context-specific nutritional strategies to optimize cognitive and neurodevelopmental outcomes later in life. Of interest, the inclusion of multicomponent supplementations could open new horizons of investigation compared to considering just one dietary component, raising the hypotheses that multiple compounds may result in a more meaningful outcome.

Overview

The individual effects of specific dietary patterns and micronutrient supplementations during pregnancy, infancy, and later childhood represent relevant research areas regarding the impact on cognitive functions. Studies have found that adherence to a Mediterranean diet and mindfulness practices during pregnancy can positively affect child's neurodevelopment. Additionally, specific dietary habits, such as regular breakfast consumption and the intake of fermented foods during pregnancy, have been linked to improved cognitive outcomes in offspring. The role of breastfeeding, particularly its duration, suggests that prolonged breastfeeding supports brain growth and cognitive development from childhood through young adulthood, even in infants growing in unfavorable intrauterine conditions. Consumption of junk food in early infancy may be not associated with adverse cognitive outcomes in low-resource settings, indicating the need to contextualize any study in this area. Micronutrient intake during pregnancy and early childhood is equally crucial for neurodevelopment. Research on key micronutrients such as vitamin D and B_{12} and iron has revealed their significant influence on cognitive trajectories. For example, maternal vitamin D levels during pregnancy have been linked to a child's intelligence quotient (IQ) at age 7. Iron supplementation in pregnant women with iron deficiency has been associated with reduced behavioral problems in children, but not in the case of a sufficient maternal iron status. The interplay between micronutrients and the developing brain, particularly in low- and middle-income countries, is further underscored by studies on nutrient formulations and fortified foods, which have shown positive results in supporting cognitive functions and myelination in infants. Emerging research underscores the role of the microbiome and its interaction with micronutrients, such as vitamin B_{12}, contributing to a positive effect of the gut-brain axis on cognition.

The studies that we have selected stress the relevance of healthy dietary patterns and targeted micronutrient supplementations to enhance functional neurodevelopment, particularly in low- and middle-income countries.

Considering all these factors (dietary patterns, micronutrient intakes, environment, and setting), there is a growing need for future studies based on machine learning approach and artificial intelligence models to disentangle from such a huge amount of data the major components linking nutrition to cognitive development in the pediatric ages. This approach could provide deeper insights to improve our understanding of the development of the cognitive functions in relation to nutrition and develop targeted recommendations and intervention strategies at either individual or population levels.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

Both authors have read and commented on the reviewed manuscripts.

Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 127–139 (DOI: 10.1159/000541853)

Nutrition and Growth in Chronic Diseases

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Introduction

Infancy, childhood, and adolescence are critical periods for growth and development. Optimal growth requires adequate nutrition, coordinated metabolic processes, and intact hormonal axis. Chronic diseases in childhood may affect nutrient intakes, absorption, energy balance, and inflammatory-hormonal system interaction. As these factors can alter the complex processes of growth, puberty, and bone mass accrual, pediatric chronic diseases present unique challenges.

For this chapter, we reviewed articles published on peer-reviewed journals over the last year, which evaluated and reported different aspects of growth and nutrition in a selected group of pediatric chronic diseases. We have selected 10 leading articles, reviewed in this chapter, focusing on inflammatory bowel disease; celiac disease; congenital heart disease; cystic fibrosis; and attention-deficit/hyperactivity disorder. The selected articles represent various topics in chronic diseases, including nutritional and feeding management or mismanagement, growth trajectories and factors that influence them, and metabolic bone disease and its complications.

Key articles reviewed for this chapter

Inflammatory Bowel Disease

Early-life diet and risk of inflammatory bowel disease: a pooled study in two Scandinavian birth cohorts

Guo A, Ludvigsson J, Brantsæter AL, Klingberg S, Östensson M, Størdal K, Mårild K

Gut 2024;73:590–600

Factors associated with reaching mid-parental height in patients diagnosed with inflammatory bowel disease in childhood and adolescent period
Choi SY, Choi S, Choe BH, Park JH, Choi KH, Lee HJ, Park JS, Seo JH, Kim JY, Jang HJ, Hong SJ, Kim EY, Lee YJ, Kang B
Gut Liver 2024;18:106–115

Celiac Disease

A significant increase in anthropometric indices during long-term follow-up of pediatric patients with celiac disease, with no endocrine disorders
Krauthammer A, Guz-Mark A, Zevit N, Waisbourd-Zinman O, Silbermintz A, Mozer-Glassberg Y, Nachmias Friedler V, Rozenfeld Bar Lev M, Matar M, Shouval D, Shamir R
Eur J Pediatr 2024;183:2173–2182

Effect of a gluten-free diet on bone mineral density in children and adolescents with celiac disease: systematic review and meta-analysis
Oliveira DDC, da Silva DCG, Kawano MM, de Castro CT, Pereira M
Crit Rev Food Sci Nutr 2024;64:5192–5202

Fracture risk among children and adolescents with celiac disease: a nationwide cohort study
Zacay G, Weintraub I, Regev R, Modan-Moses D, Levy-Shraga Y
Pediatr Res 2024;95:386–392

Congenital Heart Disease

Supplemental nutrition, feeding disorders, and renourishment in pediatric heart failure through transplantation
Zook N, Schultz L, Rizzuto S, Aufdermauer A, Hollander AM, Almond CS, Hollander SA
Pediatr Transplant 2023;27:e14601

Cystic Fibrosis

A cross-sectional study of pediatric feeding disorder in children with cystic fibrosis
Bashir A, Antos N, Miller T, Challa SA, Pan AY, Gosa M, Silverman A, Goday PS
J Pediatr Gastroenterol Nutr 2023;77:819–823

Factors associated with pubertal growth outcomes in cystic fibrosis: early growth and puberty in CF
Patil R, Magaret AS, Jain R, Taylor-Cousar J, Hughan KS, Kazmerski TM
J Cyst Fibros 2024;23:538–544

Attention-Deficit/Hyperactivity Disorder

Risk of overweight and obesity in children and adolescents with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis
Zhu Y, Wang NN, Pan D, Wang S
Child Obes 2024;20:119–127

Attention-deficit/hyperactivity disorder is not associated with overweight in adolescence but is related to unhealthy eating behavior and limited physical activity
Halt AH, Hirvonen TT, Koskela J, Kerkelä M, Hurtig T
Nord J Psychiatry 2023;77:591–599

Early-life diet and risk of inflammatory bowel disease: a pooled study in two Scandinavian birth cohorts

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Gut 2024;73:590–600
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Comments: The global prevalence of inflammatory bowel disease (IBD) is increasing, both in developed and in newly industrialized countries. The environmental changes and changes in diets can affect the intestinal microbiome and are presumed to contribute to an increase in the risk of IBD in genetically susceptible individuals [1, 2]. Most studies have evaluated associations between dietary patterns and IBD in adults, but prospective pediatric studies are scarce. A new pooled study from two prospective Scandinavian birth cohorts (All Babies in Southeast Sweden study and the Norwegian Mother, Father and Child Cohort Study) evaluated the association between early life diet and the risk of developing IBD [3]. In this study, diet quality was evaluated using specific food questions at the age of 12–18 months and 30–36 months. Consumption of specific food groups was analyzed, in addition to a diet quality score using the Healthy Eating Index [4]. The risk of developing IBD was adjusted for parental IBD history, sex, origin, education, and maternal comorbidities. The study included 81,280 participants born after 1997, with 1,304,433 person-years of follow-up, with 307 cases diagnosed with IBD. The results of this study have demonstrated that medium and high diet quality at 1 year of age (compared with low diet quality) was associated with a reduced risk of IBD, with a pooled adjusted hazard ratio (aHR) of 0.75 (95% CI = 0.58–0.98) and 0.75 (95% CI = 0.56–1.00), respectively. In addition, high versus low fish intake, as well as high vegetable intake, at 1 year was associated with a risk reduction in IBD, whereas high intake of sugar-sweetened beverages was associated with an increased risk of IBD. Interestingly, diet quality at 3 years was not associated with IBD in this study. Although there were small numbers of IBD cases in these cohorts, the large scale and prospective nature of this study adds valuable insights to the literature in understanding risk factors for the development of IBD and the association with early-life nutrition, supporting the hypothesis that early-life changes in diet, possibly affecting the gut microbiome and immune regulation, may affect the risk of developing IBD.

Factors associated with reaching mid-parental height in patients diagnosed with inflammatory bowel disease in childhood and adolescent period

Choi SY[1], Choi S[2,3], Choe BH[2,3], Park JH[4], Choi KH[3,5], Lee HJ[6], Park JS[7], Seo JH[7], Kim JY[8], Jang HJ[3,9], Hong SJ[3,10], Kim EY[3,11], Lee YJ[4], Kang B[2,3]

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Gut Liver 2024;18:106–115

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https://pubmed.ncbi.nlm.nih.gov/37638380/

Comments: Growth impairment is a common complication of pediatric-onset IBD, affecting 15%–40% of patients, mostly in children with Crohn's disease [5, 6]. The impairment of growth is a result of multifactorial pathophysiology, mainly influenced by the chronic inflammatory process that interferes with the growth hormone (GH) axis and manifests as GH resistance. In malabsorption and malnutrition, direct effects of nutrients on the growth plate, increased energy losses, and increased metabolic requirements play a role in IBD-associated growth failure [7]. Some studies have demonstrated a reduction in final height among patients with pediatric-onset IBD [8], while others report only mild or no decrease in final height [9–11].

This retrospective multicenter study by Choi et al. [12] investigated patients with pediatric-onset IBD who had reached final adult height and evaluated factors associated with reaching mid-parental height (MPH). The study included 166 patients (67% males) with IBD (77% with Crohn's disease), from 8 centers in the Republic of Korea. Overall, 54% (90/166) of patients had reached their MPH. The multivariable logistic regression analysis demonstrated that both height Z-score at diagnosis and MPH Z-score were independently associated with reaching MPH (odds ratio [OR], 8.45; 95% CI = 4.44–17.90; $p < 0.001$ and OR, 0.11; 95% CI = 0.04–0.24; $p < 0.001$, respectively). No other factors were found to be associated with reaching MPH, including sex, age at diagnosis, IBD subtype, disease severity at diagnosis and throughout follow-up, and specific treatments. The optimal cutoff level of the difference between height Z-score at diagnosis and MPH Z-score, which was associated with reaching MPH, was found to be −0.01 (with an area under the curve of 0.889). The findings of this study demonstrate that on top of growth impairment at diagnosis, parental height is a key factor in determining the final adult height of patients with pediatric IBD and should be an integral part of the assessment and target setting in these patients.

A significant increase in anthropometric indices during long-term follow-up of pediatric patients with celiac disease, with no endocrine disorders

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Eur J Pediatr 2024;183:2173–2182

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Comments: Celiac disease (CeD) is an immune-mediated enteropathy that causes an intestinal mucosal damage that can result in nutrient malabsorption, as well as chronic intestinal inflammation. Growth faltering, altered weight gain, and delayed puberty are common in CeD presentation [13]. Although most children with CeD are expected to present catch-up growth during the first few years of gluten-free diet (GFD) [14], some may continue with altered growth despite good adherence to GFD [15, 16].

The recent study by Krauthammer et al. [17] has evaluated longitudinal changes in anthropometric measurements among patients with pediatric-onset CeD, from the diagnosis and through a long-term follow-up under GFD. The study included 500 patients, diagnosed with CeD at a median (IQR) age of 5.7 (3.7–8.9) years, with a mean follow-up period of 5.5 (range 1.5–16.2) years. The study demonstrated a significant increase in weight, height, and BMI Z-scores after CeD diagnosis, with the largest improvements observed in the subgroup of patients diagnosed before 3 years of age, compared to later diagnosis ($p < 0.01$). At diagnosis, wasting was present in 19.7% and stunting in 16.4% of the cohort, and normalized in 77.3% and 64.8%, respectively, within a median (IQR) time of 0.79 (0.42–4.24) and 2.3 (0.72–6.02) years, respectively. Among 86 patients who reached final adult height, mean height Z-score increased from −0.89 (±1.37) at diagnosis to −0.51 (±1.28) at adulthood, $p < 0.05$. In this study, GFD adherence, which was reported as good among 82.7% of cohort, was not associated with normalization of wasting or stunting, probably due to the high adherence rate. Overall, this large cohort demonstrates significant improvement in anthropometric indices in pediatric patients with CeD who follow GFD, with normalization wasting or stunting in most cases. Young age at diagnosis is associated with larger improvement in weight and in linear growth, emphasizing the importance of early diagnosis of CeD.

Effect of a gluten-free diet on bone mineral density in children and adolescents with celiac disease: systematic review and meta-analysis

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Crit Rev Food Sci Nutr 2024;64:5192–5202

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Fracture risk among children and adolescents with celiac disease: a nationwide cohort study

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Pediatr Res 2024;95:386–392

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Comments: CeD is associated with metabolic bone disease and reduced bone mineral density (BMD), mainly at CeD diagnosis [18]. The malabsorption and the alternations in calcium and vitamin D balance, as well as the negative effects of increased pro-inflammatory cytokines, may cause poor skeletal maturation and bone re-modeling imbalance [19–21]. Following a strict GFD, which is the only treatment for CeD, a resolution of the inflammatory process and intestinal malabsorption occurs, as well as restoration of bone mass [22]. However, children and adolescents on GFD are at higher risk of insufficient intake of various micronutrients and might consume an unhealthy diet, especially when lacking dietary education and follow-up [23].

Oliveira et al. have conducted a systematic review and meta-analysis [24], to evaluate the effect of GFD on BMD and bone mineral content (BMC) of children and adolescents with CeD. The review included 28 studies. In the meta-analysis, GFD was found effective in increasing BMC in 5 studies, and effective in increasing BMD in 11 studies, when compared to individuals with CeD who did not adhere to the diet (the Hedge's g standardized mean difference was 0.39 [95% CI = 0.16, 0.62] for BMC and 0.29 [95% CI = 0.10, 0.47] for BMD). Among patients with untreated CeD, the difference in mean BMC and BMD from healthy individuals was −0.49 (95% CI = −0.76, −0.22) and −0.47 (95% CI = −0.72, −0.22), respectively. Overall, this meta-analysis adds an important validation to the positive association of GFD with increased BMC and BMD, in children and adolescents diagnosed with CeD.

The metabolic bone disease associated with CeD poses an increased risk of bone fractures; however, most studies are available among adult population [25], and routine bone density screening is not recommended in current pediatric guidelines for CeD [22]. The study by Zacay et al. [26] has assessed fracture risk among 2,372 children and

adolescents with CeD (aged 1–18 years), compared with a matched control group of 11,860 children, using a registry-based cohort study. The incidence of fractures in the CeD group was found to be 256 events per 10,000 patient-years, compared to 165 events per 10,000 patient-years in the matched control group ($p < 0.001$). The hazard ratio (HR) of fractures in the CeD group, compared to the matched group, was 1.57 (95% CI = 1.43–1.73, $p < 0.001$). Interestingly, the increased fracture risk in CeD versus controls was found both before and after CeD diagnosis, with HR for fractures in the prediagnosis period of 1.64 (95% CI = 1.42–1.88, $p < 0.001$) and 1.52 (95% CI = 1.26–1.71, $p < 0.001$) in the period from diagnosis to the end of the follow-up. This study emphasizes the risk of fracture complications in patients with CeD and metabolic bone disease, in the pediatric age group, both preceding and following celiac diagnosis.

Congenital Heart Disease

Supplemental nutrition, feeding disorders, and renourishment in pediatric heart failure through transplantation

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Pediatr Transplant 2023;27:e14601

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Comments: Congenital heart disease (CHD) is the most common birth defect, and infants with CHD are at high risk of poor growth due to increased energy requirements, intestinal malabsorption due to compromised blood flow, hypoxia and cyanosis, and feeding difficulties [27]. Malnutrition, underweight, and stunting are common, affecting 20%–30% of patients [28]. In children, advanced heart failure may occur due to complex CHF or acquired cardiomyopathies, with increased morbidity including malnutrition and growth failure, that may persist after ventricular assist device implantation and after heart transplant (HT) [29, 30]. Malnutrition and feeding difficulties in these patients often require nutritional rehabilitation including tube feeding assistance.

In this retrospective study by Zook et al. [31], the use of tube feeding before and after HT was evaluated, as well as the course of nutritional rehabilitation and outcome post HT. Data were collected from HT listing through 3 years posttransplant, in 104 children (46% females, with median age of 8.2 [IQR = 1.5–13.1] years at HT). The prevalence of malnutrition was 34% and 35% at the time of HT listing and the time of HT, respectively. Assisted tube feeding was conducted in 38% and 40% at the time of HT listing and the time of HT, respectively. Tube feeding persisted in 20% and 11% of patients at 1 and 3 years post HT, respectively, and was found to be significantly associated with younger age, more listing days, malnutrition or underweight at HT, and feeding disorder at HT listing or at HT. The diagnosis of feeding disorders

persisted in 10% and 2% of patients after 1 and 3 years post HT, respectively. Among patients who were malnourished at HT, malnutrition persisted in 23% and 16% patients, at 1 and 3 years post HT, respectively.
Although this study highlights the high prevalence of malnutrition and the need for assisted feeding in children with heart failure awaiting for HT, the results are encouraging, demonstrating resolution of feeding difficulties and malnutrition in most patients within 1 year posttransplant.

Cystic Fibrosis

A cross-sectional study of pediatric feeding disorder in children with cystic fibrosis

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J Pediatr Gastroenterol Nutr 2023;77:819–823
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Factors associated with pubertal growth outcomes in cystic fibrosis: early growth and puberty in CF

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J Cyst Fibros 2024;23:538–544
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Comments: Cystic fibrosis (CF) is a life-threatening genetic disorder, with a predominant lung disease as the leading cause of morbidity and mortality, as well as extrapulmonary manifestations that include exocrine pancreatic insufficiency in most patients, CF-related diabetes, and CF-related liver disease [32]. Poor nutritional status and altered growth are associated with CF, resulting mainly from nutrient malabsorption, high energy needs and increased losses, as well as recurrent infections and chronic inflammatory status [33]. Professional

international guidelines that focus on nutrition care for infants and children with CF are available, with the latest comprehensive updates published just recently [34], and are highly recommended for those interested in the nutritional aspects of CF.

Achieving optimal growth in children with CF often requires high energy intake and nutritional supplements, and hence may pose risk of feeding challenges. In the study by Bashir et al. [35], feeding dysfunction among children with CF was assessed using dietary and feeding assessment questionnaires. The study included 103 patients, with a mean age of 9.02 (±4.62) years. Overall, 60.2% of patients in the study met the criteria for pediatric feeding disorder (PFD). Among this group with PFD, 6.8% were malnourished, 9.7% needed enteral nutrition, and 29.1% needed oral high-energy beverages. In addition, 41.5% had decreased dietary food diversity. PFD was not found to be associated with any of the following factors: pancreatic enzyme replacement therapy, modulator therapies, pulmonary exacerbation frequency, lung function, maternal education, or developmental delay. This study highlights the high prevalence of PFD in children with CF, regardless of various disease characteristics. These patients should be treated by a multidisciplinary team, including nutritional, psychological, and occupational care.

CF can further cause delayed puberty, either as a result of poor nutritional status and delayed growth or by a direct effect of the genetic mutation in the CF transmembrane conductance regulator (CFTR), also found in the hypothalamus. Patil et al. [36] aimed to characterize factors associated with pubertal growth outcomes, in the new era of CF nutritional and therapeutic care. Data from the United States CF Foundation Patient Registry were used to analyze the associations between early weight-for-length/body mass index (WFL-BMI) growth trajectories and pubertal outcomes, using peak height velocity (PHV) and age at PHV (APHV) as proxy measures for puberty. The study included 9,186 participants (52% males) and found a mean APHV of 13.7 and 11.9 years for males and females, respectively. APHV and adult height were not found to be significantly associated with early WFL-BMI trajectories (before 6 years of age), after adjusting for covariates. Higher height Z-score at 2 years was associated with improved APHV and PHV for males, and improved adult height for both males and females.

In this cohort, 15.2% of males and 15.9% of females were started on CFTR modulators before the age of 18 years, and highly effective modulator therapy (HEMT) was started in 3.1% of males and 3.6% of females. The use of CFTR modulator was found to be associated with taller adult height, for both males and females, even after adjusting for WFL-BMI growth trajectory and other variables, with height gains of 0.92 and 1.02 cm, respectively. The results of this study suggest that early height, but not early WFL-BMI growth trajectories, are associated with pubertal growth outcomes. The use of CFTR modulator therapy shows the potential to improve pubertal growth outcomes; however, more research is needed to explore the evolving impact of HEMT use in early childhood.

Risk of overweight and obesity in children and adolescents with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis

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https://pubmed.ncbi.nlm.nih.gov/36952326/

Attention-deficit/hyperactivity disorder is not associated with overweight in adolescence but is related to unhealthy eating behavior and limited physical activity

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Nord J Psychiatry 2023;77:591–599

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Comments: Attention-deficit/hyperactivity disorder (ADHD) is a common disorder affecting children and adolescents, usually treated both with psychobehavioral therapies and pharmacological therapies using psychostimulants [37]. Most concerns regarding growth trajectories in ADHD have been raised regarding the potential adverse effects of medications that can include reduced appetite and gastrointestinal discomfort [38, 39]; however, the clinical effect on height and weight seems to be minimal and transient [40, 41]. In recent years, there is a growing interest in the association between ADHD, as a neuropsychiatric disorder, and obesity [42, 43]. Among the proposed mechanisms are abnormal eating patterns, sedentary lifestyle, and possible common genetic alterations. Most studies, however, were conducted among adult population.

Zhu et al. performed a systematic review and meta-analysis [44], exploring the risk of overweight and obesity in children and adolescents with ADHD. The analysis included 16 studies, with a total of 14,981 patients and 128,916 controls. The study has found a significant risk of overweight and obesity, in children with ADHD versus controls, with an OR of 1.56 (95% CI = 1.32–1.85). The risk was especially high among males, with OR for overweight and obesity of 1.45 (95% CI; 1.10–1.90), and in patients not using medication, with OR of 1.54 (95% CI; 1.22–1.94). This analysis is important in raising awareness to the increased risk of overweight/obesity in the pediatric age group of patients with ADHD; however, longitudinal comprehensive studies are further needed to explore the mechanisms underlying this association.

In the study by Halt et al. [45], the investigators assessed BMI in 124 adolescents with ADHD versus 253 controls, at the age of 16 years, in addition to data regarding physical activity and eating behavior. Patients with ADHD were classified as adolescent ADHD (diagnosed with ADHD from childhood, and still meeting the criteria at age of 16) and childhood ADHD (individuals who met the criteria in childhood but were in remission in adolescence). In this study, no significant differences were found in BMI between patients with childhood or adolescent ADHD, compared to controls. However, the results demonstrated more unhealthy eating habits among adolescents with ADHD compared to controls, including lesser consumption of vegetables and breakfasts, higher consumption of fast food, soft drinks, sweets, and potato crisps. Individuals with adolescent ADHD reported light exercising more often but strenuous exercising more seldom than controls. Patients with only childhood ADHD did not differ significantly from controls in the studied health behaviors. These interesting findings suggest that adolescents with ADHD might be at a more particular risk of unhealthy lifestyle, including nutritional risks and unhealthy eating habits, than those without ADHD. The unhealthy eating behaviors might pose a risk for developing later overweight, however not demonstrated in this study. Nonetheless, nutritional evaluation and eating habits assessment should be part of the comprehensive care of children and adolescents with ADHD.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

Both authors have read and commented on the reviewed manuscripts.

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 140–155 (DOI: 10.1159/000541854)

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

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Introduction

Early nutrition is one of the most important factors for growth in early childhood and has an impact on lifelong health. It has been associated with early metabolic programing of health such as obesity, which is known to track from childhood into adolescence and adulthood and affects both physical and mental health.

This chapter reviews important manuscripts published between July 1, 2023, and June 30, 2024, examining early nutrition and its effect on growth, body composition, and later obesity. In the current edition, 10 publications of special interest were chosen based on their contribution to the research within this field, novelty, and quality. This year several interesting systematic reviews have been published, especially regarding the composition of human milk, and also observational studies and follow-up data from a randomized controlled trial (RCT) have been included. We have grouped the articles into four topics: human milk composition and growth (five studies), enriched formula and growth (one study), maternal characteristics and offspring BMI (one study), and impact of breastfeeding and complementary feeding on later adiposity (three studies).

Key articles reviewed for this chapter

Human Milk Composition and Growth

Human milk macronutrients and child growth and body composition in the first two years: a systematic review
Brockway MM, Daniel AI, Reyes SM, Granger M, McDermid JM, Chan D, Refvik R, Sidhu KK, Musse S, Patel PP, Monnin C, Lotoski L, Geddes D, Jehan F, Kolsteren P, Allen LH, Hampel D, Eriksen KG, Rodriguez N, Azad MB
Adv Nutr 2024;15:100149

Human milk micronutrients and child growth and body composition in the first 2 years: a systematic review
Reyes SM, Brockway MM, McDermid JM, Chan D, Granger M, Refvik R, Sidhu KK, Musse S, Monnin C, Lotoski L, Geddes DT, Jehan F, Kolsteren P, Allen LH, Hampel D, Eriksen KG, Rodriguez N, Azad MB
Adv Nutr 2024;15:100082

Human milk bioactive components and child growth and body composition in the first 2 years: a systematic review
Brockway MM, Daniel AI, Reyes SM, Gauglitz JM, Granger M, McDermid JM, Chan D, Refvik R, Sidhu KK, Musse S, Patel PP, Monnin C, Lotoski L, Geddes DT, Jehan F, Kolsteren P, Bode L, Eriksen KG, Allen LH, Hampel D, Rodriguez N, Azad MB
Adv Nutr 2024;15:100127

Human milk composition and infant anthropometrics: overview of a systematic review with clinical and research implications
Azad MB, Brockway MM, Reyes SM
Int Breastfeed J 2024;19:45

Does human milk composition predict later risk of obesity? A systematic review
Vieira Queiroz De Paula M, Grant M, Lanigan J, Singhal A
BMC Nutr 2023;9:89

Enriched Formula and Growth

Infant milk formula with large, milk phospholipid-coated lipid droplets enriched in dairy lipids affects body mass index trajectories and blood pressure at school age: follow-up of a randomized controlled trial
Abrahamse-Berkeveld M, Jespers SN, Khoo PC, Rigo V, Peeters SM, van Beek RH, Norbruis OF, Schoen S, Marintcheva-Petrova M, van der Beek EM, Stoelhorst GM, Vandenplas Y, Hokken-Koelega AC; Mercurius Study Group
Am J Clin Nutr 2024;119:87–99

Maternal Characteristic and Offspring BMI

Maternal pre-pregnancy BMI, breastfeeding, and child BMI
Shipp GM, Wosu AC, Knapp EA, Sauder KA, Dabelea D, Perng W, Zhu Y, Ferrara A, Dunlop AL, Deoni S, Gern J, Porucznik C, Aris IM, Karagas MR, Sathyanarayana S, O'Connor TG, Carroll KN, Wright RJ, Hockett CW, Johnson CC, Meeker JD, Cordero J, Paneth N, Comstock SS, Kerver JM; program collaborators for Environmental influences on Child Health Outcomes
Pediatrics 2024;153:e2023061466

Impact of Breastfeeding and Complementary Feeding on Later Adiposity

Infant feeding practices and body mass index up to 7.5 years in the French nationwide ELFE study
Camier A, Cissé AH, Heude B, Nicklaus S, Chabanet C, Bernard JY, Lioret S, Charles MA, de Lauzon-Guillain B
Pediatr Obes 2024;19:e13121

Associations of infant feeding practices with abdominal and hepatic fat measures in childhood in the longitudinal Healthy Start Study
Cohen CC, Harrall KK, Hu H, Glueck DH, Perng W, Shankar K, Dabelea D
Am J Clin Nutr 2024;119:560–568

Optimal timing of introduction of complementary feeding: a systematic review and meta-analysis
Padhani ZA, Das JK, Siddiqui FA, Salam RA, Lassi ZS, Khan DSA, Abbasi AMA, Keats EC, Soofi S, Black RE, Bhutta ZA
Nutr Rev 2023;81:1501–1524

Human Milk Composition and Growth

The three systematic reviews (SRs) published in *Advances in Nutrition* used the same literature search selecting different papers relevant for three topics: macronutrients, micronutrients, and bioactive factors in human milk (HM) and child growth.

Human milk macronutrients and child growth and body composition in the first two years: a systematic review

Brockway MM[1,2,3], Daniel AI[4,5], Reyes SM[1], Granger M[6], McDermid JM[7], Chan D[2,8], Refvik R[6], Sidhu KK[6], Musse S[6], Patel PP[9], Monnin C[10], Lotoski L[2], Geddes D[11], Jehan F[12], Kolsteren P[13], Allen LH[14,15], Hampel D[14,15], Eriksen KG[16], Rodriguez N[1,2], Azad MB[1,2]

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Comments: This SR is one of three comprehensive reviews describing the relation between HM components and child growth and body composition in the first 2 years of life. All three papers have nearly the same group of authors.

WHO recommends that HM is the only diet for infants in the first 6 months of life and furthermore that breastfeeding continues to 2 years and beyond. HM is ideal as the only nutritional source for the first 6 months for healthy infants.

HM consists of about 87% water and the last part is primary macronutrients (fats, proteins, and carbohydrates), which are the main sources of energy for infant growth. Exclusive breastfed infants get the main part of their energy from carbohydrates (45%) and fats (44%). Proteins contribute only with about 8% of the energy. Carbohydrates in HM consist of digestible carbohydrates (mainly lactose, glucose, fructose) and nondigestible carbohydrates (mainly human milk oligosaccharides, HMO). HM fats are primarily triglycerides, free fatty acids (FA), and cholesterol. HM contains thousands of different proteins and the most abundant are casein, whey, and mycins. However, in some studies, total or crude protein also includes nonprotein nitrogen. In the analyses of relations between HM macronutrients and energy-demanding growth, it is important to know whether, e.g., carbohydrates include HMO and nonprotein nitrogen, which is not always obvious from the manuscripts.

In this SR, the aim was to assess and synthesize the evidence on associations between HM macronutrients and child growth and body composition in the first 2 years of life. References in English published from 1980 to March 2022 were included in the search and 9,992 abstracts were identified, 937 full texts were screened, and 57 articles were relevant for the macronutrient review.

There were several limitations both in relation to HM component analyses with considerable heterogeneity in analytic methods and variation in HM collection protocols, e.g., whether the studies used foremilk, hindmilk, or a mixture. Several studies used macronutrient concentration (g/mL) and not intake per day because milk volume was not available. Furthermore, the synthesis of results was complicated by considerable variation in anthropometric outcome measurements. It was therefore not possible to do a meta-analysis.

One of the key findings was that HM protein concentration was positively associated with infant length. There was limited evidence for an association between individual amino acids and infant growth. Total and digestible HM carbohydrate concentration tended to be positively associated with infant weight. For HM total fat concentrations, there were mixed associations with infant growth but generally inverse associations with BMI and WAZ scores. FA demonstrate inconsistent associations with several infants' growth metrics but notably not any directional associations between HM docosahexaenoic acid and head circumference, a proxy for brain size, were demonstrated.

The relative few evident associations between HM macronutrients and infant growth may be surprising. However, the abovementioned limitations could be an

explanation hiding possible associations. The authors therefore strongly recommend that future studies use validated analytic techniques and sampling protocols that reflect the temporal variations in HM macronutrients especially for fat content.

Human milk micronutrients and child growth and body composition in the first 2 years: a systematic review

Reyes SM[1,2], Brockway MM[1,2], McDermid JM[3], Chan D[1,2,4], Granger M[5], Refvik R[5], Sidhu KK[5], Musse S[5], Monnin C[6], Lotoski L[1,2], Geddes DT[7], Jehan F[8], Kolsteren P[9], Allen LH[10,11], Hampel D[10,11], Eriksen KG[12], Rodriguez N[1,2], Azad MB[1,2,5]

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Adv Nutr 2024;15:100082

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https://pubmed.ncbi.nlm.nih.gov/37315898/

Comments: Suboptimal breastfeeding, especially during the first 6 months of life, may result in more than 1 million deaths per year and has been estimated to account for about 10% of the disease burden in childhood globally [1]. One hallmark of inadequate nutrition is stunting affecting about one-third of children globally. Stunting is a major cause of morbidity and mortality. In children, micronutrients play a critical role in growth and development. Infants with nutritionally repleted mothers are born with reserves of some micronutrients (e.g., zinc, iron, and vitamin B_{12}). In some cases, this may also prevent infant deficiency if HM contents are low. However, even in well-nourished mothers' genetics, diet, health status, and other environmental factors can affect HM concentrations and bioactivity of micronutrients.

The objective of this review was to synthesize evidence of associations between HM micronutrients and child anthropometry in the first 2 years of life. References in English published between 1980 and March 2022 were included and 9,992 abstracts were identified, 1,001 full texts were screened, and 28 were relevant for the micronutrient review.

Even though HM is recommended as the only food the first 6 months of life and can be an important source of nutrients up to 2 years and beyond, the knowledge about the impact of HM micronutrients on healthy term infants' growth is very sparse. Generally, the studies were of relatively poor quality and meta-analyses were not

possible. However, current evidence suggests that HM iodine, manganese, calcium, and zinc may be positively associated with infant growth. Most of the available evidence was inconclusive. High-quality studies are missing, especially research employing system biology approaches to understand how HM micronutrients and other components working alone or in combination influence infant growth. Furthermore, most studies measure HM micronutrient concentration and not micronutrient intake because milk volume often is not available.

Human milk bioactive components and child growth and body composition in the first 2 years: a systematic review

Brockway MM[1,2,3], Daniel AI[4,5], Reyes SM[1,2], Gauglitz JM[6], Granger M[7], McDermid JM[8], Chan D[1,2,9], Refvik R[7], Sidhu KK[7], Musse S[7], Patel PP[10], Monnin C[11], Lotoski L[1,2], Geddes DT[12], Jehan F[13], Kolsteren P[14], Bode L[15], Eriksen KG[16], Allen LH[17,18], Hampel D[17,18], Rodriguez N[1,2], Azad MB[1,2,7]

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Adv Nutr 2024;15:100127

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https://pubmed.ncbi.nlm.nih.gov/37802214/

Comments: Beyond macronutrients and micronutrients, HM contains a huge number of other bioactive components. Together all these different components create a complicated biologically active system that meets the health and nutritional needs of infants and young children. All these known and unknown biological factors mean that HM is very different from formula. Some of the effects of these factors may have an actual and prolonged influence on infant's microbiome, growth, and development as well as immune function [2]. Knowledge about these bioactive components is needed for designing better HM alternatives for infants where HM is not available. A key goal for knowledge about HM may be to better prevent childhood obesity in some cases/countries and undernutrition in other cases/countries.

The aim of this SR was to assess and synthesize evidence on the associations between HM bioactive factors and anthropometry measured in the first 2 years of the child's life.

The definition of bioactive components is "components that affect biological processes or substrates and hence have an impact on body function or condition and ultimately health." HM bioactive components include growth factors, hormones, HMOs, lactoferrin, immunoglobulins, and cytokines [3].

References in English published between 1980 and March 2022 were included in the search and 9,992 abstracts were identified, 1,001 full texts were screened, and 75 articles examining bioactive factor were included. None was published before 2000.

Overall trends showed that HM leptin and adiponectin concentrations were inversely associated with infant growth. Differences in methodology used to analyze HM HMO made comparison of studies difficult. Present or near absence of the HMO 2′-FL was used in all studies to define secretor status but with conflicting results regarding differences in growth between infants of secretor and nonsecretor mothers. Furthermore, when examining associations between individual HMOs and infant growth, no consistent conclusions could be drawn.

HM immunomodulating components include cytokines, immunoglobulins, lactoferrin, lysozyme, and malondialdehyde. Research on these components is still highly exploratory. IL-6 and TNF-α were the most examined in this category. Generally, inverse relations were found between HM IL-6 and TNF-α concentrations and infant growth.

Overall, this SR showed inconsistent relations between HM bioactive components and infant growth in the first 2 years of life. The SR highlighted inconsistent data collection methods and identified several gaps in knowledge for future research. Except for HM leptin and adiponectin, research in HM bioactive components is relatively new with few results.

Human milk composition and infant anthropometrics: overview of a systematic review with clinical and research implications

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Int Breastfeed J 2024;19:45

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Comments: This is an overview and summary of the three SRs on the relation between HM composition (macronutrients, micronutrients, bioactive factors) and child growth commented above. In addition to what has already been mentioned, the authors underline the many opportunities that exist for future research to better understand the importance of HM and breastfeeding. Among these research areas, especially untargeted metabolomics and machine learning could be mentioned as new methods for expanding our knowledge.

Does human milk composition predict later risk of obesity? A systematic review

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BMC Nutr 2023;9:89

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Comments: Globally, obesity in children is a major public health problem and WHO has estimated that 16% of children and adolescents and about 38 mill children below 5 years of age live with obesity [4]. It is known that overweight and obesity often tracks into adolescence and adulthood with higher risk to develop diseases such as type 2 diabetes and cardiovascular disease at younger age than children without obesity. Genetic and lifestyle factors are major determinants of obesity, but factors acting early in life during the first 1,000 days from conception to 2 years of age also influence the risk of late obesity. Early postnatal nutrition has in several SRs been shown to influence the risk of obesity as breastfed compared to formula-fed infants have lower risk of obesity. However, the causality of this relation is discussed both because potential mechanisms are poorly understood and because of several potential confounding factors (e.g., education, social position, etc.). Suggested explanations have among other factors been related to the unique composition of HM, e.g., the lower protein content in HM compared to formula may lead to lower growth rate and reduced risk of later obesity in breastfed infants [5]. Other components in HM like HMO, long-chain polyunsaturated fatty acids, and different hormones like leptin, adiponectin, insulin, or ghrelin may also influence infant growth. However, it remains unknown whether these factors are casually related to lower later risk of obesity in breastfed infants. Examining the association between HM composition and later obesity in predominantly breastfed populations may reduce the risk of confounding in the explanation of lower risk of obesity in breastfed versus formula-fed infants.

The aim of this SR was to synthesize the existing published knowledge on possible associations between HM nutritional composition and later obesity or body composition beyond infancy.

Only studies published in English were included. The number of papers identified was 2,235, of which 1,103 were screened and 47 were eligible for full-text evaluation. A total of 10 papers from 9 original studies were included in the narrative synthesis of results.

Associations between HM composition and later BMI were reported in 8 out of the 10 selected papers. Only one study found an association between HM leptin and later lower BMI. Generally, no associations were found between HM hormones or macronutrients (protein, fat, carbohydrates) and later risk of obesity evaluated by BMI. Associations between HM composition and later measurements of body composition were investigated in 8 out of the 10 chosen papers. Only one study found an association between HM macronutrients at 4–8 weeks and later adiposity at 12 months: Carbohydrate was positive, and fat was inverse associated with later adiposity. However, no associations between HM protein or energy content and later adiposity were found.

Surprisingly, this SR found little evidence of any consistent associations between HM macronutrients and hormonal content and later obesity or adiposity. So, the well-known early protein hypothesis suggested mainly from studies with formula-fed infants may not be applicable for exclusively or predominately breastfed infants.
These kinds of SR have several limitations. The studies used varying methods for assessing HM composition, obesity, and body composition. Widely diverse and nonstandardized methods for both collecting and handling of HM samples were applied. Furthermore, most studies did not have milk volume measurements and therefore only associations between HM component concentrations and obesity/adiposity were determined. Total intake of HM components may be more relevant. Furthermore, not all studies adjusted for confounding factors.
The authors recommend that these important methodological limitations should be considered in future studies to improve identification of infants at higher risk of developing later obesity and thereby be able to prevent development of later obesity better.

Enriched Formula and Growth

Infant milk formula with large, milk phospholipid-coated lipid droplets enriched in dairy lipids affects body mass index trajectories and blood pressure at school age: follow-up of a randomized controlled trial

Abrahamse-Berkeveld M[1], Jespers SN[2], Khoo PC[3], Rigo V[4], Peeters SM[5], van Beek RH[6], Norbruis OF[7], Schoen S[1], Marintcheva-Petrova M[1], van der Beek EM[8], Stoelhorst GM[9], Vandenplas Y[10], Hokken-Koelega AC[11]; for the Mercurius Study Group

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Am J Clin Nutr 2024;119:87–99
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This article is also discussed in the chapter by Shalitin and Giannini [this vol., pp. 49–72].

Comments: Breastfed infants have different growth and adiposity patterns compared with formula-fed infants [6]. With the increasing knowledge on the composition of human milk, new improved infant formulas closer to the characteristic of human milk may be developed, thus possibly narrowing the differences in the health outcome between formula-fed and breastfed infants also in the long term.
This paper is a 5-year follow-up of an RCT where formula-fed healthy term infants were randomized to infant milk formula containing large, milk phospholipid-coated lipid droplets enriched with dairy lipids (intervention group) or a control formula with conventional small lipid droplets (control group); otherwise, the formulas were iso-caloric with a protein content of 1.97 g/100 kcal. The formulas were given for the first

4 months after birth and a breastfed group was included as reference. Anthropometry was measured at the follow-up visits at 1, 3, 4, and 5 years of age. The intervention group showed a BMI pattern more similar to the reference group of breastfed infants than to the control group. Children in the control group had higher mean BMI from 1 to 5 years of age compared with the reference group of breastfed children, while there was no difference in BMI between the intervention group and the reference group. This study demonstrates an interesting approach for achieving improved formulas, but future studies should also address the potential mechanism involved.

Maternal Characteristic and Offspring BMI

Maternal pre-pregnancy BMI, breastfeeding, and child BMI

Shipp GM[1], Wosu AC[2], Knapp EA[2], Sauder KA[3], Dabelea D[4], Perng W[3], Zhu Y[5], Ferrara A[5], Dunlop AL[6], Deoni S[7], Gern J[8], Porucznik C[9], Aris IM[10], Karagas MR[11], Sathyanarayana S[12], O'Connor TG[13], Carroll KN[14], Wright RJ[14], Hockett CW[15,16], Johnson CC[17], Meeker JD[18], Cordero J[19], Paneth N[20,21], Comstock SS[22], Kerver JM[20,21]; on behalf of program collaborators for Environmental influences on Child Health Outcomes

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Pediatrics 2024;153:e2023061466

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This article is also discussed in the chapter by Shalitin and Giannini [this vol., pp. 49–72].

Comments: The protective effects of breastfeeding against obesity in offspring born to obese mothers are understudied. In this study, the associations between breastfeeding practices and BMI for age Z-scores (BMIz) in children aged 2–6 years were analyzed stratified by maternal BMI. It is known that mothers with obesity are less likely to initiate breastfeeding and more likely to stop breastfeeding earlier than mothers with healthy weight [7].

The Environmental Influences on Child Health Outcome program includes 69 pediatric cohorts of which 21 cohorts with data from a total of 8,134 dyads were relevant and used in this analysis. Data were from different states in the United States. The mothers were divided according to pre-pregnancy BMI in four groups: underweight (BMI < 18.5 kg/m^2), healthy weight (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). The distribution of mothers in the four groups were 2.5%, 45.8%, 26.0%, and 25.6%, respectively. Because of the low sample size, the underweight group was not analyzed. The analyses were adjusted for known covariates like education level, maternal age, parity, mode of delivery, smoking, maternal race, and ethnicity.

The duration of breastfeeding (exclusive and any breastfeeding) was lower in mothers with obesity compared to mothers with overweight and mothers with healthy weight. The overall results were that breastfeeding has a protective effect on childhood obesity independent of maternal pre-pregnancy BMI. Each additional month of any or exclusive breastfeeding was associated with a lower offspring BMIz among mothers with overweight (for any breastfeeding) or obesity (for any and exclusive breastfeeding). The results suggested that for mothers with obesity exclusive breastfeeding for 6 months could lower the child BMI by 0.15 SD.

The study underlines the importance of breastfeeding for reduction of childhood obesity in offspring at least to 6 years of age independent of the mother's pre-pregnancy BMI. It also underlines that breastfeeding is especially important for mothers with obesity where the risk of childhood obesity is highest and the breastfeeding success rates are lowest. However, if the mother is breastfeeding, the effect on offspring BMI seems to be independent of maternal pre-pregnancy weight status.

Impact of Breastfeeding and Complementary Feeding on Later Adiposity

Childhood overweight and obesity are increasing globally and may track into adulthood. As obesity in adulthood is difficult to reverse and is associated with risk of noncommunicable diseases, it is important to have strategies for prevention of overweight already in early childhood. Early feeding including breastfeeding and complementary feeding (CF) might offer an important developmental window and a possibility to introduce healthy feeding practices that might have long-term impact on growth and body composition.

We have selected three articles investigating the impact of breastfeeding practices and timing of introduction of CF on later body mass index (BMI) and adiposity. They give an important contribution toward understanding the benefits of breastfeeding and optimal time for introduction and practices of CF. Furthermore, the systematic review also underlines the inconsistency in the findings within this field and the need for future studies.

Infant feeding practices and body mass index up to 7.5 years in the French nationwide ELFE study

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Pediatr Obes 2024;19:e13121

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Comments: This paper investigates the associations between breastfeeding and timing of CF with BMI until the age of 7.5 years in a recent French birth cohort. Breastfeeding has in many reviews been related to a decreased risk of overweight and obesity in later childhood [8, 9], while early introduction of CF has been associated with increased risk of overweight [10]. The findings might, however, be driven by the diet of non-breastfed infants, which have been used for comparison in many studies. This is relevant to consider as the diet of not-breastfed infants has changed through the years, especially the protein content in formula, which has been lowered since the CHOP trial [11, 12].

In the study, 9,380 children were included, of which 7,110 children had data for the complete case analyses. Data on breastfeeding and CF were collected from 2 to 10 months and BMIz was calculated at 1, 2, 3, 5, and 7.5 years. Overweight was defined according to International Obesity Task Force definition [13]. Regression models investigating the association of breastfeeding and timing of CF introduction with BMI and overweight were adjusted for known main potential confounders such as maternal age and education, family income, smoking, pre-pregnancy and paternal BMI, infant sex, and gestational age.

Ever breastfeeding was not associated with lower risk of overweight at mid-childhood compared to never breastfeeding, whereas breastfeeding for at least 6 months versus breastfeeding for 1–3 months was associated with lower BMI in infancy but not beyond. Early introduction of CF (<4 months) compared to introduction at the age of 4–6 months was associated with higher BMI throughout childhood. The findings were also confirmed by principal component analyses (PCA) and hierarchical ascendant classification based on infant feeding practices. The use of these different approaches complements the more classical analyses and supports the robustness of the results.

The study adds to the existing findings suggesting that longer duration of breastfeeding is related to lower BMI in infancy and early introduction of CF is related to higher BMI in childhood [14, 15]. Nevertheless, the study did not find a protective effect of breastfeeding on overweight at later ages, which has been suggested in literature [9, 16]. A strength of the study is the very detailed data on potential confounders and a large sample size. However, residual confounding cannot be excluded and the study demonstrates the difficulties in establishing robust and consistent results in this field as discussed in the review by Padhani below.

Associations of infant feeding practices with abdominal and hepatic fat measures in childhood in the longitudinal Healthy Start Study

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Am J Clin Nutr 2024;119:560–568

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https://pubmed.ncbi.nlm.nih.gov/38000661/

This article is also discussed in the chapter by Shalitin and Giannini [this vol., pp. 49–72].

Comments: Many studies use age- and sex-specific BMI as a proxy for adiposity as it is easy and economical to measure in large cohorts. However, BMI is a measure of both fat mass and fat-free mass and there is a growing interest in applying techniques that measure total body fat mass and fat mass in specific regions and tissues. Abdominal fat and liver fat are metabolically active insulin-sensitive tissues and may be a stronger risk factor for metabolic dysfunction than total body fat mass [17].

This approach was applied in this study. The outcomes of hepatic adipose tissue and abdominal adiposity assessed as subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were measured by magnetic resonance imaging at the age of 5 and 9 years in 356 children from a prospective cohort in Colorado. Infant feeding practices included any human milk consumption for <6 versus ≥6 months; introduction of CF at ≤4 versus >4 months; and introduction of soda at ≤18 versus >18 months. The models examining the associations between infant feeding and the outcomes across childhood were adjusted for relevant covariate such as sex, birth weight, ethnicity, maternal age, education, and pre-pregnancy BMI.

In this cohort, where 67% consumed human milk for at least 6 months, there were no associations between duration of human milk consumption and childhood adiposity outcomes. Children, who were introduced to CF at ≤4 months, showed a more rapid increase in SAT and VAT from 5 to 9 years so they had a higher SAT and VAT at 9 years but not at 5 years. For hepatic fat, a similar pattern was observed, but the associations were not significant. Children introduced early to soda showed a more rapid increase in SAT, VAT, and hepatic fat, having a higher abdominal and hepatic fat deposit at the

age of 9 years compared to children introduced to soda after the age of 18 months. The associations between CF and abdominal and hepatic adiposity deposits were independent of BMI in childhood, but the estimates were attenuated when adjusted for concurrent BMI.

The finding that the adiposity increases over time could partly be explained by accumulation of risk factors, so early-life exposures and poor nutritional habits may be worsened across childhood, i.e., early introduction of soda may be related to intake of soda and poor diet quality throughout childhood. As the authors suggest, future studies could include dietary assessments throughout childhood to investigate the modifying effect of dietary intakes in childhood and the quality of CF. This is important for optimal health recommendations for introduction of energy-dense food and beverage such as soda in early childhood. Opposite to the authors' hypothesis, intake of human milk was not associated with childhood adiposity. However, they did report a positive association between exclusive intake of human milk >4 months and faster accretion of SAT in childhood. Further studies with more detailed information on breastfeeding and larger sample size should investigate this relation further.

Optimal timing of introduction of complementary feeding: a systematic review and meta-analysis

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Nutr Rev 2023;81:1501–1524

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Comments: The timing of complementary feeding is widely recognized to have potential effects on growth and risk of overweight and obesity later in childhood and have been investigated extensively. Some studies suggest that early introduction of CF (<6 months) is associated with increased risk of obesity during childhood. However, conflicting results have been reported. Furthermore, complementary feeding practices vary between countries as well as guidelines, i.e., World Health Organization (WHO) recommends introduction of complementary food at 6 months of age [18, 19], whereas the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee and the European Academy of Allergy and Clinical Immunology recommend introduction of CF between 4 and 6 months of age [20, 21].

This SR aims to evaluate the impact of the timing of CF on health and developmental outcomes in healthy term infants. The literature search comprised studies published in English with no restrictions on publication date and resulted in 39,142 records, of which 1,819 underwent full-text review. The review comprised both RCTs (7 RCTs

from 24 articles) and observational studies (217 studies from 244 articles). The RCTs and observational studies were meta-analyzed separately. RCTs analyses compared early introduction of CF at or before 4 months with introduction at 6 months of age. For the observational studies, early introduction was investigated by comparing introduction at <3, <4, and <6 months of age with introduction at ≥3, ≥4, and ≥6 months of age, respectively, and late introduction by comparing introduction >6 and >8 months of age with introduction at ≤6 and ≤8 months of age, respectively. The outcomes included, i.a., anthropometric and developmental measures. Findings from the RCTs showed no effect of early introduction on anthropometric measures or overweight. From the analyses of the observational studies, some of the comparisons suggested an effect of early introduction on anthropometric measures but all findings were considered low-certainty evidence. Some of the findings showed that early introduction (<6 months) might increase BMIz and risk of overweight/obesity, introduction <3 might increase BMI, and introduction <4 months might increase height, whereas late introduction (>6) might decrease height and BMI. However, the quality of the observational studies covered moderate to critical risk of bias. Generally, the statistical power was insufficient as well as the adjustment for confounding variables. Therefore, the authors evaluated that the reliability of the results was inadequate to make any firm conclusions regarding the effect of early introduction of CF but that insufficient evidence might indicate concerns regarding increased BMI and obesity.

The review highlights some of the limitations in relation to achieving robust evidence and the many factors, which should be considered such as settings (low-, middle-, or high-income country), sufficient data on potential confounding variables, standardized outcome measures, and long-term follow-up to conduct robust studies, which are needed for future research. This is in line with another systematic review [10] that also concluded the need for additional research to provide more consistent results and evidence on the effect of CF introduction on later adiposity.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

Both authors have read and commented on the reviewed manuscripts.

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Published online: February 19, 2025

Phillip M, Turck D, Shamir R, Koletzko B (eds): Nutrition and Growth. Yearbook 2025. World Rev Nutr Diet. Basel, Karger, 2025, vol 128, pp 156–167 (DOI: 10.1159/000541855)

Pregnancy: The Impact of Maternal Nutrition on Intrauterine Fetal Growth

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Introduction

In this chapter of the 2025 edition of the yearbook on *Nutrition and Growth*, we review important manuscripts published between July 2023 and June 2024 addressing the association of maternal nutrition during pregnancy and intrauterine fetal growth. In the current edition, we chose ten high-impact studies as these studies enlighten us with new information about the influence and the association of maternal diet and different diet composition on fetal growth and future development. We also included a couple of animal studies due to their major findings through basic science, which was not possible among human subjects, and which hopefully will lead to further human research. We hope that this chapter will improve the medical care we provide to our patients, enrich our knowledge about the different nutritional affects, and promote researchers for innovative future studies.

Key articles reviewed for this chapter

Human Studies

Influence role of one-carbon nutrient intake and diabetes during pregnancy in children's growth and neurodevelopment: a 2-year follow-up study of a prospective cohort
Kadam I, Dalloul M, Hausser J, Vaday D, Gilboa E, Wang L, Hittelman J, Hoepner L, Fordjour L, Chitamanni P, Saxena A, Jiang X
Clin Nutr 2024;43:1216–1223

Maternal nutrition during mid-pregnancy and children's body composition at 7 years of age in the SELMA study
Svensson K, Gennings C, Hagenäs L, Wolk A, Håkansson N, Wikström S, Bornehag CG
Nutr 2023;130:1982–1992

Maternal protein intake in early pregnancy and child development at age 3 years
Miyake K, Mochizuki K, Kushima M, Shinohara R, Horiuchi S, Otawa S, Akiyama Y, Ooka T, Kojima R, Yokomichi H, Yamagata Z, Japan Environment and Children's Study Group
Pediatr Res 2023;94:392–399

Impact of preconception and antenatal supplementation with myo-inositol, probiotics, and micronutrients on offspring BMI and weight gain over the first 2 years
Lyons-Reid J, Derraik JGB, Kenealy T, Albert BB, Ramos Nieves JM, Monnard CR, Titcombe P, Nield H, Barton SJ, El-Heis S, Tham E, Godfrey KM, Chan SY, Cutfield WS and NiPPeR Study Group
BMC Med 2024;22:39

Maternal caffeine intake during pregnancy and the risk of delivering a small for gestational age baby: Kuopio Birth Cohort
Kukkonen A, Hantunen S, Voutilainen A, Ruusunen A, Backman K, Kirjavainen PV, Ylilauri M, Voutilainen R, Pasanen M, Keski-Nisula L
Arch Gynecol Obstet 2024;310:359–368

Longitudinal lipidomic profiles during pregnancy and associations with neonatal anthropometry: findings from a multiracial cohort
Song Y, Lu R, Yu G, Rahman ML, Chen L, Zhu Y, Tsai MY, Fiehn O, Chen Z, Zhang C
EBioMedicine 2023;98:104881

Maternal diet quality during pregnancy is associated with neonatal brain white matter development
Na X, Glasier CM, Andres A, Ou X
Nutrients 2023;15:5114

Maternal seafood consumption during pregnancy and cardiovascular health of children at 11 years of age
Pinar-Martí A, Fernández-Barrés S, Lázaro I, Fossati S, Fochs S, Pey N, Vrijheid M, Romaguera D, Sala-Vila A, Julvez J
Nutrients 2024;16:974

Animal Studies

Influence of maternal nutrition and one-carbon metabolites supplementation during early pregnancy on bovine fetal small intestine vascularity and cell proliferation
Daneshi M, Borowicz PP, Entzie YL Syring JG, King LE, Safain KS, Anas M, Reynolds LP, Ward AK, Dahlen CR, Crouse MS, Caton JS
Vet Sci 2024;11:146

Effects of maternal methyl donor intake during pregnancy on ileum methylation and function in an intrauterine growth restriction pig model
Lin Y, Wu J, Zhuo Y, Feng B, Fang Z, Xu S, Li J, Zhao H, Wu D, Hua L, Che L
J Anim Sci Biotechnol 2024;15:19

Influence role of one-carbon nutrient intake and diabetes during pregnancy in children's growth and neurodevelopment: a 2-year follow-up study of a prospective cohort

Kadam I[1,2], Dalloul M[3], Hausser J[1], Vaday D[1], Gilboa E[1], Wang L[4], Hittelman J[5], Hoepner L[6], Fordjour L[7], Chitamanni P[7], Saxena A[8], Jiang X[1,2]

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Clin Nutr 2024;43:1216–1223

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https://pubmed.ncbi.nlm.nih.gov/38636347/

Comments: Maternal nutrition of one-carbon (1C) metabolism, including folate, vitamin B_{12}, choline, and betaine, has been demonstrated to influence the availability of 1C units for DNA replication, biosynthesis, and epigenetic modification, thus affecting fetal growth and development. This study tried to investigate how 1C nutrient intake and status during pregnancy, as well as postnatal intake, were related to children's anthropometrics and developmental outcomes among women with or without gestational diabetes mellitus (GDM). This prospective study evaluated 28 women (20 with GDM) with food frequency questionnaire (FFQ) and blood tests at 25–33 weeks gestation. Children were evaluated at 2 years of age. Higher maternal food folate and choline intakes were associated with better language scores. Higher maternal food folate intakes were also associated with better cognitive scores. The positive relationship was only demonstrated for natural food folate but not from fortified grains. This different effect cannot be explained by the overall dietary quality. Higher 1C nutrient intakes during pregnancy were associated with lower body weight of children at 2 years of age. However, global DNA methylation of children's buccal cells was not associated with any maternal 1C nutrients. The association between maternal 1C nutrient intakes and positive offspring neurodevelopmental outcomes was demonstrated in several previous studies though others had conflicting results. Only maternal 1C nutrient intakes, but not the children's intake, were associated with the anthropometric and neurodevelopmental outcomes. Moreover, maternal nutrient status in the blood was not related to anthropometric or neurodevelopmental outcomes. This highlights the importance of 1C nutrients for prenatal programing during a specific time frame that is plastic to changes. The study's limitations are its limited type of population, its small sample size, and the limited time frame for FFQ. Nevertheless, this is the first study that comprehensively reveals how the intake of 1C nutrients early in life is associated with children's developmental outcomes.

Maternal nutrition during mid-pregnancy and children's body composition at 7 years of age in the SELMA study

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Nutr 2023;130:1982–1992

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https://pubmed.ncbi.nlm.nih.gov/37232113/

Comments: Better maternal nutrition is associated with lower body fat at 6 months of age, but not at the age of 1 year. There is uncertainty if optimal prenatal nutrition affects children's body composition in later childhood. Therefore, this study evaluated dyads of mother-child from the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy cohort to assess if prenatal nutrition is associated with children's height and body fat at the age of 7 years. Out of 2,582 women, 808 pairs were evaluated. Women completed self-reported FFQ at 25 weeks gestation. The nutrient intake was summarized into My Nutrition Index (MNI) estimating adherence to recommended intake by American Guidelines. The study found that a more nutritious diet during mid-pregnancy was associated with greater height among 7-year-old children. This is in line with previous studies. Those findings were also repeated in the sensitivity analysis including only children with normal BMI. Another finding was different body fat outcomes according to sex. Higher MNI was associated with higher body fat among boys, but lower among girls. Girls had more body fat, which is consistent with other studies. Animal models demonstrated upregulated gene expression in the female placenta of offsprings to restricted maternal pregnancy diet. Others demonstrated greater lipid storage in the female placenta and reduced expression of genes related to lipid pathways in the male placenta in cases of high-fat maternal diet. Limitations to be mentioned, the FFQ used in the study was performed only once during pregnancy, and the analysis is limited to the evaluation of food intake alone and does not include supplementation and there is no information about the gestational weight gain. In summary, enhanced prenatal diet quality was associated with greater height among children at age 7 and with more body fat among boys and the opposite for girls.

Maternal protein intake in early pregnancy and child development at age 3 years

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Pediatr Res 2023;94:392–399

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https://pubmed.ncbi.nlm.nih.gov/36624288/

Comments: Low and high maternal protein intakes have an adverse effect on fetal growth, though its effect on children growth is controversial. Several animal studies found abnormal brain development among offspring born to protein-restricted mothers. This study evaluated the correlation between low maternal protein intake and children developmental delay at age 3. In this cohort study, 77,237 patients in Japan were included. The patients completed food frequency questionnaire (FFQ) during early and midpregnancy. Children were assessed at the age of 3 by a developmental screening questionnaire. The cutoff value in this study for severely low protein (SLP) was set at >2 SD below the mean. SLP at early pregnancy was significantly associated with a higher risk of impaired communication and fine motor and problem-solving skills. The results were still significant even after adjustment for several possible cofounders. The study results show that early pregnancy levels of protein intake have a greater effect on child development than midpregnancy intake, findings which are supported in animal studies. A recent study demonstrated that high protein intake is associated with a risk of growth retardation, a finding that was not demonstrated in the current study. Maternal protein restriction results in certain amino acid deficiencies, which might explain some of the study findings. This imbalance can affect not only the risk of intrauterine growth restriction and preterm birth but also postnatal development. Several limitations to be mentioned, this is a survey questionnaires study; therefore, there might be recall bias. Secondly, the content of baby nutritional environment was not considered. To conclude, other than fetal growth, nutritional imbalance in early pregnancy affects also postnatal neurodevelopment.

Impact of preconception and antenatal supplementation with myo-inositol, probiotics, and micronutrients on offspring BMI and weight gain over the first 2 years

Lyons-Reid J[1], Derraik JGB[1,2,3,4], Kenealy T[1,5], Albert BB[1], Ramos Nieves JM[6], Monnard CR[6], Titcombe P[7], Nield H[7], Barton SJ[7], El-Heis S[7,8], Tham E[9,10,11], Godfrey KM[7,8], Chan SY[9,10,11], Cutfield WS[1,12] and NiPPeR Study Group

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BMC Med 2024;22:39

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Comments: Myo-inositol, a nonessential sugar alcohol, is thought to counteract the effects of maternal dysglycemia on offspring adiposity. Therefore, this study tried to determine whether preconception and antenatal supplementation with myo-inositol would affect a child body size and growth at the age of 2 years. In this double-blind randomized controlled trial, 586 women were allocated prior to pregnancy to either the control or intervention group. The intervention group received supplementation containing myo-inositol, vitamin D, riboflavin, vitamin B_6, vitamin B_{12}, zinc, and probiotics. The study found that preconception and antenatal supplementation with myo-inositol, probiotics, and micronutrients were associated with a lower risk of rapid infant weight gain and obesity. Furthermore, the intervention group had a more normal weight gain trajectory. Several studies demonstrated reductions in the incidence of gestational diabetes, preterm birth, and excessive fetal growth with myo-inositol supplementation. The study's results remained similar even after adjustment for pregnancy length and with exclusion of preterm deliveries. It is thought that inositol influences the barrier of the maternal-placental-fetal axis to regulate fetal growth and development. Low vitamin D levels have been associated with lower fat mass at birth, but subsequent elevated fat mass at the age of 6, while another study demonstrated that increasing maternal vitamin D intake was associated with lower weight gain trajectories, while other studies gave conflicting results. Limitations to be mentioned, the study's anthropometric measurements cannot distinguish between fat and fat-free masses. Furthermore, the intervention's multinutrient formulation limits the ability to determine the effects of specific nutrients. To conclude, preconception and antenatal supplementation with myo-inositol, probiotics, and micronutrients were associated with a lower risk of obesity at the age of 2.

Maternal caffeine intake during pregnancy and the risk of delivering a small for gestational age baby: Kuopio Birth Cohort

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Arch Gynecol Obstet 2024;310:359–368

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Comments: The European Food Safety Authority (EFSA) limits pregnant women to daily caffeine intake of 200 mg per day. Studies found that even the use within recommendations has been related to reduced fetal growth. This study aimed to examine the association between maternal 1st and 3rd trimester caffeine intake and neonatal outcome. This is a prospective study that included women in Finland who completed

food frequency questionnaires (FFQ) during the 1st trimester (2,007 women) and 3rd trimester (4,362 women), and of them, 1,262 women completed both questionnaires. The study found a median caffeine intake during the 1st trimester of 121 mg per day, which increased to 134 mg per day in the 3rd trimester. The EFSA recommendation for caffeine intake was exceeded by 32% of the study participants in the 1st and 38% in the 3rd trimester. It was demonstrated that caffeine intake during the 1st trimester is a risk factor for small for gestational age (SGA), but not during the 3rd trimester. The risk remained even after adjustment for possible cofounders such as maternal age, early pregnancy BMI, smoking, energy intake, and hypertension, and even when caffeine intake was within EFSA recommendations of ≤200 mg per day. Other observational studies also reported increased risks for SGA, however on a lower scale. One meta-analysis found that each additional 100 mg/daily of caffeine increases the risk of SGA by 10%, though the current study did not demonstrate such a dose response. Limitations to be mentioned are self-reporting, recall bias, and also factors like the type of beans, leaves, and preparation. The results should be generalized only to the Western population, due to higher consumption of coffee. In conclusion, moderate (>50 mg per day) to high maternal caffeine intake during the 1st trimester of pregnancy was associated with higher risk for a SGA baby.

Longitudinal lipidomic profiles during pregnancy and associations with neonatal anthropometry: findings from a multiracial cohort

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EBioMedicine 2023;98:104881

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Comments: Maternal lipidomic profiles have been associated with gestational diabetes mellitus (GDM), prematurity, small for gestational age (SGA), and large for gestational age (LGA) babies. However, most studies have assessed lipidomics using a single-time samples. Therefore, the authors of this study tried to examine the longitudinal and prospective association of lipidomic profiles throughout pregnancy with neonatal

anthropometrics. In this prospective study, 321 patients were evaluated in a nested case-control study with a ratio of 1:2 GDM to non-GDM. Maternal blood samples were drawn four times during pregnancy. Neonatal measurements were taken within 24 h of delivery when possible. The study demonstrated distinct trajectories during pregnancy, mainly of triglycerides (TG), phosphatidylcholine (PC), cholesteryl ester (CE), and lysophosphatidylcholine (LPC) with neonatal anthropometric measures. Increased levels of nine different TG species and diglycerides (DG) at the 2nd trimester were associated with LGA. TG at mid- and late pregnancy and TG at late pregnancy were associated with length or head circumference. The findings are partly in line with the results of past studies. Furthermore, the study's findings remain significant with TG even after correction for multiple testing and adjustment for GDM and pre-pregnancy BMI. Levels of PC, LPC, and CE during late pregnancy were inversely associated with neonatal anthropometry after adjustment to known maternal factors. Findings were similar to previous small studies. Potential limitations to be acknowledged, the relatively small sample size limited the ability to address ethnic disparities, the case-control design might affect the analyses, and concomitant changes in metabolites other than lipid species might complicate the associations of lipidomics. In conclusion, longitudinal changes of plasma TGs during early and midpregnancy and PC, LPC, and CE during late pregnancy were significantly associated with neonatal anthropometry.

Maternal diet quality during pregnancy is associated with neonatal brain white matter development

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Nutrients 2023;15:5114

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Comments: Several studies demonstrated a positive correlation between better maternal dietary intake quality with offspring's visual-spatial skills, cognitive scores, higher intelligence, and executive functions. The possible etiology might be related to brain development during early age. The author's hypothesis was that maternal dietary quality would impact fetal brain white matter (WM) microstructural development. In this cohort study, 44 healthy pregnant women to term newborn dyads were recruited. Women completed 3-day dietary intakes each trimester and data were evaluated to a Healthy Eating Index (HEI) according to Dietary Guidelines for Americans (DGA). Newborns underwent magnetic resonance imaging (MRI) examination at the age of 2 weeks in order to evaluate diffusion tensor imaging (DTI) date. Fractional anisotropy (FA) maps were processed as a DTI parameter sensitive to WM microstructural integrity. The study demonstrated a positive correlation between 1st trimester maternal sodium score and neonatal FA values, indicating better WM development (such as better myelination). This finding was not shown in past studies,

and its underlying mechanism remains unclear, but studies in experimental models suggest some potential pathways. Additional dietary sodium may improve preterm infants' postnatal growth, though sodium intake and preterm children's neurodevelopmental outcomes data are inconclusive. Limitations to be noted are the small sample size, the limited controlled potential confounders, MRI scans were conducted on a 1.5 T scanner with a relatively large voxel size, and a basic DTI protocol. To conclude, the study demonstrated that 1st trimester sodium intake pattern, which is better aligned with the DGA, was associated with better neonatal WM microstructural development measurement.

Maternal seafood consumption during pregnancy and cardiovascular health of children at 11 years of age

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Nutrients 2024;16:974

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https://pubmed.ncbi.nlm.nih.gov/38613009/

Comments: Consumption of fatty fish, the main source of *n*-3 eicosapentaenoic acid and *n*-3 docosahexaenoic acid, is known to reduce cardiovascular diseases (CVDs). However, it is still not known whether maternal fish consumption affects later offspring health, even though the fetus is fully dependent on maternal dietary *n*-3 supply. Therefore, this study aimed to evaluate if maternal gestational fish intake is associated with the cardiovascular health of 11-year-olds. In this longitudinal cohort study, 434 pairs of mother-child were evaluated. Women completed food frequency questionnaire (FFQ) during pregnancy weeks 12 and 32. Children were evaluated at the age of 11. No significant associations in arterial stiffness and retinal vascular caliber were found related to maternal gestational fish consumption. A sensitivity analysis adjusting for the child's cardiovascular covariates also did not demonstrate any association. Only one other study found contradicting results to ours, that higher late pregnancy oily fish consumption is associated with lower aortic stiffness among 9-year-old children. On the other hand, evidence for a possible long-chain *n*-3 polyunsaturated fatty acids programing effect on later cardiovascular health is inconclusive. It is possible that cardiovascular alterations will begin to appear later in life and that at this age, the variances are still minor to diagnose. Furthermore, the average fish consumption in the study was 482.5 g, which means that these women are probably above the

protective threshold. Several limitations to be mentioned, the use of FFQ is susceptible to measurement errors, this is an observational study and cannot rule out the possibility of some residual confounding, and it is still questionable whether this technology can accurately assess the cardiovascular risk of 11-year-old children. To conclude, fish consumption during the 1st and 3rd trimesters was not associated with the offspring's cardiovascular health at 11 years of age.

Animal Studies

Influence of maternal nutrition and one-carbon metabolites supplementation during early pregnancy on bovine fetal small intestine vascularity and cell proliferation

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Vet Sci 2024;11:146

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https://pubmed.ncbi.nlm.nih.gov/38668414/

Comments: Gestational nutritional and specific nutrient intake of the dam can cause lasting imprints on the fetal small intestine. Fetal intestine's proper development is important for absorption, metabolism, and overall calf health and growth trajectory. One-carbon metabolites (OCM) are thought to have a major role on gestational nutrition effect on fetal epigenetic mechanisms. The authors of this study evaluated the effects of restricted early gestation maternal diet, with or without OCM supplementation, on the bovine fetal small intestine. In this randomized control trial, 32 heifers were divided into 2X2 groups: nutritional plane (control vs. restricted) and OCM supplementation (−OCM vs. +OCM). On day 161 of gestation, heifers were slaughtered. Fetal jejunum samples were evaluated by immunohistochemistry, immunofluorescence, and image processing. No interaction between maternal intake and OCM supplementation was observed in the small intestine weight (SIW). This finding is supported by several previous studies. However, a significant effect of OCM supplementation on lowering fetal SIW in both restricted and control heifers was noted. This might be due to a possible improved cell efficiency, which results in a reduction in SIW. Capillary development was found to be affected with increased capillary area density (CAD) in the villi of fetuses subjected to restricted diet. Other past studies demonstrated conflicting results. On the other hand, maternal nutrition did not affect the expression of vascular endothelial growth factor receptor 2. Unlike previous studies, maternal nutritional had no effect on the ratio of Ki-67 (KPR), which serves as a cell proliferation index. A reduction in KPR was observed in the +OCM groups relative to the −OCM group. OCM supplementation might allow efficient

tissue maturation with optimizing metabolic efficiency instead of maximizing growth. To conclude, OCM supplementation modulates fetal vascular development in the small intestines of bovine fetuses under maternal nutrient restriction.

Effects of maternal methyl donor intake during pregnancy on ileum methylation and function in an intrauterine growth restriction pig model

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J Anim Sci Biotechnol 2024;15:19

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https://pubmed.ncbi.nlm.nih.gov/38310243/

Comments: Previous studies have shown that maternal nutrition can lead to permanent epigenetic modifications in the offspring, such as DNA methylation and histone acetylation. Intrauterine growth restriction (IUGR) leads to disparate DNA methylation in the intestine. Maternal dietary methyl donor (MET) supplementation was found to enhance the birth weight and postnatal growth rate. Therefore, this study aimed to evaluate the effects of maternal MET supplementation on gastrointestinal development. In this randomized control trial, 40 sows were allocated into control versus MET supplementation diet. Eight pairs of IUGR and normal birth weight (NBW) piglets were selected for intestinal evaluation before suckling colostrum. MET dietary supplementation did not affect the litter size, number of liveborn, or birth weight. However, it tended to decrease the IUGR incidence and to increase the body weight (BW) of piglets. When evaluating the intestinal morphology, IUGR piglets were found to have a decrease in villous height (VH) and villous/crypt ratio with an increase in crypt depth (CD) in the ileum. MET supplementation and BW had an interactive effect on CD. These findings consist previous studies. Furthermore, BW did not affect jejunum activities of maltase and sucrase. MET supplementation increased lactase and sucrase activities in the jejunum and improved the intestinal digestive function of IUGR piglets. IUGR piglets had much more differentially methylated CpG hypomethylation in the ileum. There was a significant change in methylation in the IUGR group after MET supplementation. Increased hypermethylated genes were enriched in the hormone receptor pathway via JAK-STAT, nitric oxide biosynthetic process, and dopamine receptor signaling pathway. In conclusion, IUGR might cause abnormal intestinal DNA methylation in a pig model. This can be alleviated by maternal MET supplementation, which regulates the related gene expression and their function in various biological processes.

Overall Commentary

Maternal nutrition during pregnancy has long-lasting influence on fetal growth and future health. Different types of diets and food composition affect offspring's growth, neurological, vascular, intestinal, and metabolically outcome. As clinicians and researchers, we

should remember to evaluate nutrition through all its aspects but remember that there are also genetic, demographic, and behavioral factors that influence the fetus development. Therefore, in order to provide our patients the best medical care we can, we should thrive for a thorough and personalized medicine.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

Author Index

Subject Index

RESEARCH

World Review of Nutrition and Dietetics

Editor
B. Koletzko

ISSN
0084–2230

Nutrition and Dietetics

Women's and Children's Health

Endocrinology

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Editors: M. Phillip, Petah Tikva/Tel Aviv; D. Turck, Lille; R. Shamir, Petah Tikva/Tel Aviv; B. Koletzko, Munich;
X + 186 p., hard cover, 2025.
ISBN 978–3–318–07388–1

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Editors: B. Koletzko, Munich; M. Phillip, Petah Tikva/Tel Aviv; D. Turck, Lille; R. Shamir, Petah Tikva/Tel Aviv
X + 192 p., hard cover, 2024.
ISBN 978–3–318–07340–9

126 **Nutrition and Growth: Yearbook 2023**

Editors: R. Shamir, Petah Tikva/Tel Aviv; B. Koletzko, Munich; M. Phillip, Petah Tikva/Tel Aviv; D. Turck, Lille
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ISBN 978–3–318–07056–9

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X + 190 p., hard cover, 2022.
ISBN 978–3–318–07041–5

Karger

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