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Nutrition and Growth

Yearbook 2026

Editors
Dominique Turck
Raanan Shamir
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Preface

The past year has yielded a wealth of critical research illuminating the complex and challenging relationship between nutrition and human growth across the lifespan.

This volume of the *Nutrition and Growth: Yearbook 2026* serves as a concise yet comprehensive summary of the most significant peer-reviewed manuscripts published in leading medical and scientific journals between July 1, 2024, and June 30, 2025.

Renowned experts in the field of nutrition and growth summarized findings that range from the impact of specific micronutrients on early childhood development and pubertal growth to the nutritional strategies influencing skeletal and muscular health in adolescence and beyond.

Given the space limitations, we were unable to incorporate more studies. Yet, we hope that the chosen manuscripts will still provide clinicians, researchers, and public health professionals with a streamlined, evidence-based overview of the latest advancements, highlighting key trends, controversies, and future directions in this vital area of study.

Our sincere thanks go to the associate editors who dedicated their time and expertise, significantly enhancing this work with their valuable insights.

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Malnutrition and Catch-Up Growth during Childhood and Puberty

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Introduction

Globally, the double burden of malnutrition remains a pressing challenge, marked by the simultaneous presence of undernutrition and overweight or obesity within populations. Viana and colleagues conducted a systematic review and meta-regression, which was published this year [1], aimed to estimate how common the double burden of malnutrition (DBM) is at the individual level in children and adolescents (ages 2–19). From 784 records, they retained 11 studies covering roughly 50,000 individuals from eight countries, mostly low- and middle-income settings. Across those studies, overweight/obesity prevalence ranged roughly from 8% to 37% and undernutrition indicators (stunting, anemia, or other micronutrient deficits) from about 4% up to 73%. The prevalence of individual-level DBM (an individual who is concurrently overweight/obese and undernourished or micronutrient deficient) varied widely across studies, from about 1% to 35.4%, with the higher rates concentrated in low and middle-income countries (LMICs); children in Asia and adolescents in Latin America showed some of the highest study estimates. A meta-regression that tested several candidate sources of heterogeneity (publication year, sample size, age, country income group, prevalence of overweight or undernutrition, and related variables) did not find any of them to be

significant explanations for the between-study differences. The authors conclude that DBM at the individual level is a real and concerning phenomenon in young populations, but the available evidence is sparse, heterogeneous, and not yet robust enough to support precise global estimates or to clearly identify drivers.

The paper highlights multiple limitations of the current literature. Primary among these is the lack of standardized definitions and measurement approaches: studies used different anthropometric cut-offs, different biomarkers and thresholds for micronutrient deficiency or anemia, and sometimes, inconsistent age groupings, which makes comparisons across studies unreliable. The evidence base is small (only 11 eligible studies), geographically clustered (predominantly LMICs), and commonly based on secondary datasets that limit the variables available for analysis. Many studies had limited sample sizes or unclear sampling methods, and few investigated correlates or causes of DBM; only two studies examined associated factors, and just one found clear associations. Follow-up and longitudinal data are essentially absent, so the temporal dynamics and consequences of individual-level DBM (for growth, cognition, or later NCD risk) remain unknown. Finally, reporting on combinations of multiple micronutrient deficiencies (beyond anemia/iron) was scarce.

From these shortcomings, the authors identify clear research gaps and priorities. They call first for consensus on standardized definitions, indicators, and cut-offs for DBM at the individual level so that prevalence estimates can be compared and pooled. More population-based studies are needed across diverse regions (including high-income countries), and future work should deliberately include adolescents as a vulnerable group. Studies should move beyond cross-sectional descriptions to examine determinants (socioeconomic, dietary, environmental, maternal, and household factors) and to employ longitudinal designs that can track transitions into and out of DBM and link them to health, developmental, and metabolic outcomes. There is also a need for richer micronutrient assessment (not only hemoglobin or iron), analyses of dietary patterns and food environments, and evaluations that can inform double-duty policy responses.

This year's chapter reviews the most recent data on childhood malnutrition and catch-up growth published between July 1, 2024, and June 30, 2025.

This year's chapter focuses on several main topics. The first topic addresses intervention strategies for the treatment of malnutrition, which were evaluated in several clinical trials and systematic reviews. It includes two clinical trials, by Fink et al. [2] and Tanjung et al. [3], that assessed the impact of combined approaches: home-installed growth charts with small-quantity lipid-based nutrient supplements [2] and nutritional advice with oral nutritional supplements for children with malnutrition [3]. Two additional studies – a large observational study by Potani et al. [4] and a systematic review and meta-analysis by O'Donovan et al. [5] – explore the optimal weight gain rate and caloric intake required to improve recovery from malnutrition. Finally, two systematic

reviews, by Soczynska et al. [6] and by Pajak et al. [7], evaluate the impact of plant-based milk consumption and alternative ready-to-use therapeutic foods.

The second topic addresses the effects of microbiome-targeted interventions – prebiotics, probiotics and synbiotics – on growth parameters in children. It includes three systematic reviews and meta-analyses on these interventions in healthy children by Kebbe et al. [8], Mirzohreh et al. [9], and An et al. [10]. A fourth systematic review and meta-analysis by Paiandeh et al. [11] on microbiome targeted the interventions in children with malnutrition.

The third topic addresses new insights on the etiology and mechanisms of undernutrition and stunting, and includes three recent reviews by Ebrahim and Manji [12], Petscavage et al. [13], and Islam et al. [14].

Key articles reviewed for this chapter

Nutritional Interventions in Malnutrition

The impact of home-installed growth charts and small-quantity lipid-based nutrient supplements (SQ-LNS) on child growth in Zambia: a four-arm parallel open-label cluster randomised controlled trial
Fink G, Locks LM, Lauer JM, Chembe M, Henderson S, Sikazwe D, Billima-Mulenga T, Parkerson D, Rockers PC
BMJ Glob Health 2024;9:e015438

Comparative analysis of nutritional advice and a combined approach for addressing impending stunting in infants: a clinical trial
Tanjung C, Fikri B, Prawitasari T, Massi N, Zainuddin AA, Juliaty A, Yullyana DS, Dwitya S, Shimojo N, Ohno H, Koletzko B
Nutrients 2024;16:2832

The relationship between energy provided and growth during severe wasting treatment
Potani I, Tausanovitch Z, Ritz C, Briend A, Coulibaly IN, Ouédraogo CT, Manda G, Kangas ST
Matern Child Nutr 2024;20:e13693

Weight gain among children under five with severe malnutrition in therapeutic feeding programmes: a systematic review and meta-analysis
O'Donovan G, Allen D, Nkosi-Gondwe T, Anujuo K, Abera M, Kirolos A, Olga L, Thompson D, McKenzie K, Wimborne E, Cole TJ, Koulman A, Lelijveld N, Crampin AC; CHANGE Study Collaborators Group; Opondo C, Kerac M
EClinicalMedicine 2025;81:103083

A systematic review on the impact of plant-based milk consumption on growth and nutrition in children and adolescents
Soczynska I, da Costa BR, O'Connor DL, Jenkins DJ, Birken CS, Keown-Stoneman CD, D'Hollander C, Calleja S, Maguire JL
J Nutr 2024;154:3446–3456

A global scoping review on alternative ready-to-use therapeutic foods
Pajak P, Teshome S, Berton A, Stobaugh H, Fleet A, Khatiwada D, Cichon B
Matern Child Nutr 2025;21:e70035

The Effects of Microbiome-Targeted Interventions – Prebiotics, Probiotics and Synbiotics – on Growth Parameters

Effects of infant formula supplemented with prebiotics on the gut microbiome, gut environment, growth parameters, and safety and tolerance: a systematic review and meta-analysis
Kebbe M, Leung K, Perrett B, Reimer RA, Adamo K, Redman LM
Nutr Rev 2025;83:422–447

Effect of prebiotics on growth metrics in infants: a GRADE approach systematic review and meta-analysis of randomized clinical trials
Mirzohreh ST, Sohrabnavi A, Panahi P, Nikniaz Z, Farhangi MA, Daneghian S, Nikniaz L
Nutr Res 2025;137:22–46

Effect of pro-, pre- and synbiotic supplementation on the growth of infants and children: an umbrella systematic review and meta-analysis
An S, Kong J, Ghorbani A, Dehghani A, Alizadeh S
J Paediatr Child Health 2025;61:354–368

The effect of probiotic, prebiotic, and synbiotic supplements on anthropometric measures and respiratory infections in malnourished children: a systematic review and meta-analysis of randomized controlled trials
Paiandeh M, Maghalian M, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M
BMC Pediatr 2024;24:702

The Etiology and Mechanisms of Undernutrition and Stunting

Role of infant and early-childhood nutrition on gut inflammation, stunting, growth, and development in the African context: a narrative review
Ebrahim M, Manji K
Nutr Clin Pract 2025;40:534–542

Associations between extreme weather events and child undernutrition: evidence from sub-Saharan Africa, 2010–2019
Petscavage K, Mutua MK, Wagner AL, Treleaven E
J Epidemiol Community Health 2025;79:359–365

Drivers of stunting and wasting across serial cross-sectional household surveys of children under 2 years of age in Pakistan: potential contribution of ecological factors
Islam M, Ali S, Majeed H, Ali R, Ahmed I, Soofi S, Bhutta ZA
Am J Clin Nutr 2025;121:610–619

The impact of home-installed growth charts and small-quantity lipid-based nutrient supplements (SQ-LNS) on child growth in Zambia: a four-arm parallel open-label cluster randomised controlled trial

Fink G[1,2], Locks LM[3,4], Lauer JM[4], Chembe M[5], Henderson S[6], Sikazwe D[7], Billima-Mulenga T[5], Parkerson D[6], Rockers PC[3]

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BMJ Glob Health 2024;9:e015438
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Comments: This study by Fink et al. evaluated the impact of home-installed growth charts and small-quantity lipid-based nutrient supplements (SQ-LNS) on child growth and development in Zambia through a well-designed, four-arm cluster-randomized controlled trial. The interventions were tested both independently and in combination, with a total of 2,291 caregiver–child dyads participating across three diverse districts. The findings reaffirm the known benefits of SQ-LNS supplementation, which significantly improved linear growth, reduced stunting, and enhanced hemoglobin levels and child development. Growth charts, when implemented alone, did not improve growth outcomes but were associated with modest improvements in hemoglobin, reduced anemia, and improvement in child development, suggesting some effect on caregiver behavior and dietary choices.

Surprisingly, no additive or synergistic effects were found when the two interventions were combined. Contrary to the researchers' expectations, the group receiving both SQ-LNS and growth charts did not experience greater improvements than those receiving SQ-LNS alone, and the combined intervention was actually less effective than the single-component approaches.

The authors suggest several possible explanations for this diminished impact. It is possible that caregivers receiving both interventions experienced intervention fatigue or confusion, especially since the growth charts did not directly reinforce the use of the supplements. Some caregivers may have changed the way they used the supplements – such as mixing them with other foods promoted by the charts, which could have affected the ingested amount and nutrient absorption. Additionally, the growth charts' messaging might have unintentionally competed with, rather than complementing, the goals of the supplementation. The reduced engagement with the charts observed in the combined group supports this interpretation.

Overall, this unexpected outcome highlights the importance of carefully designing integrated interventions. Merely combining two effective strategies does not guarantee greater impact; without harmonized messaging and behavioral alignment, interventions may inadvertently undermine each other. Future studies should explore how best to integrate behavioral and nutritional approaches to maximize both adherence and outcomes.

Comparative analysis of nutritional advice and a combined approach for addressing impending stunting in infants: a clinical trial

Tanjung C[1], Fikri B[2], Prawitasari T[3], Massi N[4], Zainuddin AA[5], Juliaty A[2], Yullyana DS[6], Dwitya S[7], Shimojo N[8], Ohno H[9], Koletzko B[10]

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Nutrients 2024;16:2832

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https://pubmed.ncbi.nlm.nih.gov/39275150/

Comments: This nonrandomized clinical trial by Tanjung et al. evaluated the effectiveness of nutritional advice (NA) alone versus a combination of NA and oral nutritional supplements (ONS) in infants aged 6–12 months with weight faltering (WF) in community-based settings in Makassar, Indonesia. Infants below the 5th percentile for weight increment received NA plus ONS, while those between the 5th and 15th percentile received NA only. Over 3 months, both groups improved, but the NA-plus-ONS group achieved greater weight gain (264.1 vs. 137.4 g, $p < 0.001$) and length gain (2.35 cm vs. 2.14 cm, $p < 0.001$). A higher proportion of infants in the NA-plus-ONS group recovered from WF and maintained growth improvements, with fewer cases of weight loss compared to the NA-only group. The findings suggest that interventions should begin at below the 15th percentile, with ONS added for those below the 5th percentile to accelerate recovery and sustain growth.

However, this important study had several limitations. Its 3-month follow-up was too short to assess long-term growth outcomes. The design was nonrandomized because ethical considerations prevented withholding ONS from severely affected infants, which may have introduced selection bias. There was crossover between groups when infants' growth status changed, potentially confounding results. No laboratory assessments were performed, limiting insights into nutritional and health status changes. Finally, the study was conducted in one urban setting, which may limit generalizability.

Future research should include longer follow-up to assess sustained benefits, randomized designs where ethically feasible, and broader geographic and socioeconomic representation. Including biochemical and health outcome measures would strengthen the understanding of intervention impacts. Studies should also explore the mechanisms by which combined NA and ONS promote catch-up growth and examine cost-effectiveness, especially in resource-limited settings.

The relationship between energy provided and growth during severe wasting treatment

Potani I[1,2], Tausanovitch Z[1], Ritz C[3], Briend A[4,5], Coulibaly IN[6], Ouédraogo CT[6], Manda G[7], Kangas ST[1]

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Matern Child Nutr 2024;20:e13693

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https://pubmed.ncbi.nlm.nih.gov/39101244/

Comments: Potani et al. investigated in this study whether the amount of energy provided at admission influences catch-up growth in children with severe acute malnutrition (SAM), specifically those with a mid-upper arm circumference (MUAC) below 115 mm. Using data from an operational cohort in Mali, the researchers examined the relationship between initial energy intake (in kcal/kg/day) and growth outcomes, including weight gain velocity, change in MUAC-for-age Z-score, and weight-for-age Z-score. Children were treated with a simplified protocol: 1,000 kcal/d of therapeutic food until MUAC reached ≥115 mm for 2 consecutive weeks, then 500 kcal/d until discharge when MUAC was ≥125 mm for 2 weeks. Results showed that higher energy intake at admission was significantly associated with greater weight gain and improvements in anthropometric indicators. Specifically, every 10 kcal/kg/d increase in energy was linked to a weight gain velocity increase of approximately 0.34–0.47 g/kg/d.

Importantly, while the positive relationship is clear, the authors caution that further research is needed to determine the optimal rate of weight gain. Excessive or overly rapid weight gain could have unintended metabolic or long-term health consequences, and thus, balancing therapeutic benefit with safety remains essential.

In summary, the discussion supports the conclusion that higher energy provision at admission enhances recovery and growth among children with SAM, but also calls for refined guidance on optimal dosing to ensure both effectiveness and safety in treatment protocols.

Weight gain among children under five with severe malnutrition in therapeutic feeding programmes: a systematic review and meta-analysis

O'Donovan G[1], Allen D[1], Nkosi-Gondwe T[1,2], Anujuo K[1,3], Abera M[4], Kirolos A[5], Olga L[6], Thompson D[7], McKenzie K[7], Wimborne E[8], Cole TJ[9], Koulman A[6], Lelijveld N[1,10], Crampin AC[1,2]; CHANGE Study Collaborators Group[11]; Opondo C[12], Kerac M[1]

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Comments: This systematic review and meta-analysis by O'Donovan, aimed to inform policy and program discussions on optimal rate of weight gain in children being treated for severe malnutrition. The systematic review examined weight gain in 168 therapeutic feeding programs involving over 240,000 children with severe malnutrition. On average, children in inpatient programs gained 8.8 g/kg/d, those in outpatient programs gained 3.9 g/kg/d, and those in hybrid programs gained 3.4 g/kg/d. More than three-quarters of outpatient programs fell below 5 g/kg/d, and only a small fraction of all programs – mostly inpatient – achieved gains of 10 g/kg/d or more. Children with edematous malnutrition tended to gain weight more slowly than those without edema, although few studies accounted for edema resolution in their calculations. Outpatient programs also had substantially longer lengths of stay than inpatient care (about 51 vs. 16 days), but generally low mortality rates. The analysis found only weak and inconsistent evidence that slower weight gain at the program level was associated with higher mortality, and no consistent associations with recovery, default, or relapse rates.

The study concludes that outpatient care typically produces slower weight gain and longer treatment durations than inpatient care, but with comparably low mortality. Many outpatient programs fall short of WHO's suggested weight gain range of 5–10 g/kg/d and older Sphere standards. The authors highlight the need for clearer and more standardized reporting of weight gain, particularly accounting for edema, and call for more research to determine optimal weight gain targets that balance short-term recovery with potential long-term health risks associated with rapid catch-up growth. Several limitations temper the findings. The analysis relied on program-level rather than individual-level data, limiting the ability to explore patient-specific factors. Considerable heterogeneity existed between studies in population characteristics, program protocols, and methods of calculating weight gain, with many not adjusting for edema resolution. A notable proportion of studies were excluded from the meta-analysis due to incomplete reporting, and those included may represent higher-quality programs linked to research rather than typical field

performance. The review also lacked data on postdischarge outcomes and did not assess the actual therapeutic food intake or adherence.

Future research should focus on identifying the optimal rate of weight gain in different settings, exploring subgroup differences by age, sex, and comorbidities, and assessing postdischarge survival and functional recovery. Standardized protocols for measuring and reporting weight gain are urgently needed, along with studies that use biomarkers and other indicators beyond weight to assess treatment success.

A systematic review on the impact of plant-based milk consumption on growth and nutrition in children and adolescents

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Comments: This systematic review by Soczynska et al. assessed the impact of plant-based milk consumption on growth and nutritional status in children and adolescents, drawing on six studies that included three cross-sectional analyses, one prospective cohort, and two clinical trials, with a combined total of 15,815 participants. The observational evidence indicated that children who consumed plant-based milks tended to have lower body mass index, shorter stature, and reduced serum vitamin D concentrations compared with those consuming cow's milk. The small and low-quality clinical trials provided limited evidence, showing minimal effects of plant-based milk on growth. However, one trial reported that adolescent girls with low calcium intake who consumed fortified soy milk had higher bone density than peers who avoided soy milk.

The review concluded that children drinking plant-based milks may be at risk of lower BMI, height, and certain micronutrient intakes compared with those drinking cow's milk, but that fortified soy milk could support bone health in some populations. The authors emphasized the need for well-designed longitudinal studies and randomized controlled trials to clarify whether these associations persist over time, whether the effects differ between children

and adolescents or by plant-based milk type, and to elucidate the underlying mechanisms. The evidence base has several important limitations. The majority of studies were observational and cross-sectional, limiting the ability to infer causality. The available trials were small, short in duration, and often of low methodological quality, making it difficult to draw firm conclusions about long-term effects. Many studies did not differentiate between various plant-based milks or account for fortification levels, which are critical to nutritional outcomes. Confounding by overall dietary patterns, socioeconomic status, and health behaviors was not always adequately addressed. Furthermore, most studies relied on self-reported dietary intake, which may be prone to recall bias and underreporting.

Research gaps are substantial. There is a need for large-scale, high-quality prospective studies and randomized trials that follow children over time to assess growth, bone health, and micronutrient status in relation to plant-based milk consumption. Future work should examine different types of plant-based milks separately, with careful consideration of fortification content and bioavailability of nutrients. Investigations should also explore the potential mechanisms linking plant-based milk consumption to growth patterns, and evaluate how these beverages fit within the broader dietary contexts, especially in populations reducing or avoiding animal-sourced foods.

A global scoping review on alternative ready-to-use therapeutic foods

Pajak P[1], Teshome S[2], Berton A[1], Stobaugh H[3], Fleet A[4], Khatiwada D[4], Cichon B[1]

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https://pubmed.ncbi.nlm.nih.gov/40418157/

Comments: This scoping review by Pajak et al. examined the effectiveness of alternative ready-to-use therapeutic foods (RUTFs) compared to the standard peanut-based RUTF in treating severe acute malnutrition (SAM) in children. The main alternative type assessed was milk-free, lipid-based RUTFs, often made with soy, maize, chickpea, and sorghum, or other locally available plant-based ingredients. Across the included studies, recovery rates, weight gain, and length of stay in treatment were generally comparable between standard and alternative RUTFs, suggesting that these alternatives can be viable in settings where peanuts or milk are costly, unavailable, or culturally unacceptable. The review concluded that alternative RUTF formulations have the potential to support effective SAM management while improving cost-effectiveness and supply chain sustainability.

However, the existing literature has important limitations. Many studies were small in scale, conducted in single-country settings, and varied widely in their formulations, making direct comparisons difficult. Follow-up periods were often short, limiting the ability to assess long-term growth and relapse rates. There was also a lack of standardized outcome measures, and few studies examined acceptability, adherence, or potential allergenicity of alternative RUTFs. Research gaps remain in determining the optimal nutrient composition of these alternatives, understanding their performance in diverse contexts, and evaluating their cost-effectiveness and scalability in real-world health systems. Future research should also address long-term health and developmental outcomes to confirm that alternative RUTFs can fully match the benefits of the standard formulation.

The Effects of Microbiome-Targeted Interventions – Prebiotics, Probiotics and Synbiotics – on Growth Parameters

Effects of infant formula supplemented with prebiotics on the gut microbiome, gut environment, growth parameters, and safety and tolerance: a systematic review and meta-analysis

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Effect of prebiotics on growth metrics in infants: a GRADE approach systematic review and meta-analysis of randomized clinical trials

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Nutr Res 2025;137:22–46

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Comments: Over the past year, several systematic reviews and meta-analyses have examined the effects of interventions targeting the gut microbiome on children's growth. The above-mentioned manuscripts present two recent meta-analyses focused on the impact of prebiotic-supplemented infant formulas compared with standard formula or human milk on gut microbiota composition and growth parameters in healthy infants: Kebbe et al. studied infants aged 0–6 months, and Mirzohreh et al. studied infants aged 0–12 months. Both studies included only randomized controlled trials.

Kebbe et al.'s meta-analysis found that prebiotic formulas increased the abundance of *Bifidobacterium* species compared with standard formulas, but showed no difference when compared with human milk. In terms of growth parameters, there were no significant differences between groups for weight gain, weight and length Z-scores, head circumference, or BMI Z-scores, except for weight Z-scores, which were higher in the prebiotic formula group compared with human milk. Mirzohreh et al.'s meta-analysis

similarly found no significant differences in weight, height, or head circumference gain between infants fed with prebiotic formulas and those fed with standard formulas or breast milk. However, like Kebbe, they noted that certain prebiotic combinations, such as FOS/GOS or PDX/GOS/LOS, were associated with modestly higher weight gain. Overall, these findings support earlier studies suggesting that while prebiotic supplementation may promote favorable gut microbial development, it does not significantly influence growth parameters in healthy infants compared with standard formulas.

Effect of pro-, pre- and synbiotic supplementation on the growth of infants and children: an umbrella systematic review and meta-analysis

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https://pubmed.ncbi.nlm.nih.gov/39949153/

Comments: This umbrella systematic review and meta-analysis by An et al. included 26 meta-analyses conducted in populations of healthy children, including preterm infants, and examined a range of microbiome-targeted interventions, including prebiotics, probiotics, and synbiotics. The pooled effects of all interventions showed modest but significant improvements in weight and height gain, with no significant effects on BMI or head circumference. Similar results were observed in studies on preterm infants.

The effect of probiotic, prebiotic, and synbiotic supplements on anthropometric measures and respiratory infections in malnourished children: a systematic review and meta-analysis of randomized controlled trials

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BMC Pediatr 2024;24:702

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Comments: This systematic review and meta-analysis by Paiandeh et al. aimed to summarize the potential benefits of microbiome-targeted interventions on anthropometric outcomes in children with malnutrition, aged 2 months to 6 years. The analysis included 12 studies, mostly from low- and middle-income countries (LMICs), with a total of over 3,000 children and interventions lasting 4 weeks to 1 year. The meta-analysis revealed modest and uncertain improvements in weight and height gain for all supplements compared with control groups. However, the heterogeneity of the included studies – in terms of type of malnutrition, type and duration of interventions, and outcome assessments – limits the strength of the conclusions. Overall, this study does not support a substantial benefit of microbiome-targeted interventions on growth in children with malnutrition. Nevertheless, these findings highlight the need for larger, well-designed studies to re-evaluate this topic.

The Etiology and Mechanisms of Undernutrition and Stunting

Role of infant and early-childhood nutrition on gut inflammation, stunting, growth, and development in the African context: a narrative review

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Comments: This narrative review by Ebrahim and Manji describes the main causes and perpetuating factors of stunting in children, from the perspective of African LMICs. They highlight the role of poor sanitation, which leads to chronic exposure to gut pathogens, resulting in environmental enteric dysfunction (EED) and impaired nutrient absorption. This is compounded by suboptimal breastfeeding and limited dietary diversity during weaning, contributing to growth faltering and poorer neurodevelopment. To address these challenges, the authors recommend promoting and supporting exclusive breastfeeding, establishing human milk banks across African countries, and conducting further studies on the potential benefits of probiotic supplementation.

Associations between extreme weather events and child undernutrition: evidence from sub-Saharan Africa, 2010–2019

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Comments: Recent climate changes have raised awareness of the impact of extreme weather events on the nutritional status of children living in vulnerable areas of the world. This important study by Petscavage et al. aimed to assess the effects of natural disasters on wasting, stunting, and anemia in young children. The authors analyzed data from 51 Demographic and Health Surveys (DHS) across 30 sub-Saharan African countries, including over 320,000 children under 5 years of age, and collected data on natural disasters experienced by these children according to relevant timing and region. In this cohort, 9% of children had been exposed to a natural disaster in the preceding 3 months, and 20% within the preceding year, with droughts and floods being the most common events. Exposure within 3 months was most strongly associated with wasting, indicating acute malnutrition, with a relative risk of 1.17 (95% CI 1.12–1.22) compared with unexposed children. Further analyses confirmed a negative impact of natural disasters on wasting, but not on stunting or anemia. These findings suggest that in sub-Saharan Africa, acute malnutrition is the most critical health outcome of extreme weather events for children under 5 years, highlighting the need for targeted interventions following natural disasters.

Drivers of stunting and wasting across serial cross-sectional household surveys of children under 2 years of age in Pakistan: potential contribution of ecological factors

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https://pubmed.ncbi.nlm.nih.gov/39788298/

Comments: While the impact of direct and indirect drivers on linear growth and wasting in young children has been extensively studied through studies of risk factors as well as drivers of change in positive deviant examples of progress [15], there is remarkably little information of the role of ecological and environmental factors (such as heat exposure, drought, agriculture outputs, and food insecurity) in contributing to linear growth and wasting in children.

In this in-depth study by Islam et al., the authors evaluated the association of length-for-age Z-score (LAZ) and weight-for-length Z-score (WLZ) with geotagged ecological climate indicators among children aged under 2 years in Pakistan using representative household-level sub-nationally representative nutrition surveys (2011 and 2018), containing geotagged data from 29, 887 children and mothers. Dietary intake and food security data for 140 districts were linked to gridded data on temperature, precipitation and soil moisture, and district measures of agriculture production of edible crops.

A number of positive associations of linear growth (LAZ) were identified with improved socioeconomic conditions ($\beta = 0.06$), food security ($\beta = 0.10$), birth size ($\beta = 0.26$), maternal age ($\beta = 0.02$), body mass index ($\beta = 0.02$), height ($\beta = 0.02$), and dietary score ($\beta = 0.03$). Negative associations with LAZ were found for increased temperature, precipitation, diarrhea, household crowding, and parity. Wasting relationships were also comparable with higher surface temperatures and excess precipitation alongside increased diarrhea

prevalence and higher maternal parity. The association of stunting and wasting in childhood in Pakistan with multifactorial drivers is well known, and this analysis suggests that other long-term climatic factors could also be associated. Other studies provide further insights into possible mechanisms [16] and association with linear growth retardation with heat exposure in pregnancy [17] and population level [18]. These findings underscore the need for further research and the potential integration of climatic mitigation and adaptation with nutrition response strategies at primary care level.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscript.

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Stunting in Developing Countries

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Introduction

In 2024, a change in the global trend of childhood stunting was reported. The Joint Child Malnutrition estimates released by UNICEF, WHO, and World Bank indicate that the prevalence of stunting of all children under five is now 23.2% corresponding to 150.2 million children in total. This figure represents a slight increase in proportion of children stunted from 22.3% in 2022, as well as an increase in the number of children affected from 148.1 million in 2022 [1]. A recent study using analysis from 56 Demographic and Health Survey (DHS) datasets mainly from low- and middle-income countries (LMICs) reported that infants below the age of 6 months account for 19.9% of this prevalence [2]. Previous evidence from analysis of pooled longitudinal data from large cohorts in LMICs highlighted the importance of the prenatal onset of stunting, and that early postnatal growth faltering predisposed children to subsequent and persistent growth faltering in the first 2 years of life [3].

Child stunting is one of the indicators under Sustainable Development Goal (SDG) indicators target 2.2 [4]. Nearly all children affected by stunting live in South Asia (31.4%) and Africa (30.3%); hence, it is projected that many countries in Africa and South Asia are unlikely to meet the SDG target. Notwithstanding, with less than 5 years left to 2030 SDG target timeline, countries are accelerating bold steps towards combatting stunting. In the

wake of the changing funding landscape for research and implementation, it is important that evidence-based, cost-effective, and sustainable interventions are considered. The multifactorial pathways of causation or associations with stunting mean that multisectoral interdisciplinary approaches will need to be applied throughout the life course. A holistic approach towards combatting stunting should therefore expand beyond food-based intervention and include targeting the social and environmental determinants of health that should include the geopolitical environment.

In our selection of articles published in the period July 1st 2024 to June 30th 2025, a substantial part of the write-up is attributed to the discussion on the complexity of stunting, its causes and consequences, encouraging readers to expand their thinking beyond nutrition.

Key articles reviewed for this chapter

Population, Aetiology and Mechanisms

Malnutrition in infants aged under 6 months: prevalence and anthropometric assessment – analysis of 56 low- and middle-income country DHS datasets
Kerac M, James PT, McGrath M, Brennan E, Cole T, Opondo C, Frison S
BMJ Global Health 2025;10:e016121

Correlates of body composition in children with stunting: a cross-sectional study in Uganda
Lewis JI, Mbabazi J, Mutumba R, Ritz C, Filteau S, Briend A, Michaelsen KF, Mølgaard C, Wells JC, Mupere E, Friis H, Grenov B
J Nutr 2024;154:3105–3115

Planetary Health

Effect of heat stress in the first 1000 days of life on fetal and infant growth: a secondary analysis of the ENID randomised controlled trial
Bonell A, Vicedo-Cabrera AM, Moirano G, Sonko B, Jeffries D, Moore SE, Haines A, Prentice AM, Murray KA
Lancet Planet Health 2024;8:e734–e743

Landscape fire air pollution as a mediator in drought and childhood stunting pathway in low- and middle-income countries
Li JJ, Wang P, Sutton C, Harker R, Xue T, Chen K
Environ Sci Technol 2024;58:16728–16737

Stunting and Concurrence with Other Conditions

The association between atopic dermatitis and linear growth in children – a systematic review
Gerard G, Ng WWV, Koh JKJ, Varughese SM, Loke KY, Lee YS, Ng NBH
Eur J Pediatr 2024;183:5113–5128

Wasting coexisting with underweight and stunting among children aged 6–59 months hospitalised in Garissa County Referral Hospital, Kenya
Wambua M, Kariuki SM, Abdullahi H, Abdullahi OA, Ngari MM
Matern Child Nutr 2025;21:e13754

Maternal Risk Factors

Early life exposure to economic shocks and association with childhood malnutrition: a pooled analysis of 230 nationwide surveys from 68 low-income and middle-income countries
Silva NJ, Paixão ES, Brachowicz N, Barreix G, Landin-Basterra E, Rubio FA, Boccia D, Ribeiro-Silva RC, Barreto ML, Naheed A, Macicame I, Naniche D, Rasella D
Lancet Glob Health 2025;13:e1367–e1377

Brain Development

Childhood brain morphometry in children with persistent stunting and catch-up growth
Koshy B, Thilagarajan VV, Berkins S, Banerjee A, Srinivasan M, Livingstone RS, Mohan VR, Scharf R, Jasper A, Kang G
PLoS One 2025;20:e0306500

Executive functions and associated brain volumetry in children with persistent stunting and catch-up growth
Koshy B, Thilagarajan VV, Livingstone RS, Srinivasan M, Mohan VR, Beulah R, Jasper A, John S, Kang G
Sci Rep 2025;15:13845

Innovations

Contactless infant height measurement for enhanced early detection of stunting using computer vision techniques
Risfendra, Aripriharta, Suherman, Gheri Febri Ananda, Dwi Sudarno Putra, Fahm
IEEE Access 2025;13:42364–42376

Commentary and Policy – Beyond Nutrition

Stop stunting – a misguided campaign by well-meaning nutritionists
Hermanussen M, Scheffler C
Am J Hum Biol 2024;368:e24068

Malnutrition in infants aged under 6 months: prevalence and anthropometric assessment – analysis of 56 low- and middle-income country DHS datasets

Kerac M[1], James PT[2], McGrath M[3], Brennan E[2], Cole T[4], Opondo C[5,6], Frison S[1]

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Comments: To address the limitations of weight-for-length Z-score (WLZ < −3), WHO updated its guidelines to include infants with poor growth and anthropometry and infants with known risk factors for poor growth and for poor birth outcomes. To support this, Kerac et al. analysed 56 Demographic and Health Survey (DHS) datasets from low- and middle-income countries (LMICs). The authors assessed malnutrition prevalence of infants under 6 months, and compared wasting and underweight enrolment criteria for malnutrition programmes through their data quality, overlap, and strength of association with established household/maternal/infant characteristics. Based on the analysis, 17.4% of the infants (95% CI: 16.9–18.0) were underweight (weight-for-age Z-score [WAZ] < −2), 15.5% (95% CI: 15.0–6.0) wasted (WLZ), 19.9% (95% CI: 19.3–20.5) stunted (length-for-age Z-score [LAZ] < −2), and 1.4% concurrently wasted and stunted (WaSt; WLZ < −2 and LAZ). Examining the data quality, results showed that LAZ (3.8%) and WLZ (7.5%) had more extreme values while WAZ had fewer flagged values (0.6%). Additionally, overlap between the old WHO criterion (WLZ < −3) and new criteria (WAZ or WLZ < −2) were observed and varied by region. For instance, in East Asia/Pacific and Eastern Europe/Central Asia, WAZ prevalence was not greater than that of WLZ, while in Latin America/Caribbean, WAZ prevalence was larger than that of WLZ. Notably, underweight captured all infants who were concurrently WaSt, as well as many severely wasted, though not all. In contrast, overlap between stunting and severe wasting was minimal. Household/maternal/infant characteristics had stronger associations with underweight than wasting. Overall, the study supported using underweight as a criterion for enrolment to malnutrition management programmes, given its better data quality, stronger associations with household/maternal/infant characteristics, and ability to capture WaSt.

Correlates of body composition in children with stunting: a cross-sectional study in Uganda

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Comments: Lewis et al. analysed baseline data from the MAGNUS intervention trial to examine how stunting severity, infection and inflammation and breastfeeding practices influenced body composition (BC) among 750 stunted Ugandan children aged 12–59 months. BC was estimated using bioelectrical impedance analysis, and the resulting fat mass (FM), fat free mass (FFM), fat mass index (FMI), and fat free mass index (FFMI) Z-scores compared to UK references. Overall, 42% (n = 314) of the children were severely stunted (HAZ < −3) and 5% (n = 38) were moderately wasted (−3 < WHZ < −2), indicating a high prevalence of malnutrition. While the participants had lower mean FMZ (−1.08, 95% CI; −1.15, −1.01), FFMZ (−2.25, 95% CI −2.32, −2.18), FMIZ (−0.46, 95% CI; −0.54, −0.38), and FFMIZ (−0.18, 95% CI; −0.26, −0.11), many children still had higher FFMIZ than the UK reference median. This potentially reflects the body's adaptive conservation of lean mass relative to height under nutritional stress. Further, HAZ was correlated with both FM (β = 0.14, 95% CI; 0.06, 0.22, p < 0.001) and FFM (β = 0.74, 95% CI; 0.67, 0.81, p < 0.001), but these associations were absent on adjusting for height (FMI: β = 0.07, 95% CI; −0.03, −0.17, p = 0.18 and FFMI: β = −0.04, 95% CI; −0.16, 0.07, p = 0.47). This suggests that reduced height directly influenced fat and fat free mass indices. The authors further report that chronic inflammation was more strongly correlated with lower FFM and greater FMI than acute inflammation. The long-term deficits in lean mass suggest that the detrimental effects of inflammation extend beyond height and potentially increase long-term risk of metabolic dysfunction and non-communicable diseases (NCDs) in adulthood. These findings are particularly important for LMICs undergoing nutrition transitions, where the interplay between inflammation, infection, and anaemia not only contributes to growth faltering and altered BC but also poses long-term risks to metabolic health.

Effect of heat stress in the first 1000 days of life on fetal and infant growth: a secondary analysis of the ENID randomised controlled trial

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Comments: The study published in *The Lancet Planetary Health* in 2024 is a secondary analysis of the longitudinal pregnancy cohort data from the Early Nutrition and Immunity Development (ENID) trial in West Kiang, the Gambia, which occurred between 2010 and 2015. The ENID study assessed micronutrient supplementation in the first 100 days of life starting from 20 weeks' gestation and collected anthropometric data prospectively. The current study examined the effects of heat stress, as measured by the Universal Thermal Climate Index (UTCI), on intrauterine growth restriction based on indicators like length-for-gestational age Z-score (LGAZ), weight-for-gestational age Z-score (WGAZ), and head circumference-for-gestational age Z-score (HCGAZ) at birth and postnatal infant anthropometry indicators, such as weight-for-age Z-score (WAZ) and weight-for-height Z-score (WHZ). The study found that heat stress during the first 1,000 days of life (conception to age 2) can negatively impact foetal and infant growth. Specifically, with each 1°C increase in mean daily maximum UTCI exposure, in the first trimester, they observed a reduction in WGAZ. Postnatally, the effect varied with age; for example, infants aged 12 months exposed to a mean daily UTCI of 30° C (preceding 90-day period) versus 25°C UTCI, we observed reductions in mean WHZ (−0.43 [95% CI −0.57 to −0.29]) and mean WAZ (−0.35 [95% CI −0.45 to −0.26]). The study's findings contribute to a growing body of evidence highlighting the importance of considering environmental factors like heat stress in the context of early childhood development, especially in a warming world.

Landscape fire air pollution as a mediator in drought and childhood stunting pathway in low- and middle-income countries

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Comments: The authors argue that increased fine particulate matter ($PM_{2.5}$) from drought-induced wildfires mediates the drought-stunting pathway. To investigate this, they analysed geocoded Demographic and Health Survey (DHS) data from 2000 to 2014, covering 350,796 under-five children across 44 LMICs. Using mixed-effect regression analysis, they found that each 1-unit decrease in the Standardized Precipitation Evapotranspiration Index (SPEI), indicating more severe drought, was associated with a 2.16% [95% CI: 0.79, 3.49%] increase in stunting risk and 0.57 [95% CI: 0.55, 0.59%] $\mu g/m^3$ increase in fire-sourced $PM_{2.5}$. Additionally, each 1-$\mu g/m^3$ increase in 24-month average exposure window to fire-sourced $PM_{2.5}$ was associated with a 2.46% [95% CI: 2.16, 2.76%] increase in stunting risk. No significant association was reported between short-term drought exposure windows and stunting, suggesting that long-term exposure to fire-sourced $PM_{2.5}$, unlike short-term exposure windows, is a stronger mediator in the drought-stunting pathway. Causal mediation analysis showed that the co-occurrence of drought-wildfire events significantly mediated the drought-stunting pathway, accounting for a quarter (26.7% [95% CI: 14.5, 36.6%]) of drought-induced childhood stunting, highlighting its significance in child growth. However, the spatial SPEI exposure data in their analysis may not accurately reflect individual drought or $PM_{2.5}$ exposure. Additionally, despite adjusting for several covariates, some residual confounding may have persisted due to missing data. Their findings should therefore be interpreted in light of these limitations. In conclusion, this study using large nationally representative data found a robust association between drought severity and childhood stunting and identified fire-sourced $PM_{2.5}$ as a mediator in this pathway. These findings highlight the long-term effects of drought on child growth outcomes in LMICs. Future research could explore longer-term mediation effects to understand the contribution of this pathway to stunting in older children under 5 years.

Stunting and Concurrence with Other Conditions

The association between atopic dermatitis and linear growth in children – a systematic review

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This manuscript is also discussed in the chapter by Kotnik et al. [this vol., pp. 32–47].

Comments: There is a greater appreciation that even in LMICs stunting could be caused by an undiagnosed or poorly managed medical condition in early childhood. Atopic dermatitis is a common and increasing problem in LMICs affecting approximately 1 in 5 children from a cross-sectional survey in Bangladesh [5]. Gerard et al. sought to address the inconsistencies in the evidence and the association between atopic

dermatitis (AD) and linear growth in early childhood. In this systematic review, they evaluated the association between atopic dermatitis (AD) and linear growth in children. They included fourteen studies (>50,000 patients). However, 11 studies scored low in quality of evidence. They concluded that the current evidence on the association between childhood AD and poor linear growth is weak and inconsistent. However, patients with more severe AD, earlier disease onset, poorer sleep quality, and higher nutritional restrictions appear more susceptible to linear growth impairment. Topical steroid use was not associated with shorter stature in patients with AD.

Wasting coexisting with underweight and stunting among children aged 6–59 months hospitalised in Garissa County Referral Hospital, Kenya

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Comments: Wambua et al. conducted a retrospective review of records of 624 children aged 6–59 months admitted with acute illness at Garissa County referral hospital, Kenya, between January 2017 and December 2019. The study examined the coexistence of wasting with underweight and/or stunting. Overall, the prevalence of wasting (95%), underweight (83%), and stunting (28%) was unacceptably high. The co-occurrence of wasting with underweight was more frequent (81%, 95% CI; 78, 84) than that of wasting and stunting (26%, 95% CI; 22, 29). Notably, all children who were concurrently wasted and stunted were also underweight, and every underweight child had at least an additional form of malnutrition. Only 15% of the wasted children had no other form of malnutrition, with 85% being concurrently underweight. Given this, and that WAZ is a well-established predictor of mortality risk, the authors recommend further investigation into the validity of WAZ as an indicator for identifying children with multiple forms of malnutrition. This could inform the development of unified protocols for assessment and management of the coexisting forms of malnutrition. While an association between diarrhoea and the coexistence of wasting with stunting (aRR = 2.96, 95% CI; 2.06, 4.23), as well as between anaemia and the co-occurrence of wasting with underweight (aRR = 1.23, 95% CI; 1.03, 1.47) was reported, these should be interpreted with caution as potential confounding may not have been fully adjusted for. Their findings should also be interpreted within the context of Northeastern Kenya, an arid region with very high levels of malnutrition. Nevertheless, the findings underscore the need to integrate the management of wasting and other forms of malnutrition through community-based programmes and the need for early screening of malnutrition at community level.

Early life exposure to economic shocks and association with childhood malnutrition: a pooled analysis of 230 nationwide surveys from 68 low-income and middle-income countries

Silva NJ[1,2], Paixão ES[3], Brachowicz N[1], Barreix G[1,2], Landin-Basterra E[1,2], Rubio FA[1,4], Boccia D[5], Ribeiro-Silva RC[6], Barreto ML[4,7], Naheed A[8], Macicame I[9], Naniche D[1,2], Rasella D[1,2,10]

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Comments: Silva et al. pooled cross-sectional data from the DHS and national-level longitudinal income data involving 1,643,898 children under the age of 5 years across 68 LMICs. They investigated how early life exposure to economic shocks influence childhood malnutrition in three time points – at the year of interview, at birth, and all years within the first 1,000 days. The findings showed that any exposure to negative income shocks in the year of the interview, increased the risk of wasting by 5.4% (prevalence ratio [PR] 1.054; 95% CI 1.029–1.080), severe wasting by 12.7% (PR 1.127; 95% CI 1.079–1.176), and severe stunting by 2% (PR 1.020; 95% CI 1.003–1.037). Exposure to negative income shocks in the year of birth increased the risk of stunting by 2.7% (PR 1.027; 95% CI 1.019–1.036), wasting by 3.5% (1.035; 95% CI 1.014–1.056), severe stunting by 6.1% (PR 1.061; 95% CI 1.045–1076), WaST by 5.3% (PR 1.053; 95% CI 1.017–1.091), and double burden of malnutrition by 4.9% (PR 1.049; 95% CI 1.006–1.093). Meanwhile, exposure to negative income shocks during the first 1,000 days of life was positively associated with stunting (PR 1.023; 95% CI 1.012–1.033) and severe stunting (1.052; 95% CI 1.033–1.072). Findings by wealth quintiles showed that income shocks increased wasting prevalence (poorest: PR 1.073; 95% CI 1.025–1.122; richest: PR 0.990; 95% CI 0.925–1.060 in the year of the interview), stunting prevalence (poorest: 1.030; 95% CI 1.014–1.046; richest: 1.007; 95% CI 0.979–1.036 in the year of birth), and WaSt prevalence (poorest: 1.11; 95% CI 1.049–1.195; richest: 0.936; 95% CI 0.837–1.047 in the year of birth) among the poorest quintile but not the richest. These findings underscore the need for addressing poverty and economic stability to ensure that all children have the opportunity for optimal growth.

Childhood brain morphometry in children with persistent stunting and catch-up growth

Koshy B[1], Thilagarajan VV[1,2], Berkins S[3], Banerjee A[3], Srinivasan M[4], Livingstone RS[5], Mohan VR[2], Scharf R[6], Jasper A[5], Kang G[2,4]

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Comments: Although the association between childhood stunting and cognitive impairment in LMICs has been well-established [6], the mechanisms and causal pathways are not known. In this very ambitious study, Koshy et al. used magnetic resonance imaging (MRI) to evaluate childhood brain volumes at 9 years of age in a community-based birth-cohort follow-up study in Vellore, south India. Specifically, they sought to explore the effects of early childhood stunting and catch-up growth on brain morphometry. They grouped the children in four based on anthropometric assessments at 2, 5, and 9 years: (i) "never stunted" (NS), (ii) "stunted at 2 years and caught up by 5 years" (S2N5), (iii) "stunted at 2 and 5 years and caught up by 9 years" (S2N9), (iv) "always stunted" (AS). 178 (71%) children (mean age of 9.54) underwent neuroimaging. The total brain volume, subcortical volume, bilateral cerebellar white matter, and posterior corpus callosum showed a declining trend from NS to AS. In addition, regional cortical brain analysis showed significant lower bilateral lateral occipital volumes, right pallidum, bilateral caudate, and right thalamus volumes between NS and AS. Persistent childhood stunting is associated with reduced total brain and subcortical volumes, networking/connecting centres (thalamus, basal ganglia, callosum, cerebellum), and visual processing area of lateral occipital cortex. These data provide useful insights into the impact of the stunting and/or it shared adverse exposures on brain volume.

Executive functions and associated brain volumetry in children with persistent stunting and catch-up growth

Koshy B[1], Thilagarajan VV[1,2], Livingstone RS[3], Srinivasan M[4], Mohan VR[2], Beulah R[1], Jasper A[5], John S[3], Kang G[2,4]

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Comments: Executive functions (EFs) are a set of cognitive processes that help individuals plan, organise, and regulate their thoughts and actions to achieve goals [7]. In this related analysis, Koshy et al. combined the brain MRI images with the EF assessment using FAS phonemic fluency test, colour cancellation test (to assess concentration, selective attention, and reading challenges in children), and colour trials tests (CTTs, to evaluate efficient visuomotor tracking while minimising the influence of language). At 9 years, 205 (82%) children underwent the FAS phonemic fluency test. The never stunted (NS) group had significantly higher test scores compared to always stunted (AS) group (11.52 vs. 7.4, $p = 0.02$). In CTT, a significant difference in near misses score was observed between NS and AS groups (0.12 vs. 0.38, $p = 0.03$). Upon evaluating unimodal brain association areas, volumes of right occipital fusiform gyrus (9,991 mm^3 vs. 9,313 mm^3; $p = 0.04$; $\eta^2 = 0.11$) and left lateral occipital cortex (13,458 mm^3 vs. 12,559 mm^3; $p = 0.03$; $\eta^2 = 0.07$) were significantly higher among NS compared to AS group. Considering higher order association areas, only left pars triangularis was found to be significantly reduced among AS children compared to the NS group (4,284 mm^3 vs. 3,291 mm^3; $p = 0.01$; $\eta^2 = 0.07$). Similarly, there was also significance visible in the basal ganglia regions and the cerebellum. Their data show that the changes in brain volumes with stunting are associated with EF dysfunction in verbal fluency and inhibitory control. This needs to be evaluated in other populations, but the costs of the MRI scans may render this challenging.

Innovations

Contactless infant height measurement for enhanced early detection of stunting using computer vision techniques

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Comments: Engineers from Indonesia have developed a contactless method of measuring length and height in children and validated this method using two samples of baby dolls and 12 infants. The method ideally uses computer vision technique that measures infants lying down in imperfect postures such as the infantile positions by detecting critical body key points essential for full length estimation. To measure, the baby is placed on a green mat with a fixed size of 100 cm, and using a webcam at a height of 135 cm, the image of the baby is captured with the entire reference mat. This method successfully identified the doll's height as 37.71 cm for the 38-cm doll and 48.36 cm for the 49-cm doll. Among the 12 infants, the system achieved highly accurate height measurements, achieving an average accuracy of 98.48%. The results of this study highlight that the modified Media Pipe framework is an effective tool for measuring infant height with high reliability and accuracy. Perfecting this technique could potentially provide a reliable and efficient way of measuring length and height of infants and children at their homes and or during a pandemic.

Commentary and Policy – Beyond Nutrition

Stop stunting – a misguided campaign by well-meaning nutritionists

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Comments: This is an interesting and thought-provoking commentary by 2 authors from Germany who were invited to evaluate a "stop stunting" campaign in Indonesia. Here, they summarise their personal and their Indonesian colleagues' perceptions

of the government efforts to improve child growth in Indonesia. They note that the "stop stunting" campaign committed 23 ministries and consumed an estimated 3.9 billion USD per year to coordinate the nutrition activities that address the many underlying causes of stunting. Since its introduction, the activity is estimated to have reached 3.9 million mothers and 10.6 million children under the age of 2 years in 75,000 villages. Since its introduction, between 2017 and 2021, the national stunting rates declined from 30.8% to 24.4%, which sounds good. However, the authors argue that this success corresponds to a height increase of less than 4 cm in 27 years, which is less than what would be an expected catch-up in height after successful refeeding, suggesting that lack of nutrition is just one piece in the short stature puzzle that the larger social, political, and economic circumstances interfere with human growth. The suggestion therefore is for countries to look at improving more upstream social-economic-political level changes to achieve a significant change in stunting. Countries need to move beyond nutrient-focussed stop stunting campaigns.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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The Physiology and Mechanisms of Growth

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Introduction

This chapter presents a selection of articles published between July 1, 2024, and June 30, 2025, focused on the physiology and mechanisms of growth. Collectively, these studies illustrate the multifactorial determinants of growth, ranging from prenatal exposures and social environments to genetic disorders, chronic disease, and therapeutic interventions, underscoring the importance of an integrated approach to understanding child development.

The reviewed articles elucidate diverse mechanisms underlying child growth, spanning epigenetic regulation, extracellular matrix biology, hormonal pathways, and behavioral influences. They reveal how genetic variation, environmental exposures, and therapeutic interventions converge on shared physiological processes, such as endochondral ossification, chondrocyte hypertrophy, and growth hormone dynamics. Together, these findings advance a mechanistic framework that links molecular and systemic regulation with clinical outcomes in child development.

While this selection offers valuable insights, it is not exhaustive, and other significant studies may not be included. Readers are encouraged to further explore the literature for a more comprehensive understanding of this evolving field.

Key articles reviewed for this chapter

Biological mechanisms for Allen's rule: DNA methylation as mediator of the association between in utero exposure to environmental heat and tibial growth in childhood
Straight B, Qiao X, Ngo D, Hilton CE, Olungah CO, Lalancette C, Naugle A, Needham BL
Am J Hum Biol 2025;37:e70086

Adoption or placement in foster care and catch-up in linear growth and development: a meta-analysis of individual participant data
Leroy JL, Angel MD, Frongillo EA
Adv Nutr 2025;16:10039510

Early childhood height, weight, and BMI development in children with monogenic obesity: a European multicentre, retrospective, observational study
Zorn S, de Groot CJ, Brandt-Heunemann S, von Schnurbein J, Abawi O, Bounds R, Ruck L, Guijo B, Martos-Moreno GÁ, Nicaise C, Courbage S, Klehr-Martinelli M, Siebert R, Dubern B, Poitou C, Clément K, Argente J, Kühnen P, Farooqi IS, Wabitsch M, van den Akker E
Lancet Child Adolesc Health 2025;9:297–305

Association of nighttime sleep duration at 1.5 years with height at 3 years: the Japan environment and children's study
Kawai M, Baba S, Tanigawa K, Ikehara S, Kawasaki R, Iso H
J Clin Endocrinol Metab 2025;110:e1866–e1873

Accelerated linear growth during erdafitinib treatment: an FGFR-related, but growth factor and sex steroid-independent mechanism?
Raimann A, Stepien N, Azizi AA, Hartmann G, Gojo J
Horm Res Paediatr 2024 Jul 31:1–5

Growth failure in aggrecan deficiency is due to decreased extracellular matrix and impaired growth plate chondrocyte hypertrophy
Bendre A, Ottosson L, Baroncelli M, Dou Z, Nilsson O
Bone 2025;200:117594

Clinical characteristics of pathogenic ACAN variants and 3 year response to growth hormone treatment: real-world data
Renes JS, Reedijk AMJ, Losekoot M, Kant SG, Van der Steen M, Van der Kaay DCM, Hokken-Koelega ACS, Van Duyvenvoorde HA, de Bruin C
Horm Res Paediatr 2024;97:456–469

Treatment of short stature in aggrecan-deficient patients with recombinant human GH: 3 year response
Muthuvel G, Dauber A, Alexandrou E, Tyzinski L, Hwa V, Backeljauw P
J Endocr Soc 2024;8:bvae177

The association between atopic dermatitis and linear growth in children: a systematic review
Gerard G, Ng WWV, Koh JKJ, Varughese SM, Loke KY, Lee YS, Ng NBH
Eur J Pediatr 2024;183:5113–5128

Decreased risk of reduced linear growth among children with atopic dermatitis receiving dupilumab: a cohort study
Chen TL, Ma SH, Ou WF, Chen CC, Wu CY
J Am Acad Dermatol 2025 Aug 18:S0190-9622(25)02646-5

The effect of dupilumab on growth parameters in paediatric atopic dermatitis patients
Piccolo V, Russo T, Nowowiejska J, Argenziano G, Mazzatenta C, Bassi A
Dermatol Pract Concept 2025;15:5420

Long-term growth and nutrition outcomes in children following intestinal transplant
Miri A, Iverson AK, Law N, Lee J, Quiros Navarrete RE, Reyes-Santiago EM, Nakayuenyongsuk W, Mercer DF, Vargas LM, Merani S, Grant WJ, Langnas AN, Quiros-Tejeira RE
J Pediatr Gastroenterol Nutr 2025;80:490–497

Retrospective review of growth in pediatric intestinal failure after weaning from parenteral nutrition
Nucci AM, Bashaw H, Kirpich A, Rudolph J
Nutr Clin Pract 2025;40:176–187

Biological mechanisms for Allen's rule: DNA methylation as mediator of the association between in utero exposure to environmental heat and tibial growth in childhood

Straight B[1], Qiao X[2], Ngo D[3], Hilton CE[4], Olungah CO[5], Lalancette C[6], Naugle A[7], Needham BL[8]

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Comments: In their 2025 study, Straight et al. provide compelling molecular evidence supporting Allen's Rule in humans. It was first proposed in 1877 by zoologist Joel Asaph Allen that animals (including humans) living in hot climates tend to have longer limbs, while those in cold climates tend to have shorter limbs. This is due to thermoregulatory needs: longer limbs increase surface area, enhancing heat dissipation, whereas shorter limbs help conserve heat by reducing surface exposure in colder environments.

This ecogeographical pattern has long been observed across species and human populations. For example, groups in equatorial regions often exhibit longer legs and arms compared to populations in arctic or alpine regions. While traditionally explained by natural selection, recent research explores developmental and epigenetic mechanisms behind these adaptations.

Straight et al. (2025) contribute to this understanding by showing that in utero exposure to high environmental temperatures (specifically land surface temperature (LST) >37°C) is associated with increased tibial length and tibia index (the proportion

of tibial length to total stature) in children. The study was conducted among Samburu pastoralist children in northern Kenya, a region highly vulnerable to climate change. Using saliva-derived DNA methylation data from the Illumina MethylationEPIC BeadChip, the researchers identified 37 CpG sites that significantly mediated the relationship between prenatal heat exposure and tibial growth. These CpGs were located near genes involved in skeletal development, thermoregulation, immune function, and cellular repair, suggesting plausible biological pathways for how heat stress in utero can influence limb growth.

Crucially, the third trimester of gestation emerged as the most sensitive period, aligning with the phase of rapid fetal growth. The study's robust design – including high-resolution LST data, trimester-specific exposure windows, and adjustments for maternal stress, nutrition, and sibling clustering – adds credibility to its findings.

Moreover, the study integrates this biological evidence with health implications: while heat promotes leg lengthening, emotional and nutritional stress (often exacerbated by climate change) can suppress tibial growth, leading to shorter limbs. Importantly, shorter leg length is associated with a range of adverse long-term health outcomes, such as cardiovascular disease, insulin resistance, hypertension, and poor metabolic capacity. In contrast, longer tibiae are linked to better organ development and lifelong health potential.

Altogether, this research not only provides modern molecular validation for Allen's Rule but also underscores the lasting effects of climate-related prenatal stress on growth and health. It emphasizes that tibial length can serve as a biomarker of early life conditions, and that epigenetic imprinting may shape adaptive human morphology in response to environmental challenges. These findings carry significant implications for public health and resilience strategies in the context of accelerating global climate change.

Adoption or placement in foster care and catch-up in linear growth and development: a meta-analysis of individual participant data

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Adv Nutr 2025;16:10039510

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https://pubmed.ncbi.nlm.nih.gov/39993655/

Comments: Leroy et al. present a meta-analysis of individual participant data to investigate the association of adoption or foster care placement with catch-up in linear growth and child development in children under 5 years of age. The study highlights the potential for significant recovery in linear growth when children are moved from low-resource to high-resource environments, while also noting the more limited recovery in developmental outcomes.

The study conducted a 2-stage meta-analysis using individual participant data, drawing from 9 adoption studies that included 485 children under 5 years old. The analysis focused on the height-for-age difference (HAD) as the primary outcome, which is the difference between measured height and the median sex-specific and age-specific height from the WHO growth standard. This metric is considered more appropriate for evaluating changes than height-for-age Z-scores (HAZ).

Adoption significantly reduced the children's accumulated height deficit by 77%, or approximately 3.0 cm (95% CI: 1.9, 4.1 cm), with a mean age at follow-up of 32.3 months. At baseline, children had a mean age of 15.8 months and a length deficit of 3.9 cm. Catch-up growth was observed in both girls (3.6 cm; 95% CI: 2.9, 4.2 cm) and boys (2.5 cm; 95% CI: 1.9, 3.1 cm), with girls showing a larger point estimate. Children adopted after 24 months of age showed substantial catch-up (2.2 cm; 95% CI: 0.6, 3.7 cm), suggesting that the potential for recovery is not limited to younger children. The magnitude of catch-up in child development (mean reduction in deficit of 46%) was smaller compared to that in linear growth. This indicates that while linear growth can recover, developmental outcomes are less likely to fully reverse.

The findings highlight that profound and comprehensive improvements in a child's environment, such as those provided by adoption from low-income to high-income settings, can lead to significant linear growth catch-up. However, the partial reversal of accumulated height deficit was larger than the recovery in developmental outcomes, emphasizing the need to prevent deficits from occurring rather than solely focusing on correction. The study also challenges the notion that linear growth retardation is largely irreversible after 24 months of age, suggesting that the "first 1,000 days" window for growth is not a strict biological limitation.

Early childhood height, weight, and BMI development in children with monogenic obesity: a European multicentre, retrospective, observational study

Zorn S[1,2], de Groot CJ[3,4], Brandt-Heunemann S[1,2], von Schnurbein J[1], Abawi O[3], Bounds R[5], Ruck L[6], Guijo B[7], Martos-Moreno GÁ[7,8], Nicaise C[9], Courbage S[9], Klehr-Martinelli M[10], Siebert R[2,10], Dubern B[9,11], Poitou C[11,12], Clément K[11,12], Argente J[7,8,13], Kühnen P[6,14], Farooqi IS[5], Wabitsch M[1,2], van den Akker E[3]

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https://pubmed.ncbi.nlm.nih.gov/40246357/

Comments: The multicenter study by Zorn et al. offers a valuable contribution to the characterization of early growth trajectories in individuals with monogenic obesity. Utilizing retrospective data from six European centers, the study examined height, weight, and BMI development from birth to 5 years of age in a cohort of 147 individuals with genetically confirmed monogenic obesity, and compared them with 113 children presenting with severe obesity of unknown genetic etiology.

Participants were stratified according to the presence of biallelic (likely) pathogenic variants in LEP, LEPR, POMC, PCSK1, or MC4R, as well as monoallelic MC4R variants. Growth patterns diverged significantly among genetic subgroups. From 6 months of age, individuals with biallelic variants displayed markedly elevated BMI values compared to both monoallelic MC4R carrier and control children. Notably, biallelic LEP, LEPR, and MC4R variants were associated with a rapid increase in BMI during infancy, followed by a plateau, while POMC-related obesity exhibited a continued upward trajectory in BMI through age 5. Children with monoallelic MC4R variants demonstrated a more gradual BMI increase, aligning with trajectories observed in polygenic or common obesity, albeit with consistently lower BMI values than biallelic cases after 6 months. Interestingly, accelerated linear growth was observed exclusively in children harboring biallelic MC4R variants, becoming apparent from the age of 1 year and resulting in significantly elevated height SDS compared to other groups.

A key clinical implication of the study is the identification of an optimal BMI cutoff (≥24.0 kg/m^2 at the age of 2 years) for distinguishing children with biallelic variants from those with nongenetic forms of severe obesity. The ROC curve analysis demonstrated high diagnostic performance (sensitivity 0.96, specificity 0.83, AUC 0.96). In contrast, BMI performed poorly in differentiating monoallelic MC4R cases from controls, underscoring the diagnostic limitations for this subgroup. The authors also appropriately highlight the potential impact of transitioning from supine to standing height measurements at age 2 on BMI interpretation and cutoff accuracy.

Overall, this study advances our understanding of early phenotypic manifestations of monogenic obesity and supports the implementation of BMI-based screening thresholds to prompt early genetic evaluation. The distinct early-life growth patterns reported, particularly in biallelic cases, may enhance clinical recognition and enable timely intervention in affected individuals.

Association of nighttime sleep duration at 1.5 years with height at 3 years: the Japan environment and children's study

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J Clin Endocrinol Metab 2025;110:e1866–e1873

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https://pubmed.ncbi.nlm.nih.gov/39288009/

Comments: The study "Association of Nighttime Sleep Duration with Early Childhood Height" provides compelling evidence for the importance of nighttime sleep in supporting linear growth during early childhood. Drawing on data from the Japan Environment and Children's Study (JECS) – a large-scale, prospective birth cohort – the authors examine over 52,000 term singleton births, making this one of the most statistically robust investigations into the sleep-growth relationship to date.

The primary finding is that longer nighttime sleep duration at 1.5 years of age is positively associated with taller stature at 3 years, defined as height at or above the 75th percentile. After adjusting for a wide range of confounders (including socioeconomic status, maternal health, nursery attendance, and environmental tobacco exposure), children who slept 9.5–10 h, 10.5–11 h, and ≥11.5 h per night had significantly higher odds of tall stature compared to those who slept ≤9 h. The observation of a linear trend strengthens the evidence for a dose-response effect.

Crucially, the study differentiates between nighttime sleep and total sleep duration (which includes daytime naps). Only nighttime sleep showed a significant association with height outcomes, suggesting that sleep timing and architecture, rather than total duration, play a critical role in growth. This finding aligns with known physiological processes: growth hormone (GH) secretion peaks during slow-wave (non-REM) sleep, which predominates in the early part of the night. Disruptions to nighttime sleep – whether from irregular schedules, sleep fragmentation, or insufficient duration – may blunt GH secretion, and, consequently, impede longitudinal bone growth.

Moreover, the study's stratified analyses show that this association holds across various subgroups (e.g., by sex, presence of siblings, exposure to tobacco smoke, and nursery attendance), indicating the robustness and generalizability of the results. These findings resonate with broader literature linking sleep quality to hormonal regulation, immune development, and cognitive performance in early childhood.

One limitation acknowledged is the reliance on caregiver-reported sleep duration, which may introduce measurement error. However, given the large sample size and consistent trends observed, the findings retain high epidemiological relevance.

From a public health perspective, this study highlights nighttime sleep as a modifiable determinant of early childhood growth. In contrast to genetic and socioeconomic factors, sleep duration and timing are potentially actionable through parent education and behavioral interventions. Promoting consistent bedtimes and longer nighttime sleep may offer a noninvasive strategy to support optimal physical development during critical growth periods.

In conclusion, this study reinforces the biological and developmental importance of nighttime sleep in early childhood. It provides strong evidence that adequate nighttime sleep supports linear growth, likely through its influence on endocrine function, particularly GH dynamics. These findings have important implications for pediatric health policy, emphasizing that healthy sleep patterns should be prioritized alongside nutrition and physical activity in strategies to promote optimal child growth and development.

Accelerated linear growth during erdafitinib treatment: an FGFR-related, but growth factor and sex steroid-independent mechanism?

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Comments: The recent study reporting accelerated linear growth in pediatric CNS tumor patients treated with erdafitinib, a selective FGFR1–4 tyrosine kinase inhibitor (TKI), presents a compelling and unexpected insight into the regulation of postnatal growth. Traditionally, linear growth is regulated by growth hormone, insulin-like growth factor-1 (IGF-1), and sex steroids, particularly during puberty. However, this report describes a rapid and significant growth spurt in two heavily pretreated children with severe prior growth impairment, independent of these conventional pathways.

Erdafitinib's target, fibroblast growth factor receptor 3 (FGFR3), is a well-established negative regulator of chondrocyte proliferation and growth plate activity. Inhibiting FGFR3, therefore, may release this suppression and promote physeal expansion. Supporting this mechanism, both patients exhibited growth plate widening and increased metaphyseal mineralization without accelerated skeletal maturation, as evidenced by wrist imaging. These skeletal changes, alongside the absence of elevated IGF-1 or sex steroid levels, reinforce a FGFR3-specific, hormone-independent mechanism of growth acceleration.

This observation is particularly significant in pediatric oncology, where growth failure due to corticosteroid use, cranial irradiation, and hypopituitarism is common. The potential for pharmacological FGFR3 inhibition to restore growth in such cases may open a novel therapeutic avenue – not only in oncology, but also in the management of certain growth disorders.

While the findings are based on a small cohort and require confirmation in larger, controlled studies, they introduce an important paradigm shift. Erdafitinib's growth-promoting effect – previously unrecognized – may have profound implications for clinical decision-making in pediatric patients, especially before epiphyseal closure, and warrants further investigation into FGFR3-targeted therapies for short stature and skeletal dysplasias.

Growth failure in aggrecan deficiency is due to decreased extracellular matrix and impaired growth plate chondrocyte hypertrophy

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Comments: Aggrecan, the principal proteoglycan of the growth-plate extracellular matrix, is critical for columnar organization, hypertrophic chondrocyte enlargement, and resistance to compressive loading. Heterozygous *ACAN* (the aggrecan gene) loss-of-function is an established cause of familial short stature, frequently associated with advanced bone age and early osteoarticular complications. Nevertheless, the primary growth-plate lesion and its signalling correlates remain incompletely defined, and the mechanistic basis for reported growth hormone (GH)/insulin-like growth factor-1 (IGF-1) responsiveness is uncertain. The Acan+/– murine model offers a useful platform to investigate cellular and pathway-level determinants of impaired endochondral ossification and to refine therapeutic hypotheses relevant to paediatric growth.

The investigators in this paper sought to define the cellular and molecular mechanisms by which heterozygous *ACAN* loss-of-function causes impaired linear growth. They employed the well-characterized heterozygous cartilage matrix-deficiency mouse (Acan+/–) and included longitudinal auxology with growth-plate histomorphometry, single-cell RNA sequencing (scRNA-seq), and signalling read-outs.

Although Acan+/– mice were of normal size at birth, both sexes developed progressive postnatal growth failure due to shortening of long bones, with earlier divergence in females; nonskeletal organs were unaffected, indicating a primary endochondral disorder. Proliferative activity within the growth plate was largely preserved. In contrast, two consistent abnormalities explained reduced elongation: (i) decreased extracellular matrix between proliferative columns and (ii) smaller terminal hypertrophic chondrocytes. Subtle reductions in overall growth-plate height and zonal dimensions were most evident in rapidly growing, younger animals. scRNA-seq demonstrated ~50% reduction of total Acan mRNA (consistent with haploinsufficiency) without compensatory upregulation of alternative proteoglycans. Matrix genes (*Col9a2*, *Col9a3*) were downregulated across resting, proliferative, and hypertrophic zones; selected collagens and Aebp1 showed zone-specific increases. Perturbations in linker/core histone genes (e.g., *Hist1h1c*, *Hist1h1e*, *Hist1h2be*) were also observed.

Camk1D was upregulated across zones, while phosphorylation of Akt (Thr308) was reduced, especially in prehypertrophic and hypertrophic chondrocytes, implicating Camk1D-mediated suppression of PI3K/Akt signalling as a proximate constraint on hypertrophic cell enlargement.

These data establish that growth failure in aggrecan deficiency is driven principally by matrix paucity and impaired chondrocyte hypertrophy, rather than a proliferation defect. The identified Camk1D suppression of PI3K/Akt signal perturbation provides a plausible molecular bridge between aggrecan insufficiency and reduced hypertrophic cell size, aligning with known roles of PI3K/Akt in promoting hypertrophic differentiation.

These findings offer biological plausibility for the modest, yet potentially clinically meaningful, responses to growth hormone (GH) reported in children with ACAN variants, given that GH increases circulating IGF-1 and activates PI3K/Akt in growth-plate chondrocytes. They also nominate testable adjunctive strategies, enhancing proteoglycan synthesis and/or restoring Akt signalling as potential approaches to augment linear growth in this genotype. While translational studies are required, the mechanistic framework supports prepubertal initiation of GH where indicated and motivates biomarker-driven evaluation of chondrocyte signalling in future trials.

The evidence derives from a single-centre murine model; scRNA-seq was performed predominantly in postnatal day-18 females; and the Camk1D-Akt relationship, although internally consistent, remains correlative in vivo. Extrapolation to adult height effects in humans is therefore inferential.

Aggrecan haploinsufficiency compromises longitudinal bone growth through decreased extracellular matrix and restricted hypertrophic chondrocyte enlargement, accompanied by Camk1D upregulation and dampened Akt activation in the growth plate. This mechanistic insight substantiates GH/IGF-1–based therapy as a rational first-line intervention and highlights future, mechanism-guided strategies aimed at proteoglycan biology and PI3K/Akt restoration.

Clinical characteristics of pathogenic ACAN variants and 3 year response to growth hormone treatment: real-world data

Renes JS[1,2], Reedijk AMJ[1], Losekoot M[3], Kant SG[4], Van der Steen M[5], Van der Kaay DCM[6], Hokken-Koelega ACS[1,6], Van Duyvenvoorde HA[3], de Bruin C[7]

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Treatment of short stature in aggrecan-deficient patients with recombinant human GH: 3 year response

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Comments: Aggrecan (ACAN) haploinsufficiency is an established monogenic cause of familial short stature. The clinical spectrum is heterogeneous and may include mild body disproportion, advanced bone age (BA), and early-onset osteoarticular disease,

although these features are not universal. The two studies summarized here advance the evidence base beyond case reports by (i) characterizing phenotype and genotype-phenotype relationships in a national cohort and (ii) quantifying a standardized 3-year response to recombinant human growth hormone (rhGH).

In the Dutch real-world registry study by Renes et al., children with pathogenic/likely pathogenic ACAN variants treated with GH for ≥1 year were identified through a national registry. Twenty-five distinct variants were observed among 36 patients. Baseline height standard deviation score (SDS) was −2.6 (IQR −3.2 to −2.2). Approximately 20% lacked classical clinical "flags" (no clear disproportion, dysmorphism, or BA advancement), highlighting that ACAN variants may present as apparently idiopathic short stature. Truncating variants were associated with shorter stature at presentation than non-truncating variants (median −2.8 vs. −2.1 SDS; $p = 0.002$). Advancement of BA did not segregate with variant class or location. Missense changes clustered within the G1 and G3 domains, and osteochondritis dissecans/early osteoarthritis occurred across domains, not confined to G3. Prepubertal children treated with GH achieved a median +1.0 height SDS over 3 years of GH, whereas those initiating in puberty gained +0.5 SDS with GH ± pubertal modulation (gonadotropin-releasing hormone analogues or aromatase inhibition). In prepubertal children, BA did not accelerate during therapy. Limited adult-height data ($n = 10$) suggest some individuals attain ≥−2 SDS, with variability related to treatment timing and adjuncts. Safety was acceptable: IGF-1 excursions >+2 SDS were managed by dose adjustment; two incident scoliosis were reported (one braced).

In the US prospective study by Muthuvel et al., 10 treatment-naïve, prepubertal children with ACAN haploinsufficiency received open-label rhGH at ~50 μg/kg/day with IGF-1-guided downtitration. Median cumulative Δheight SDS at 3 years was +1.21. Height velocity increased from 5.2 cm/year pretreatment to 8.3, 7.7, and 6.8 cm/year in years 1–3, respectively. Predicted adult height (PAH) improved by a median +6.8 cm. BA relative to chronological age showed no overall acceleration (median Δ −0.1); expected maturation increases were observed only in participants entering puberty late in follow-up. No GH-related adverse events were recorded.

Given that up to one in five affected children lack disproportion or BA advancement, ACAN analysis should be included in gene panels for apparently nonsyndromic short stature. Both studies support prepubertal initiation of GH to maximize gains in height SDS and PAH, with the largest increment in year 1 and sustained, smaller gains thereafter. GH did not globally accelerate BA in prepubertal starters; however, progression into puberty attenuates response. Consideration of timed pubertal modulation (GnRHa and/or aromatase inhibition) in selected cases with rapid skeletal maturation or poor PAH may be necessary although outcomes of adult height is unknown and further research is needed. Real-world data suggest that lower initial GH doses (e.g., ~1.0 mg/m^2/day) may suffice in younger children, with escalation if Δheight SDS is <0.5 after the first year while maintaining IGF-1 within target range.

Neither study was randomized; use of adjunctive therapies in the registry study complicates causal attribution, and adult-height outcome is currently unknown. Priority questions include optimal age for GH initiation, criteria and timing for pubertal modulation, and head-to-head dosing strategies to balance growth response with IGF-1 exposure.

Across these two study designs, 3 years of GH therapy in ACAN haploinsufficiency yields approximately +1.0 to +1.2 height SDS and improved PAH without overall acceleration of BA, particularly when initiated prepubertally. These data support routine inclusion of ACAN in genetic evaluation of short stature and an individualized management strategy combining GH with selective pubertal modulation.

The association between atopic dermatitis and linear growth in children: a systematic review

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This manuscript is also discussed in the chapter by Mwangome et al. [this vol. pp. 17–31].

Comments: Paediatric atopic dermatitis (AD) has been variably linked to impaired linear growth, with putative mediators including disease severity, sleep disturbance, and nutritional restriction. This PRISMA-compliant systematic review evaluated the strength and consistency of this association and potential modifiers.

The protocol was registered on PROSPERO (CRD42024548419). PubMed, Embase, Scopus, and Cochrane were searched from inception to June 30, 2024 for observational studies reporting quantitative associations between AD and linear growth in individuals <18 years. Study quality was appraised with the Joanna Briggs Institute tools, and certainty of evidence graded using GRADE. Due to heterogeneity in AD definitions, growth outcomes, and comparators, meta-analysis was not undertaken. Fourteen studies (9 cross-sectional, 5 cohort) comprising 50,146 children with AD were included.

Evidence for a universal growth deficit in AD was weak and inconsistent: 2/14 studies reported a strong negative association, 5/14 a smaller negative association, and 7/14 no association between AD and height standard deviation score (SDS) or percentiles. All three studies graded as moderate certainty reported reduced height in children with AD; the remaining studies were graded low certainty. Several cohorts suggested a transient impact on linear growth i.e., shorter stature in early childhood with subsequent catch-up, consistent with a constitutional-delay pattern. Secondary analyses implicated greater AD severity, earlier disease onset, sleep disruption, and dietary restriction as risk factors for poorer linear growth. Use of topical corticosteroids was not associated with reduced stature.

Current data do not support a strong, generalized association between childhood AD and impaired linear growth. Instead, risk appears concentrated in defined subgroups, and growth failure, when present, may be temporary. These findings highlight the likely importance of modifiable factors (sleep quality and nutrition) alongside disease control in mediating auxologic outcomes. Routine auxologic surveillance is advisable in children with AD, with greater vigilance for those with moderate-severe disease, early onset, prominent nocturnal symptoms, or restrictive diets. Management should prioritize aggressive eczema control, optimization of sleep, and avoidance of unnecessary elimination diets. Appropriate topical corticosteroid use should not be curtailed on the basis of growth concerns alone.

All included studies in this systematic review were observational, with heterogeneous outcome definitions and limited follow-up, and several relied on self-report for AD status and exposures, constraining causal inference and precluding quantitative synthesis. The aggregate evidence indicates no robust, universal association between paediatric AD and poor linear growth. However, a subset of patients, characterized by greater disease severity, earlier onset, sleep disturbance, and dietary restriction appears at increased risk for

temporary growth deceleration. Structured growth monitoring coupled with comprehensive, steroid-sparing disease management and nutritional intervention, if necessary, is warranted.

Decreased risk of reduced linear growth among children with atopic dermatitis receiving dupilumab: a cohort study

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The effect of dupilumab on growth parameters in paediatric atopic dermatitis patients

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Comments: Growth impairment in children with atopic dermatitis (AD) has been variably reported and mechanisms remain multifactorial (inflammation, sleep disruption, nutrition, and corticosteroid exposure). Two recent papers add complementary evidence: a large, propensity-matched electronic health record cohort analysis and a detailed case report describing growth catch-up with dupilumab.

The US TriNetX-based retrospective cohort (2018–2023) by Chen et al. including 745,046 paediatric patients compared children with AD to non-AD controls, and, within AD, emulated a target trial to contrast dupilumab initiation with conventional systemic immunomodulators (methotrexate, azathioprine, cyclosporine, or mycophenolate). After 1:1 propensity score matching, AD was associated with higher risks of reduced stature over 5 years (height <5th percentile: RR 1.15, 95% CI 1.12–1.18; <25th: RR 1.13, 1.08–1.21; <50th: RR 1.22, 1.20–1.25). Elevated risks were most evident in males and in children >6 years; associations attenuated in strata without sleep disturbance or systemic corticosteroid exposure, suggesting effect modification. In the target trial emulation (n = 6,124; 3,062 dupilumab vs. 3,062 conventional immunomodulators), dupilumab was associated with a lower 5-year risk of reduced stature (<5th percentile: RR 0.69, 0.57–0.84; <25th: RR

0.70, 0.54–0.91; <50th: RR 0.74, 0.58–0.95). Protective associations were strongest in males, children >6 years, and those with BMI ≥20; findings persisted across on-treatment and restriction sensitivity analyses.

The research letter by Piccolo et al. describes a child with severe, early-onset AD who experienced marked dermatologic improvement on dupilumab with parallel movement of height from the 10–25th to 25–50th percentile and weight from <3rd to 10–25th percentile over 48 weeks. The authors hypothesize contributions from improvements in inflammation, sleep, and bone mineralization markers to the observed auxologic changes. While anecdotal, the case offers face validity to the cohort signals and underscores the need for prospective growth monitoring in treated children.

The cohort study's scale, matching strategy, target-trial framework, and multiple sensitivity analyses strengthen inference. Nonetheless, residual confounding cannot be excluded; severity metrics (e.g., EASI), pubertal timing, treatment adherence, socioeconomic factors, and dietary practices were incompletely captured. Height percentiles, rather than velocity, were primary outcomes, which may dilute responsiveness to short-term change. The case report provides granular clinical detail but cannot establish causality or generalizability. Taken together, the two reports should be read as hypothesis-generating and supportive rather than definitive.

Prospective, longitudinal studies with standardized auxology (including growth velocity and predicted adult height), bone age, pubertal staging, validated AD severity measures, sleep metrics, nutritional assessments, and corticosteroid exposure are needed. Randomized or well-designed comparative effectiveness studies should test whether early dupilumab initiation improves short- and long-term growth outcomes versus other systemic strategies and define which patient subsets benefit most. Mechanistic work linking type-2 inflammation, sleep architecture, GH/IGF-1 axis activity, and growth plate dynamics would further clarify biological plausibility.

Current evidence suggests a small but measurable association between paediatric AD and reduced stature, and indicates that dupilumab may mitigate this risk relative to conventional systemic immunomodulators. Until prospective confirmation is available, best practice should couple aggressive disease control with sleep optimization, steroid stewardship, appropriate nutrition, and systematic growth monitoring.

Long-term growth and nutrition outcomes in children following intestinal transplant

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Retrospective review of growth in pediatric intestinal failure after weaning from parenteral nutrition

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Comments: Intestinal transplantation (ITx) for paediatric intestinal failure (IF) increasingly improves survival into adolescence and adulthood; however, the durability of linear growth and nutritional adequacy after parenteral nutrition (PN) weaning remains poorly described. Two recent studies provide complementary evidence across the IF-ITx continuum: a single-centre cohort with up to 15-year follow-up after ITx, and a two-centre retrospective review of growth after PN weaning in IF – including subanalyses by diagnosis, transplant status, and glucagon-like peptide-2 (GLP-2) analogue exposure.

In the study by Miri et al., the ITx cohort included 133 children transplanted between 1993 and 2014 who survived ≥5 years; longitudinal mixed-effects and general estimating equation models assessed height, weight, BMI Z-scores, time to PN and tube-feeding (TF) weaning, and micronutrient profiles, with prespecified modifiers (isolated vs. multivisceral graft, steroid exposure, partial gastrectomy, persistent ostomy, developmental delay, and rejection).

In the study by Nucci et al., the IF cohort included 362 infants diagnosed <12 months; 150 (41%) weaned from PN and contributed growth trajectories for up to 5 years postwean. Subgroups included 46 transplanted children and 14 treated with teduglutide for >6 months. Outcomes were weight and length/height Z-scores and BMI, stratified by primary diagnosis and transplant status.

In the study by Miri et al., after ITx, linear growth improved over 15 years (height Z-score increased; $p < 0.001$), whereas BMI Z-score showed a modest downward trend (range ≈ +0.5 to −0.35). Isolated ITx was associated with better height Z-scores than multivisceral transplant ($p = 0.04$). Neither long-term steroid use nor prednisolone dose (>0.2 vs. ≤0.2 mg/kg/day) significantly influenced height or BMI Z-scores. PN was discontinued rapidly (median 34 days post-ITx), yet TF support often persisted; 60% ultimately weaned from TF, with a median 48 months to full oral diet. Partial gastrectomy, permanent ostomy, and developmental delay independently prolonged TF dependence. Micronutrient deficits remained prevalent long-term: iron deficiency decreased from 56% at ITx to 27% at 15 years, whereas vitamin D deficiency affected 33% at ITx and 50% at 15 years; zinc deficiency was present in 16% at ITx and 28% at 15 years.

In the study by Nucci et al., after PN weaning in the IF cohort, growth was generally maintained rather than accelerated in nontransplanted children (median Z-score change within ±0.5), with diagnosis-specific nuances: small bowel atresia showed accelerated linear growth from year 3, while necrotizing enterocolitis (NEC) tended to remain stable. In contrast, most transplanted children exhibited catch-up in weight and length/height beginning ~2–2.5 years after PN wean. During teduglutide therapy ($n = 14$; median 840 days), auxology was largely stable; ~40% had early weight acceleration (first 6 months),

~31% demonstrated catch-up in linear growth between 6 and 12 months, and five children weaned from PN within 1 year of treatment.

Across both cohorts, sustained linear growth is achievable after ITx, with only modest change in BMI. Growth after PN weaning in nontransplanted IF is typically stable rather than rapidly restorative. Transplant status modifies trajectory: catch-up is more common posttransplant, while surgical and neurodevelopmental factors (partial gastrectomy, persistent ostomy, and developmental delay) principally influence feeding route and TF dependence rather than long-term height or BMI. Persistent vitamin D and zinc deficits highlight the need for structured micronutrient surveillance. GLP-2 analogue therapy facilitates PN reduction in selected cases, but available data suggest neutral to modest effects on growth velocity over 1–3 years.

Prospective, diagnosis-stratified cohorts should incorporate growth velocity and predicted adult height, body composition, bone health, pubertal timing, and quality-of-life endpoints; comparative studies are needed to clarify the growth impact of surgical choices (e.g., gastrectomy) and to test whether GLP-2–based strategies or standardized feeding programs materially alter long-term stature and TF independence.

Long-term auxologic outcomes after ITx are favourable for height, while growth post-PN weaning in nontransplanted IF is largely preserved but seldom exhibits early catch-up. Targeted management of feeding route determinants and rigorous micronutrient surveillance constitute the principal opportunities to optimize nutrition and growth across the IF-ITx pathway.

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Obesity, Metabolic Syndrome, and Nutrition

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Introduction

Obesity represents a significant global public health challenge, currently affecting over 300 million children worldwide. This condition carries profound implications for both physical and psychological health, and is likely to persist into adulthood, thereby increasing the risk of long-term morbidity and premature mortality. The etiology of obesity is multifactorial, encompassing a complex interaction between genetic predispositions and modifiable environmental influences, particularly sedentary lifestyles and excessive caloric intake.

Emerging evidence highlights the critical role of the early life environment in shaping long-term physiological and metabolic trajectories.

Early and crucial developmental periods represent critical window during which nutritional exposures can exert lasting effects on future disease susceptibility.

Adverse intrauterine conditions may initiate metabolic programming processes that predispose individuals to lifelong health challenges. Maternal obesity during pregnancy has been consistently linked to increased risks of obesity and metabolic disorders in the offspring. Several studies reviewed in this chapter focus on in utero exposures and their associations with childhood obesity and metabolic outcomes.

Maternal dietary patterns, including adherence to a Mediterranean diet or consumption of a high-protein, low-glycemic index diet, may influence fetal metabolic development, highlighting the importance of prenatal nutrition in the intergenerational transmission of obesity risk. In addition, nutritional practices during infancy and early childhood play a pivotal role in shaping long-term health. Exclusive breastfeeding for the first 6 months of life is recommended to support optimal growth and development, and has been proposed as a potential protective factor against obesity.

Some of the included studies investigated associations between breastfeeding and adiposity outcomes, including early adiposity rebound (AR), a known predictor of later adiposity and metabolic disease, which appears to be less prevalent in breastfed infants. One study reported that breast milk lipid profiles were associated with AR status, suggesting a regulatory effect on the metabolic risk later in life. Other findings indicated that breastfeeding may attenuate the impact of genetic susceptibility to obesity and modify associations between gestational diabetes exposure and subsequent adiposity when paired with healthy postnatal feeding behaviors, such as limiting sugary beverage consumption.

Additional studies examined the influence of dietary composition in later childhood on adiposity outcomes. A nutritionally balanced diet in childhood is essential for appropriate growth and the prevention of diseases in late childhood or adulthood. One large surveillance study offered new insights into how trace elements in drinking water may relate to BMI in pediatric populations. Meanwhile, research from low- and middle-income countries highlighted the growing impact of ultra-processed food consumption on the health and wellbeing of young children. Another longitudinal study emphasized the importance of sustained adherence to the Mediterranean diet as a predictor of BMI trajectories over time.

Several studies assessed the relationship between specific dietary components, such as calcium intake, nut consumption, and adherence to the Indo-Mediterranean diet (characterized by high intake of whole grains, spices, mustard oil, fruits, vegetables, and fish), and cardiometabolic risk factors in pediatric populations.

In light of the substantial health burden associated with childhood obesity, there is an urgent need for effective public health strategies that prioritize nutritional interventions and support policy efforts to cultivate healthy dietary behaviors from infancy onward.

In this year's edition of the Yearbook chapter focused on nutrition, obesity, and metabolic comorbidities across early life stages, we highlight 14 notable articles published between July 2024 and June 2025. These selections represent key advances in the understanding of how early-life nutrition influences the development of obesity and metabolic health from infancy through childhood and into young adulthood.

Key articles reviewed for this chapter

Maternal Diet during Pregnancy and Risk of Childhood Obesity

Effects of Mediterranean diet during pregnancy on the onset of overweight or obesity in the offspring: a randomized trial
Coppola S, Paparo L, Bedogni G, Nocerino R, Costabile D, Cuomo M, Chiariotti L, Carucci L, Agangi A, Napolitano M, Messina F, Passariello A, Berni Canani R
Int J Obes (Lond) 2025;49:101–108

Effect of a high-protein and low-glycaemic index diet during pregnancy in women with overweight or obesity on offspring metabolic health – a randomized controlled trial
Mogensen CS, Magkos F, Zingenberg H, Geiker NRW
Pediatr Obes 2025;20:e13191

Nutrition during Infancy and Risk of Childhood Obesity

Interaction between breastfeeding duration and an obesity genetic risk score to predict body fat composition in European adolescents: the HELENA study
Baxevanis GK, Iglesia I, Seral-Cortes M, Sabroso-Lasa S, Flores-Barrantes P, Gottrand F, Meirhaeghe A, Kafatos A, Widhalm K, Hockamp N, Molnár D, Marcos A, Nova E, González-Gross M, Gesteiro E, Gutiérrez Á, Manios Y, Anastasiou CA, Rodríguez G, Moreno LA on behalf of the HELENA Study Group
Pediatr Obes 2025;20:e13205

Fetal exposure to gestational diabetes severity and postnatal infant feeding in the first year of life associated with preadolescent obesity: a prospective cohort
Sun B, Lo JC, Greenspan LC, King AS, Davis JN, Faith MS, Wakimoto P, Josefson JL, Basi T, Quesenberry CP Jr, Hudson EA, Lowe W, Metzger B, Gunderson EP
Obesity (Silver Spring) 2025;33:996–1010

Efficacy of a 24-month behavioral intervention focused on sugary beverage reduction for Latino mother-infant dyads: evidence from a randomized controlled trial
Machle CJ, Berger PK, Salvy SJ, Rios C, Durazo-Arvizu R, Goran MI
Am J Clin Nutr 2025;121:355–366

Exploring the association between human breast milk lipids and early adiposity rebound in children: a case-control study
Sawane K, Takahashi I, Ishikuro M, Takumi H, Orui M, Noda A, Shinoda G, Ohseto H, Onuma T, Ueno F, Murakami K, Higuchi N, Furuyashiki T, Nakamura T, Koshiba S, Ohneda K, Kumada K, Ogishima S, Hozawa A, Sugawara J, Kuriyama S, Obara T
Nutrition 2025;135:112739

Nutrition during Childhood and Risk of Childhood Obesity

Adherence to the Mediterranean diet and changes in body mass index
Homs C, Berruezo P, Según G, Torres S, Ribera M, Sauri A, Tejada J, Ródenas J, Juton C, Milà R, Fíto M, Gómez SF, Schröder H
Pediatr Res 2025;97:1911–1917

The modifying effects of lifestyle behaviors on the association between drinking water micronutrients and BMI status among children and adolescents aged 7~17: a population-based regional surveillance in 2022
Chen M, Zhang X, Jiang J, Yang T, Chen L, Liu J, Song X, Zhang Y, Wang R, Qin Y, Dong Z, Yuan W, Guo T, Song Z, Ma J, Dong Y, Song Y, Qin Y
Nutrients 2024;16:3931

Cashew nut consumption reduces waist circumference and oxidative stress in adolescents with obesity: a randomized clinical trial
de Oliveira LFN, Maia CSC, Nogueira MDA, Dias TDS, Firmino MAD, Loureiro APM, Marzola EL, Nunes PIG, Santos FA, Freire WBS, Fortunato RS, Loureiro ACC
Nutr Res 2025;134:60–72

Nutrition transition's latest stage: are ultra-processed food increases in low- and middle-income countries dooming our preschoolers' diets and future health?
Popkin BM, Laar A
Pediatr Obes 2025;20:e70002

Nutrition and Risk of Obesity-Related Comorbidities

Association between calcium intake from different food sources during childhood and cardiometabolic risk on adolescence: the Generation XXI birth cohort
Silva S, Severo M, Lopes C
Pediatr Obes 2024;19:e13158

Dietary lipid profile in Spanish children with overweight or obesity: a longitudinal study on the impact of children's eating behavior and sedentary habits
García S, Ródenas-Munar M, Argelich E, Mateos D, Ugarriza L, Tur JA, Bouzas C
Nutrients 2025;17:494

Skipping breakfast and nutrient density: influence on obesity, blood pressure, glucose, and cholesterol in elementary school students
Mun H, Oh SW
Obes Res Clin Pract 2025;19:94–100

Effect of Indo-Mediterranean diet versus calorie-restricted diet in children with non-alcoholic fatty liver disease: a pilot randomized control trial
Deshmukh A, Sood V, Lal BB, Khanna R, Alam S, Sarin SK
Pediatr Obes 2024;19:e13163

Maternal Diet during Pregnancy and Risk of Childhood Obesity

Effects of Mediterranean diet during pregnancy on the onset of overweight or obesity in the offspring: a randomized trial

Coppola S[1,2], Paparo L[1,2], Bedogni G[3,4], Nocerino R[1,2], Costabile D[2], Cuomo M[2,5], Chiariotti L[2,5], Carucci L[1,2], Agangi A[6], Napolitano M[6], Messina F[6], Passariello A[7], Berni Canani R[1,2]

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Comments: The Mediterranean diet (MD) is widely regarded as one of the healthiest dietary patterns, characterized by high intakes of fiber, antioxidants, polyphenols, essential vitamins, and a balanced ratio of essential fatty acids. It has been associated with numerous health benefits, including the prevention of excessive weight gain in adults and children [1, 2]. Increasing attention has been directed toward the role of maternal nutrition during pregnancy as a strategic target for preventing obesity and overweight in offspring, potentially through mechanisms related to fetal programming and epigenetic modulation of gene expression.

While prior observational studies, both prospective and retrospective, have reported inconsistent findings regarding the impact of MD during pregnancy on offspring adiposity, the present well-designed, parallel-arm randomized controlled trial (RCT) offers robust evidence. Specifically, adherence to an MD pattern during pregnancy was associated with a significantly lower risk of overweight or obesity in offspring at 2 years of age, compared to the control group. Notably, this protective effect occurred independently of maternal gestational weight gain, which did not differ between groups.

An important mechanistic insight from the study is the observed increase in DNA methylation at the promoter region of the *leptin* gene in cord blood mononuclear cells among the MD group. Given leptin's central role in appetite regulation, metabolism, and fat distribution, and its established association with neonatal adiposity [3], this epigenetic modification may suggest reduced gene expression and a potential pathway through which MD influences early growth trajectories. The findings are consistent with the hypothesis that epigenetic mechanisms mediate the long-term effects of maternal nutrition on offspring health [4]. A diet rich in plant-based foods, as characterized by the MD, has been shown to enhance maternal gut microbiome diversity, supporting the proliferation of microbial taxa and metabolites capable of influencing epigenetic regulation. This study contributes to a growing body of evidence indicating that maternal dietary patterns can exert lasting effects on offspring metabolic outcomes, potentially through epigenetic programming and early modulation of the infant gut microbiome and energy homeostasis pathways.

Among the strengths of this trial are its randomized controlled design and the adjustment for potential maternal confounders such as prepregnancy BMI, smoking status, and socioeconomic indicators, thereby enhancing the validity of causal inferences. However, several limitations must be acknowledged. The relatively small sample size ($n = 97$) may limit the generalizability of findings and statistical power for subgroup analyses. Dietary adherence was assessed through self-reported food frequency questionnaires, which are susceptible to recall and reporting biases. Additionally, the study did not account for postnatal environmental influences, such as infant feeding practices and physical activity, which could have impacted the observed outcomes. The epigenetic analyses were conducted on a limited number of samples ($n = 22$), and the study population was restricted to women of Caucasian ethnicity, thereby limiting external validity to more diverse populations.

Despite these limitations, the study provides compelling evidence in support of dietary counseling during pregnancy as a potential early-life intervention to prevent childhood obesity, a condition that remains difficult to reverse once established. Integrating structured MD guidance into routine prenatal care may offer a low-cost, low-risk public health strategy with long-term benefits.

Future research should aim to evaluate the persistence of these effects into later childhood and adolescence. Moreover, implementation studies are warranted to determine effective methods for delivering and maintaining dietary interventions across diverse populations and healthcare settings.

Effect of a high-protein and low-glycaemic index diet during pregnancy in women with overweight or obesity on offspring metabolic health – a randomized controlled trial

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Comments: Prepregnancy overweight and excessive gestational weight gain (GWG) are well-established risk factors for maternal complications and increased susceptibility to obesity in the offspring [5].

Previous data showed that increased exposure to protein during fetal development may influence the future offspring protein requirements and appetite regulation with contribution to calorie overconsumption and weight gain [6]. Additionally, high-protein intake during infancy (from birth to 2 years) is associated with later obesity outcomes [7] suggesting a long-term risk for overweight and obesity in offspring with prolonged exposure to high-protein levels during early life.

The APPROACH (An Optimized Programming of Healthy Children) randomized controlled trial (RCT) previously demonstrated that, in pregnant women with overweight or obesity, adherence to a high-protein and low-glycemic-index (HPLGI) diet during the second and third trimesters resulted in reduced GWG and fewer maternal complications compared to a moderate-protein moderate-glycemic-index (MPMGI) diet. However, no significant differences were observed in offspring birth weight between the groups [8].

This RCT provides important insights into the influence of maternal dietary composition on early childhood metabolic health, specifically among offspring of women with overweight or obesity. While no significant differences were identified in BMI Z-scores, fat mass, fat-free mass, or body fat percentage between groups during the first 5 years of life, there was a tendency toward less favorable body composition and cardiometabolic profiles in the HPLGI group. Notably, offspring born to mothers in the HPLGI group exhibited higher glucose levels and a trend toward lower insulin levels at birth. At 3 years of age, these children had lower HDL cholesterol and elevated triglyceride levels. By 5 years, total cholesterol and LDL cholesterol concentrations were higher in the HPLGI group compared to the MPMGI group.

Key strengths of the study include its randomized controlled design, which minimizes selection bias and enhances causal inference. Additionally, the focus on women with overweight or obesity, populations at increased risk for adverse perinatal and intergenerational metabolic outcomes, adds clinical relevance and applicability to the findings. However, the study also presents several limitations. Dietary intake data during follow-up were limited, with no detailed information on offspring energy or macronutrient intake beyond breastfeeding and timing of solid food introduction. Self-reported maternal dietary intake introduces potential recall and social desirability bias. Attrition of approximately 30% during follow-up may have influenced outcome estimates. Furthermore, the lack of long-term follow-up beyond age 5 restricts conclusions regarding the persistence of observed metabolic trends. The generalizability of the findings is limited, as the study population consisted exclusively of women with overweight or obesity and may not reflect outcomes in women of normal weight or those from different cultural or socioeconomic backgrounds.

This study adds to the growing body of literature investigating the role of prenatal nutrition in shaping offspring metabolic trajectories. The findings raise important considerations regarding the potential unintended consequences of HPLGI dietary interventions during pregnancy on offspring metabolic health. Maternal protein intake may therefore help explain the effect of the HPLGI diet on offspring metabolic markers, which would imply that the recommendation for limited protein consumption from infancy to 2 years of age may need to be extended to cover the fetal life as well (i.e., pregnancy). These results underscore the need for caution in formulating maternal dietary guidelines and highlight the importance of further research, including long-term follow-up studies in diverse populations and mechanistic investigations, to validate these findings and inform public health policy.

Nutrition during Infancy and Risk of Childhood Obesity

Interaction between breastfeeding duration and an obesity genetic risk score to predict body fat composition in European adolescents: the HELENA study

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Comments: Breastfeeding has been associated with a reduced risk of overweight and obesity in children and adolescents [9]. The present study, based on data from the HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) cohort, offers important insights into the interaction between early-life nutrition and genetic predisposition to obesity. Specifically, it investigates whether the duration of breastfeeding moderates the relationship between a polygenic obesity risk score and adolescent body fat composition.

In this cohort of European adolescents, a significant interaction effect was observed between breastfeeding duration and the polygenic obesity risk score on various body composition parameters, independent of socioeconomic status, diet quality, and physical activity. Specifically, longer breastfeeding duration appeared to attenuate the influence of genetic predisposition on obesity development.

These findings contribute meaningfully to the expanding field of gene, environment interaction research, which seeks to elucidate the sources of individual variation in susceptibility to obesity. Notably, in this study, the adolescents at high genetic risk who were breastfed for at least 1 month had lower mean adiposity indices compared to those who were never breastfed, indicating that breastfeeding may counteract genetic susceptibility to obesity.

Among the study's strengths is the inclusion of a large (n = 751), geographically diverse sample of European adolescents, enhancing the external validity and generalizability of the findings across various Western European populations. However, several limitations should be noted. The reliance on retrospectively reported breastfeeding data introduces potential recall bias. Moreover, the cross-sectional design limits the ability to draw causal inferences regarding the influence of breastfeeding on the developmental trajectory of genetic obesity risk. Despite statistical adjustments, residual confounding by unmeasured variables, such as maternal prepregnancy BMI, gestational weight gain, timing of complementary feeding, and the home food environment, cannot be ruled out.

Nonetheless, the study contributes valuable evidence to the hypothesis that modifiable early-life exposures, such as breastfeeding, may attenuate genetic risk for obesity. While the findings align with current public health recommendations promoting breastfeeding, further longitudinal studies are needed to replicate these results and elucidate the biological mechanisms underlying these interactions. The integration of genetic risk assessment with individualized early-life interventions may represent a promising approach in the development of personalized strategies for obesity prevention.

Fetal exposure to gestational diabetes severity and postnatal infant feeding in the first year of life associated with preadolescent obesity: a prospective cohort

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Comments:

Children exposed to gestational diabetes mellitus (GDM) in utero face an elevated risk of developing obesity and metabolic disorders later in life [10]. Modifiable postnatal dietary factors, such as breastfeeding, formula feeding, and sugary beverage intake, may serve as important intervention targets to mitigate the effects of intrauterine GDM exposure [11]. This prospective cohort study provides meaningful insights into the interplay between GDM severity, early infant feeding practices, and the development of obesity during preadolescence. By jointly examining prenatal and postnatal influences, the study addresses a critical gap in life-course epidemiology – specifically, how intrauterine metabolic programming interacts with early-life behavioral exposures to shape long-term child health outcomes.

The findings of this study showed that inadequate (<6 months) or adequate breastfeeding combined with sugar-sweetened beverages (SSB)/fruit juice (FJ) intake from birth to age 1 year was associated with a 1.5- to 1.9-fold higher risk of developing obesity compared with adequate breastfeeding (≥6 months) with no SSB/FJ intake in preadolescent youth exposed to GDM in utero. These findings were independent of exposure to GDM severity (i.e., gestational age at diagnosis, treatment type, and maternal glycemic control under treatment) and covariates, including prepregnancy BMI, gestational weight gain, and sociodemographic factors.

Key strengths of this study include its prospective longitudinal design, which follows a well-characterized birth cohort from the prenatal period through preadolescence. This approach enhances the temporal validity of exposure-outcome relationships and minimizes recall bias. The study benefits from detailed characterization of maternal glycemic status, allowing for nuanced examination of GDM severity in relation to obesity risk. Additionally, the inclusion of comprehensive infant feeding data, such as breastfeeding duration and timing of solid food introduction, enables assessment of both potential modifying effects and independent contributions to obesity risk. Adjustment for a broad range of sociodemographic, maternal, and infant covariates further strengthens causal inference. Nevertheless, some limitations should be acknowledged. Residual confounding may persist due to unmeasured factors such as maternal dietary quality, physical activity, or paternal BMI, which could influence both GDM severity and child weight trajectories. Moreover, reliance on self-reported infant feeding practices introduces the possibility of recall bias.

In conclusion, this study makes an important contribution to the understanding of early-life determinants of childhood obesity by linking the severity of intrauterine hyperglycemia with postnatal feeding behaviors. The findings underscore the potential value of a dual-intervention approach that combines maternal glycemic control during pregnancy with promotion of optimal infant feeding practices to reduce the risk of childhood obesity. While methodologically robust and highly relevant, further research is warranted to elucidate underlying mechanisms and evaluate targeted interventions across diverse populations.

Efficacy of a 24-month behavioral intervention focused on sugary beverage reduction for Latino mother-infant dyads: evidence from a randomized controlled trial

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Comments: Obesity and its associated comorbidities disproportionately impact minoritized racial and ethnic populations, as well as individuals from low-income households [12]. Interventions targeting young children often face challenges in achieving sustained parental engagement, and existing programs have demonstrated variable effectiveness. There is a pressing need for innovative strategies that not only improve maternal adherence but also foster healthy weight-related behaviors in both mothers and their children. The postpartum period represents a critical window of opportunity for the adoption of long-term healthy lifestyle behaviors, particularly when appropriate support systems are in place [13].

This randomized controlled trial (RCT) evaluates the long-term effectiveness of a culturally tailored, 24-month behavioral intervention aimed at reducing sugar-sweetened beverage (SSB) consumption among Latino mother-infant dyads. The study addresses a significant public health concern, especially in Latino communities, where early-life SSB intake is common and strongly linked to elevated risks of obesity and metabolic dysregulation in children.

Among the key strengths of the study is its culturally adapted intervention model, which integrates cultural relevance and community-based engagement, factors known to enhance participant adherence and long-term program sustainability. By targeting the mother-child dyad, rather than focusing solely on the child, the intervention acknowledges and leverages the influential role of mothers in shaping early dietary habits. The extended 24-month intervention period, combined with repeated follow-up assessments, enabled a comprehensive evaluation of behavioral changes during infancy and toddlerhood, periods that are particularly critical for obesity prevention. Furthermore, the study employed both 24-h dietary recalls and anthropometric measurements, offering a multidimensional assessment of behavioral and physiological outcomes. However,

several limitations warrant consideration. The intervention's focus on Latino families limits the generalizability of findings to other racial, ethnic, or socioeconomically diverse populations. Dietary intake assessments relied partly on maternal self-report, introducing potential for recall and social desirability biases. The absence of objective metabolic or biochemical markers (e.g., insulin sensitivity, lipid profiles) limits the capacity to draw conclusions regarding the intervention's impact on metabolic health. The study does not have a reliable measure of participant adherence to the intervention protocol beyond the measured consumption of free sugars from beverages at each time point. Additionally, the high-intensity nature of the intervention, characterized by frequent contact and home visits, may pose challenges for real-world implementation in resource-limited settings.

Despite these limitations, the study offers valuable insights into the potential of early, family-centered interventions to reduce SSB consumption in Latino populations. The findings demonstrate that a 2-year intervention targeting SSB and juice intake can lead to initial reductions in maternal consumption, particularly when supplemented by frequent contact and the provision of bottled water. However, reductions in SSB consumption were not sustained during the second year as the intensity of the intervention declined, and no significant changes were observed in weight or body composition outcomes. Future research is warranted to assess the broader applicability, biological impact, cost-effectiveness, and long-term sustainability of such interventions. Moreover, efforts to scale culturally responsive interventions must consider adaptation to diverse populations and real-world implementation constraints. This trial contributes meaningfully to the growing body of literature on early-life obesity prevention and highlights the critical role of culturally-tailored, family-focused strategies in addressing health disparities.

Exploring the association between human breast milk lipids and early adiposity rebound in children: a case-control study

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Comments: Body mass index (BMI) is globally accepted as a main measure for defining obesity. Typically, BMI rises rapidly during the first year of life, then decreases to its lowest point around age 6, before rising again throughout childhood. This second increase is known as the adiposity rebound (AR). The timing of AR has been shown to predict the risk of obesity in adulthood [14]. Research, including several studies and meta-analyses, indicates that an early AR, occurring before age five, is linked not only to obesity but also to higher levels of triglycerides and cholesterol during adolescence and adulthood [14]. Therefore, AR serves as a valuable marker not only for childhood adiposity but also for future risks of obesity and metabolic diseases.

Breastfeeding has been identified as a protective factor against childhood adiposity and early AR, as reported in various cohort studies and meta-analyses. Breast milk contains many nutrients essential for child growth, with lipids playing a crucial role. However, the specific types of lipids involved in AR are not yet well understood. Comprehensive lipid analysis may help identify specific lipids connected to AR, which could aid in early detection and serve as targets for interventions to reduce disease risk later in life.

In a study by Sawane K. and colleagues, the authors performed a case-control study involving 184 mother-child pairs from the Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study. In all mothers, breast milk samples were collected 1 month after birth, and a detailed lipid profiling, identifying 667 lipid molecules across 12 classes, was performed. The study found associations between certain lipid concentrations in breast milk and the child's AR status. Specifically, fatty acid-hydroxy fatty acid was positively linked to early AR in exclusively breastfed pairs, while cholesterol ester was negatively associated with early AR across all pairs and those exclusively breastfed.

A relevant strength of the study is the highly selected population included in the analysis. Particularly, authors did not include obese mothers, thus reducing confounding effects of maternal adiposity. However, some major limitations need to be evaluated, particularly the small sample size as well the use of breast milk samples precollected as a part of the biobank project. In addition, no information regarding the nutritional intake or dietary behaviors of both the mother and infant was available. Finally, breast milk was collected at 1 month only, thus the lack of longitudinally collected samples do not allow to properly characterize changes in lipid composition over the course of lactation and particularly their effect on AR.

These results offer new insights into how breastfeeding may influence childhood adiposity and the risk of metabolic disorders in adulthood. Further longitudinal research is needed to explore the long-term metabolic effects of these breast milk components during the growth of children and adolescents with overweight or obesity.

Adherence to the Mediterranean diet and changes in body mass index

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Comments: The Mediterranean diet (MedDiet) is widely recognized as one of the most balanced and health-promoting dietary patterns globally, characterized by a high intake of plant-based proteins, low-glycemic-index carbohydrates, monounsaturated fatty acids, dietary fiber, and antioxidants [15]. A better understanding of the effects of MedDiet-based interventions on anthropometric outcomes could support their integration into obesity prevention strategies targeting the pediatric population. A previous meta-analysis, which included all randomized controlled trials (RCTs) up to March 2023, demonstrated that MedDiet-based interventions led to modest but statistically significant reductions in BMI, as well as a notable decrease in obesity prevalence among children and adolescents when compared to control groups [16]. The current study examined the association between MedDiet adherence and longitudinal changes in BMI in a cohort of children aged 8–12 years. The findings indicated that higher adherence to the MedDiet at baseline was associated with a reduction in BMI Z-score at follow-up. However, this association lost statistical significance after adjusting for baseline BMI Z-score. Moreover, the magnitude of change in BMI Z-score (≤0.20 units) was not considered clinically meaningful. No significant association was observed between baseline MedDiet adherence and the incidence of excessive weight at follow-up.

Strengths of this study include its longitudinal design, which allows for stronger inferences regarding potential causal relationships between dietary patterns and BMI trajectories. The use of standardized MedDiet adherence scores enhances the consistency and reliability of dietary assessments. Additionally, the analyses accounted for several important confounding variables, including age, physical activity, and screen time, thereby improving the internal validity of the findings. However, several limitations should be acknowledged. The reliance on self-reported dietary intake data may introduce recall and social desirability bias. Furthermore, the use of BMI as an outcome measure limits the ability to distinguish between fat mass and

lean mass, which may mask relevant changes in body composition. The study sample, drawn exclusively from a Spanish population, may also limit the generalizability of the findings to more diverse or international pediatric populations.

Despite these limitations, the study contributes valuable evidence to the existing literature on the role of the MedDiet in pediatric health. The findings suggest that higher adherence to the MedDiet may be associated with more favorable BMI trajectories in children. Specifically, the consumption of vegetables, nuts, and dairy products was negatively associated with a high increase in BMI.

Future research employing objective dietary biomarkers and more precise measures of body composition is warranted to better elucidate the impact of the MedDiet on pediatric obesity prevention and management.

The modifying effects of lifestyle behaviors on the association between drinking water micronutrients and BMI status among children and adolescents aged 7~17: a population-based regional surveillance in 2022

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Comments: Dietary strategies aimed at preventing weight gain or promoting weight loss often recommend increasing water intake (for example, "drink at least eight glasses of water daily") alongside reducing calorie consumption and boosting physical activity. However, there is limited evidence about the relationship between regular monitoring of drinking water characteristics and BMI in children and adolescents, especially concerning micronutrients in drinking water.

Chen and colleagues conducted a large-scale regional and population-based study, analyzing data from over 170,000 children and adolescents aged 7–17 years and more than 5,000 drinking water samples. Their findings revealed associations between certain drinking water parameters, such as nitrate nitrogen, pH, total hardness, and chemical oxygen demand, and BMI or BMI Z-scores. Additionally, the study suggested that maintaining a healthy lifestyle can help reduce the negative impact of fluoride, chloride, and sulfate on BMI Z-scores.

Strengths of this study include the availability of a large population that allowed to employ a systematic and comprehensive assessment approach, coupled with highly accurate monitoring of common diseases and drinking water indicators, thus strongly supporting the validity of the results. In addition, reported data were further supported by a sensitivity analysis to verify the robustness of the results and better understand whether drinking water indicators may influence BMI in various demographic subgroups.

However, some important limitations mainly regarding the selection of the study population that was limited to students within a large regional surveillance system, which does not include children and adolescents outside the school system, might limit the extension of the results. In addition, in the study, no information regarding the amount or sources of their water consumption was available. More importantly, no records were available regarding the use of soft drinks utilized by the students, which might affect the fluoride and chloride intake.

Despite these limitations, this extensive surveillance provides valuable insights into the complex relationship between drinking water micronutrients and BMI in youth. The influence of different drinking water components on BMI varies, highlighting the importance of continued research, particularly among girls and urban populations. Water plays a crucial role in the body's structure, forming cells, tissues, and organs, and functions acting in nutrient hydrolysis, cell regulation, nutrient transport, and temperature balance. Overall, the study underscores the need to further investigate the effects of drinking quality water on growth, especially in urban settings, and emphasizes how healthy lifestyle behaviors can mitigate potential harmful effects. These findings could inform future improvements in drinking water standards and support targeted lifestyle interventions to promote better health among children and adolescents.

Cashew nut consumption reduces waist circumference and oxidative stress in adolescents with obesity: a randomized clinical trial

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Comments: Several multidimensional strategies have been proposed to prevent and manage overweight and obesity. Dietary guidelines primarily focus on reducing overall energy intake while improving diet quality. This improvement is often achieved by replacing unhealthy snacks consumed between main meals with nutrient-dense foods such as nuts – including walnuts, hazelnuts, almonds, pistachios, cashews, Brazil nuts, pecans, and pine nuts [17]. Nuts are rich sources of unsaturated fatty acids, plant-based proteins, dietary fibers, vitamins, minerals, and bioactive compounds such as plant sterols and antioxidants. Growing epidemiological evidence supports daily nut consumption as an effective strategy for the primary prevention of obesity [17].

Beyond prevention, emerging research also suggests that nuts may play a role in obesity treatment. Since diet is the main source of these nutrients, further studies are needed to evaluate their potential benefits in preventing and managing childhood obesity. However, to date, few studies have focused on the metabolic effects of nut consumption in children. In one such study, de Oliveira et al. conducted a 12-week randomized clinical trial involving 142 adolescents divided into four groups. Participants were randomly assigned to receive either 30 grams of roasted cashew nuts combined with nutrition education (cashew nut group, CNG) or nutrition education alone (control group, CG). The study's key findings indicated that nut consumption led to a reduction in waist circumference and significantly improved oxidative stress markers. These results support the potential of nut intake to reduce systemic oxidative stress associated with obesity.

The study design, particularly the RCT design of the study, represents one of the major strengths of this report. In addition, the groups evaluated in this study were homogeneous regarding energy intake, macronutrients, and TDAC, which further strengthens the evidence that the observed effects were indeed associated with the intervention.

Some major limitations of the study are related to the short intervention-period and the availability of surrogate markers of body composition. Particularly, data obtained by using the bioelectrical impedance analysis (BIA) method need to be validated with the gold standard dual-energy X-ray absorptiometry (DXA) method. More importantly, authors reported a high rate of absenteeism during the first week of data collection and dropouts throughout the follow-up period, and thus new studies are needed to confirm the reported results.

While the exact role of nuts in obesity prevention and treatment is not fully understood, several mechanisms have been proposed to explain their benefits. These include incomplete energy absorption from nuts, increased feeling of fullness, and hunger regulation due to their high fiber content and prebiotic effects on gut microbiota [8]. Specifically, cashew nuts have been studied for their ability to modulate chronic and acute inflammatory and oxidative processes. Given their nutrient composition, incorporating nuts into a healthy diet may help control inflammation and oxidative stress in children and adolescents with obesity – a condition characterized by chronic low-grade inflammation [18,19].

Nutrition transition's latest stage: are ultra-processed food increases in low- and middle-income countries dooming our preschoolers' diets and future health?

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https://pubmed.ncbi.nlm.nih.gov/40012243/

Comments: Over recent decades, global eating patterns have dramatically changed due to multiple influences such as sociocultural shifts, industrialization, technological progress, and the globalization of food production [20, 21]. In numerous countries, a distinct nutritional transition is evident, marked by the substitution of traditional and freshly cooked meals

with a rising consumption of highly processed products, known as ultra-processed foods (UPFs) [20, 21]. UPFs undergo extensive physical, chemical, or biological alterations from their original form, frequently including additives such as preservatives, flavorings, nutrients, and other approved food substances [20, 21]. These foods contain ingredients and additives rarely used in home cooking, aimed at enhancing taste, shelf life, and convenience. While their composition and examples differ by region, all share the trait of extensive processing. Designed for immediate consumption with minimal preparation, UPFs provide long shelf life, quick and easy preparation, and appealing taste, which make them competitive alternatives to whole or freshly prepared foods. However, nutritionally, they tend to be high in saturated fats, sugars, and sodium, and are calorie-dense but poor in essential nutrients, protein, fibers, and micronutrients [20, 21]. A large number of researches have linked UPF consumption to adverse health effects. Numerous cross-sectional and cohort studies have demonstrated that high intake of UPFs significantly contributes to the rise of noncommunicable diseases (NCDs), including obesity, type 2 diabetes, dyslipidaemia, and hypertension [22]. Alarmingly, Popkin and colleagues reported particularly concerning trends in low- and middle-income countries. Their findings show increased rates of overweight and obesity among women of reproductive age and children, with a greater impact observed in lower socioeconomic groups. Moreover, these countries have experienced rapid growth in sales of UPFs and sugary beverages, alongside early introduction of sugar-sweetened beverages (SSBs) to infants and young children. There has also been a significant rise in the purchase of infant and toddler foods, with ultra-processed products making up a large portion of toddlers' diets (aged 6–23 months) and maternal diets. These findings are cause for serious concern and, if confirmed by further research, demand urgent global intervention. Strong food policy measures are essential to mitigate these adverse effects.

Nutrition and Risk of Obesity-Related Comorbidities

Association between calcium intake from different food sources during childhood and cardiometabolic risk on adolescence: the Generation XXI birth cohort

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Comments: Evidence from pooled analysis of cross-sectional studies suggested an inverse association between total dairy consumption and obesity [23]. However, the relationship between dietary calcium intake and body mass measures in children remains inconclusive, with previous studies yielding mixed results. Notably, one

large-scale European cohort study reported that dietary calcium intake may influence body fat accumulation during developmental stages, with the association primarily driven by calcium derived from dairy sources, whereas no significant effects were observed for calcium from non-dairy sources [24]. The present study examines the longitudinal association between childhood calcium intake from various food sources and cardiometabolic risk in adolescence, utilizing data from the Generation XXI birth cohort – a large, well-established prospective study based in Portugal. The primary objective was to investigate the potential influence of total dietary calcium, and particularly calcium from dairy versus non-dairy sources, on later cardiometabolic outcomes, including obesity, blood pressure, lipid profile, and insulin resistance.

Overall, the results of this study support that total calcium intake has a protective effect on BMI, waist circumference, and diastolic blood pressure at 13 years of age, but is dependent on total energy intake. However, a protective effect on cardiometabolic risk was observed for calcium from vegetables, even after adjustment for energy intake.

A key strength of this study lies in its longitudinal design, which enables the assessment of temporal relationships between early dietary exposures and later health outcomes. The use of a large, population-based birth cohort enhances the robustness and generalizability of the findings within the Portuguese context. Dietary calcium intake was estimated using validated dietary assessment tools, and the analysis differentiated between specific food sources (e.g., milk, yogurt, cheese, and nondairy items), offering nuanced insights into their respective roles in shaping cardiometabolic health trajectories. The analyses were rigorously adjusted for a comprehensive set of sociodemographic, perinatal, and lifestyle factors.

Nonetheless, several limitations warrant consideration. The reliance on dietary recalls introduces the possibility of recall bias and misreporting. Despite extensive covariate adjustment, residual confounding – such as unmeasured parental dietary patterns or genetic predisposition to metabolic conditions – may still affect the results. Moreover, given that the cohort is based in Portugal, where dietary behaviors, calcium fortification policies, and food availability may differ from other contexts, caution is needed when generalizing the findings to other populations.

Overall, this study contributes meaningful evidence to the field of pediatric nutrition by underscoring that the health effects of calcium intake may differ according to food source. The findings support the notion that the food matrix and co-ingested nutrients influence cardiometabolic risk beyond the effects of calcium alone. Future research, including interventional trials and studies utilizing objective biomarkers, is warranted to confirm these findings and guide the development of dietary recommendations for early cardiometabolic risk reduction.

Dietary lipid profile in Spanish children with overweight or obesity: a longitudinal study on the impact of children's eating behavior and sedentary habits

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Comments: Childhood obesity has become a critical global health concern. In 2022, it was estimated that more than 390 million children and adolescents aged 5–19 were overweight or obese, along with 37 million children under the age of 5. Projections suggest that this trend will continue to worsen. If current patterns persist, by 2050, an additional 3.33 million children aged 5–14, 3.41 million adolescents aged 15–24, and 41.4 million adults aged 25 and older will be overweight or obese. The total number of affected children and adolescents could reach 43.1 million, and adults may reach 213 million by that time. Alarmingly, in most US states, one in three adolescents aged 15–24 is expected to have obesity by 2050 [25].

Obesity during childhood and adolescence may affect not only mental health, social interactions, and physical abilities (such as participation in sports and sleep quality), but can also lead to serious health conditions before adulthood. The growing prevalence poses both immediate health challenges and long-term consequences. In the United States, obesity has also determined a dramatic increase of several cardiovascular risk factors, such as dyslipidemia and hypertension, over the past 3 decades. In addition, type 2 diabetes rates have nearly doubled in the last 20 years. Childhood and adolescent obesity is rarely resolved naturally and is a strong predictor of adult obesity, making early intervention critical.

Monitoring overweight and obesity prevalence at the population level is essential for predicting future disease burden and implementing effective prevention strategies. Addressing this public health crisis requires a deep understanding of the factors contributing to obesity and related metabolic disorders. Sedentary behaviors, especially screen time and lack of physical activity, are now widely recognized as major risk factors for poor metabolic health in children. Diet is equally important. Eating behaviors are shaped by both intrinsic and extrinsic influences, including appetite regulation, food preferences, and environmental cues. These behaviors affect food selection, portion sizes, and overall dietary patterns, which in turn influence children's nutritional status and health outcomes.

Emerging research has emphasized the need to better understand how specific eating behaviors impact diet quality, energy balance, and nutrient intake. However, the connection between eating behaviors and dietary fat intake is still not well explored.

In the study by Silvia García et al., authors evaluated data obtained in a longitudinal randomized controlled trial conducted over 9 months, involving 90 children aged 2–6 years with overweight or obesity. Particularly, the results of this study have shown that reductions in screen-time-related sedentary habits are associated with a lower intake

of total fat and saturated fat. Conversely, increases in screen-time-related sedentary habits correlate with higher consumption of these dietary fats. This increased fat intake has been linked to a specific eating behavior in children, namely the "Desire to Drink", an understanding of which can help to manage children's eating and sedentary behaviors to improve their diets and, consequently, their overall health.

The major strengths of this study are the longitudinal design, which allows a possible cause-effect relationship between children's eating behaviors, screen time, and dietary lipid profiles, and the study's sample size and the inclusion of children from diverse backgrounds strengthen its generalizability and relevance to different populations. In addition, in the present study, authors evaluated a comprehensive assessment of dietary intake, including the measurement of essential fatty acids, which contributes to a more detailed understanding of children's lipid profile and overall nutritional status. Finally, the use of an established tool, such as the child eating behavior questionnaire, allowed for a comprehensive assessment of children's eating behaviors.

Despite these strengths, there are some limitations, particularly related to the self-reported data for certain behaviors, which may introduce biases related to recall accuracy or social desirability, as well as the lack of information regarding other factors, such as physical activity levels, sleep patterns, genetic background, or family environment, that could also be determinants of dietary habits in young children.

Childhood obesity is a multifactorial issue driven by energy imbalance and influenced by a complex interplay of biological, environmental, and socioeconomic factors. Children need varied and balanced diets not only to prevent obesity but also to establish healthy lifelong eating habits. Numerous determinants shape eating behaviors, ranging from physiological traits (e.g., satiety signals, taste sensitivity), psychological characteristics (e.g., emotional state, food preferences), and food literacy, to broader environmental and systemic factors, like food environments and supply chains.

Several theoretical models have outlined the diverse influences on food choices, which vary by age group and differ between children and adults [26]. A complete understanding of these determinants and their impact on metabolic outcomes is essential. Both academic research [27] and international organizations, such as the WHO [28], emphasize the importance of adopting a systems-thinking approach to improve children's diets and reduce the burden of obesity.

Skipping breakfast and nutrient density: influence on obesity, blood pressure, glucose, and cholesterol in elementary school students

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Comments: Healthy eating plays a vital role in preventing both malnutrition and non-communicable diseases. Modern dietary patterns, often high in refined carbohydrates, sugars, and trans fats, have significantly contributed to the increasing

prevalence of childhood obesity [28]. Overconsumption of energy-dense, nutrient-poor foods further worsens this issue. Across Europe, dietary habits vary considerably. For instance, WHO surveillance data shows lower consumption of savory snacks in Northern Europe, while vegetable intake is particularly low in Western Asia, especially among boys [28]. These differences are shaped by a complex mix of socioeconomic, cultural, and environmental factors, such as food accessibility, cultural traditions, and national dietary guidelines. The modern concept of a healthy diet emphasizes balanced macronutrient intake, along with increased consumption of fruits, vegetables, whole grains, legumes, and nuts, while reducing intake of salt, sugar, saturated fats, and highly processed foods. Traditional dietary models, like the Mediterranean diet, offer beneficial frameworks that support long-term health.

One dietary behavior of particular concern is breakfast skipping, which has been associated with an increased risk of overweight and obesity in children. A recent meta-analysis highlighted this trend across different regions, including Western, Asian, and Pacific populations, suggesting a protective role of regular breakfast consumption in maintaining healthy weight among children and adolescents [29]. Although the association between breakfast skipping and cardiometabolic risk is well-documented, the mechanisms remain poorly understood. Moreover, studies examining this association from the perspective of nutrient patterns are limited.

In the study by Mun et al., authors attempted to evaluate the possible associations between breakfast skipping, obesity, and cardiometabolic risk in elementary school students and identify its association with nutritional patterns. Interestingly, by evaluating data on 3,590 elementary school students obtained from the Korea National Health and Nutrition Examination Survey (2013–2020), authors were able to show that elementary school students who skipped breakfast had more frequently obesity and cardiometabolic risk factors. Of note, these associations might be assumed from dietary nutrient patterns characterized by higher fat and sodium density despite lower daily caloric consumption.

The major strength of this study is the use of the nationally representative KNHANES data, which allow a comprehensive analysis of all the possible associations of breakfast frequency with obesity parameters, cardiometabolic risk factors, and nutrient density in elementary school students.

Some limitations, however, need to be highlighted, particularly regarding the cross-sectional study design and the 24-h recall method, that might affect the associations reported. In addition, this study was conducted on a South Korean population. Further evaluation is required to determine whether these findings can be generalized to other ethnic groups.

Although there are some limitations, these data add relevant information on the hypothesized mechanisms linking skipping breakfast habits with obesity and overweight. In fact, the mechanisms linking breakfast skipping with obesity are complex. It is hypothesized that regular breakfast consumption improves metabolic function, enhances insulin sensitivity, and promotes better satiety, particularly when the meal is high in fiber. Skipping breakfast, on the other hand, may lead to increased total energy intake later in the day and reduced physical activity, both of which contribute to weight gain. There is also evidence that breakfast skipping disrupts circadian regulation of metabolism. It has been linked to impaired insulin secretion after meals, delayed insulin peaks, and reduced levels of insulin and C-peptide. Additionally, levels of GLP-1, a hormone that supports insulin secretion, are significantly lower when breakfast is skipped, while glucagon and free fatty acids are elevated. This disruption impairs glucose homeostasis and contributes to metabolic dysregulation throughout the day [30]. Moreover, skipping breakfast has

been associated with reduced expression of key clock genes, such as Per1, Cry1, Ror, Sirt1, and Clock, which are essential for regulating circadian hormone secretion and postprandial glycemia [30]. Other research has linked breakfast skipping to overactivity of the hypothalamic-pituitary-adrenal (HPA) axis and disrupted cortisol rhythms, further emphasizing its systemic effects on metabolic health [31]. Understanding these mechanisms is crucial for developing effective nutritional strategies to combat childhood obesity and support lifelong metabolic health.

Effect of Indo-Mediterranean diet versus calorie-restricted diet in children with non-alcoholic fatty liver disease: a pilot randomized control trial

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Comments: Increased body fat in children and adolescents with overweight and obesity is a key factor linked to the risk of developing nonalcoholic fatty liver disease (NAFLD). This condition affects approximately 4%–11% of all children, with a higher prevalence among those who are overweight or obese. Specifically, NAFLD's global prevalence reaches nearly 45% in specialized child obesity clinics and about 34% in the general population of overweight or obese youths aged 1–19 years, regardless of the diagnostic methods used. Besides obesity, other factors, such as genetic predisposition, epigenetic influences, gut microbiota, eating habits, and sedentary lifestyles, also contribute to the risk of NAFLD. Consequently, NAFLD has become one of the most common chronic liver diseases in both adults and children over recent years. Its rapid increase worldwide highlights the urgent need for new research focused on effectively counteracting this growing health issue.

In the study by Deshmukh et al., researchers investigated whether an Indo-Mediterranean diet is more effective than a standard caloric-restricted diet in treating NAFLD among overweight Indian children and adolescents with biopsy-confirmed disease. The study found that both diets improved various anthropometric, clinical, imaging, and biochemical parameters. However, the Indo-Mediterranean diet showed greater benefits in reducing controlled attenuation parameter (CAP) values and body weight/BMI over 180 days in these patients.

The main strength of this study is the opportunity to have patients with liver biopsy-proven NAFLD. On the other side, the single center design and shorter period of follow-up (6 months) represent the main limitations. However, these encouraging results warrant further research into dietary treatments across different stages of NAFLD. NAFLD represents a spectrum of liver damage that ranges from simple steatosis, characterized by triglyceride accumulation in more than 5% of liver cells or fat fraction above 5.6%, as measured by proton magnetic resonance spectroscopy (HMRS), to more advanced stages involving inflammation and fibrosis known as nonalcoholic steatohepatitis (NASH). Without treatment, the disease can progress to severe liver conditions such as cirrhosis and hepatocellular carcinoma (HCC), although recent evidence suggests that HCC can also develop in fatty liver without cirrhosis [32]. Given that many prenatal and postnatal factors influence

the development of NAFLD, a deeper understanding of its molecular mechanisms is essential. The goal is to design comprehensive strategies, including optimal dietary interventions, to alter the disease's progression and reduce related cardiovascular and metabolic complications. Although no definitive treatment currently exists, several drugs show promise in modifying liver steatosis, inflammation, and fibrosis. Nonetheless, more research is urgently needed, especially in pediatric populations, to identify the best multifactorial approaches for managing this significant condition in children and adolescents.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

Both authors have read and commented on the reviewed manuscripts.

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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. The most widely studied epigenetic mechanism is methylation of DNA, which is 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 the modification of histones, which are structural proteins in the cell nucleus around which DNA 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. DNA methylation and histone modifications also affect telomeres, the protective caps on the ends of chromosomes, by modulating telomere length and the activity of the enzyme telomerase, which maintains telomeres. Telomeres as repetitive DNA-protein structures at the ends of chromosomes protect these from degradation, fraying, and fusing with other chromosomes. Telomere lengths shorten with cell divisions and throughout an individual's lifetime, thereby functioning like a cellular clock limiting cellular lifespan and affecting aging and cancer risk.

For this chapter, the US National Library of Medicine (PubMed) was searched with the terms "(epigenetic*) AND ((nutrit*) OR (growth))" and the filter "humans" for the time period July 1, 2024, to June 30, 2025. 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.

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Sci Adv 2024;10:eadr2084

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Yaskolka Meir A, Wang G, Hong X, Hu FB, Wang X, Liang L
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Maternal vitamin D deficiency is a risk factor for infants' epigenetic gestational age acceleration at birth in Japan: a cohort study
Kawai T, Jwa SC, Ogawa K, Tanaka H, Aoto S, Kamura H, Morisaki N, Fujiwara T, Hata K
Nutrients 2025;17:368

The one-carbon metabolism as an underlying pathway for placental DNA methylation – a systematic review
van Vliet MM, Schoenmakers S, Gribnau J, Steegers-Theunissen RPM
Epigenetics 2024;19:2318516

Cognitive benefits of folic acid supplementation during pregnancy track with epigenetic changes at an imprint regulator
Hilman L, Ondičová M, Caffrey A, Clements M, Conway C, Ward M, Pentieva K, Irwin RE, McNulty H, Walsh CP
BMC Med 2024;22:579

Improvements in lung function following vitamin C supplementation to pregnant smokers are associated with buccal DNA methylation at 5 years of age
Shorey-Kendrick LE, McEvoy CT, Milner K, Harris J, Brownsberger J, Tepper RS, Park B, Gao L, Vu A, Morris CD, Spindel ER
Clin Epigenetics 2024;16:35
Correction: Clin Epigenetics 2024;16:59

Epigenetic signature of very low birth weight in young adult life
Kuula J, Czamara D, Hauta-Alus H, Lahti J, Hovi P, Miettinen ME, Ronkainen J, Eriksson JG, Andersson S, Järvelin MR, Sebert S, Räikkönen K, Binder EB, Kajantie E
Pediatr Res 2025;97:229–238

Parental epigenetic age acceleration and risk of adverse birth outcomes: the Norwegian mother, father and child cohort study
Magnus MC, Lee Y, Carlsen EØ, Arge LA, Jugessur A, Kvalvik LG, Morken NH, Ramlau-Hansen CH, Myrskylä M, Magnus P, Håberg SE
BMC Med 2024;22:554
Correction: BMC Med 2025;23:9

Epigenetic clock at birth and childhood blood pressure trajectory: a prospective birth cohort study
Hu J, Yaskolka Meir A, Hong X, Wang G, Hu FB, Wang X, Liang L
Hypertension 2024;81:e113–e124

Is exposure to pesticides associated with biological aging? A systematic review and meta-analysis
Zuo S, Sasitharan V, Di Tanna GL, Vonk JM, De Vries M, Sherif M, Ádám B, Rivillas JC, Gallo V
Ageing Res Rev 2024:99:102390

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

Abnormal DNA methylation within HPA-axis genes years after paediatric critical illness
Coppens G, Vanhorebeek I, Güiza F, Derese I, Wouters PJ, Téblick A, Dulfer K, Joosten KF, Verbruggen SC, Van den Berghe G
Clin Epigenetics 2024;16:31

Developmental origins of psycho-cardiometabolic multimorbidity in adolescence and their underlying pathways through methylation markers: a two-cohort study
Choudhary P, Ronkainen J, Carson J, Karhunen V, Lin A, Melton PE, Jarvelin MR, Miettunen J, Huang RC, Sebert S
Eur Child Adolesc Psychiatry 2024;33:3157–3167

Epigenetic timing effects on child developmental outcomes: a longitudinal meta-regression of findings from the Pregnancy and Childhood Epigenetics Consortium
Neumann A, Sammallahti S, Cosin-Tomas M, Reese SE, Suderman M, Alemany S, Almqvist C, Andrusaityte S, Arshad SH, Bakermans-Kranenburg MJ, Beilin L, Breton C, Bustamante M, Czamara D, Dabelea D, Eng C, Eskenazi B, Fuemmeler BF, Gilliland FD, Grazuleviciene R, Håberg SE, Herberth G, Holland N, Hough A, Hu D, Huen K, Hüls A, Jarvelin MR, Jin J, Julvez J, Koletzko B, Koppelman GH, Kull I, Lu X, Maitre L, Mason D, Melén E, Merid SK, Molloy PL, Mori TA, Mulder RH, Page CM, Richmond RC, Röder S, Ross JP, Schellhas L, Sebert S, Sheppard D, Snieder H, Starling AP, Stein DJ, Tindula G, van IJzendoorn MH, Vonk J, Walton E, Witonsky J, Xu CJ, Yang IV, Yousefi PD, Zar HJ, Zenclussen AC, Zhang H, Tiemeier H, London SJ, Felix JF, Cecil C
Genome Med 2025;17:39

Cesarean delivery and blood DNA methylation at birth and childhood: meta-analysis in the Pregnancy and Childhood Epigenetics Consortium

Wang S[1], Casey E[2], Sordillo J[3], Aguilar-Lacasaña S[4,5,6], Morales Berstein F[7,8], Biedrzycki RJ[9], Brescianini S[10], Chen S[11], Hough A[12], Isaevska E[13], Kim WJ[14], Lecorguillé M[15], Li SS[16], Page CM[17,18], Park J[19], Röder S[20], Salontaji K[21], Santorelli G[12], Sun Y[22,23], Won S[19,24], Zillich E[25], Zillich L[26,27], Annesi-Maesano I[28], Arshad SH[4,5,6], Bustamante M,[21,29] Cecil CAM[7,8], Elliott HR[30], Ewart S[31,32], Felix JF[33], Gagliardi L[17,34], Håberg SE[20], Herberth G[15], Heude B[35], Holloway JW[2,36], Huels A[37], Karmaus W[22,23], Koppelman GH[38], London SJ[39,40], Mumford SL[10], Nisticò L[13], Popovic M[33], Rusconi F[39,40], Schisterman EF[41], Stein DJ[42], Send T[43,44], Tiemeier H[23,45], Vonk JM[4,5,6], Vrijheid M[16], Wiemels JL[25], Witt SH[12], Wright J, Yeung EH[40], Zar HJ[46], Zenclussen AC[20], Zhang H[37], Chavarro JE[1,44], Hivert MF[3,47]

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Health, University of Memphis, Memphis, TN, USA; [38]National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; [39]Department of Biostatistics, Epidemiology and Informatics and Department of Obstetrics and Gynecology, Perelman School of Medicine, Philadelphia, PA, USA; [40]Epidemiology Branch, Division of Population Health Research, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA; [41]South African Medical Research Council (SAMRC) Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Rondebosch, South Africa; [42]Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [43]Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [44]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [45]University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, The Netherlands; [46]South African Medical Research Council (SAMRC) Unit on Child and Adolescent Health, Department of Paediatrics, University of Cape Town, Rondebosch, South Africa; [47]Diabetes Unit, Massachusetts General Hospital, Boston, MA, USA
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Comments: Siwen Wang and coworkers from the Pregnancy and Childhood Epigenetics Consortium performed a meta-analysis of epigenome-wide association studies on associations between mode of delivery and blood DNA methylation at birth, as well as its persistence in early childhood. They included 9,833 term newborns from as many as 19 pregnancy cohorts, and 2,429 children aged 6–10 years from 6 child cohorts. The results indicate that 6 CpGs in cord blood were associated with cesarean delivery, but no CpGs in childhood were associated with delivery mode. This is a very impressive study with a large number of included cohorts and individuals from different geographic locations, which add strength to the results and their generalizability. Cesarean delivery is linked to a variety of differences in hormonal, physical, microbial, and medical exposures compared to vaginal birth, as well as a higher risk of adverse health outcomes, including obesity, infections, allergy, diabetes, malignancies, and altered neurodevelopment. Therefore, it is of great interest to explore possible molecular mechanisms that may mediate the effects of cesarean delivery on offspring health. However, the limited and relatively small differences in DNA methylation related to birth mode in this study do not provide indications for a major role of this mechanism.

Newborn DNA methylation age differentiates long-term weight trajectories: the Boston Birth Cohort

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Comments: Anat Yaskolka Meir from the Harvard T.H. Chan School of Public Health and coworkers assessed gestational age (GEAA) estimated by DNA methylation assessed in cord blood cells (GAmAge) of 831 newborn infants from a US low-income, multi-ethnic birth cohort. GAmAge was related to categories of BMI trajectories until the age of 18 years. GAmAge could differentiate a consistently normal BMI pattern from overweight development in preschool or school age. The longitudinal design with a long follow-up period is a major strength of this study. Provided that results will be replicated in other populations, GAmAge might serve to help enable early prediction of later overweight risk.

Maternal vitamin D deficiency is a risk factor for infants' epigenetic gestational age acceleration at birth in Japan: a cohort study

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Comments: Tomoko Kawai from the National Research Institute for Child Health and Development in Tokyo, Japan, and collaborators studied 157 mother-child pairs from a Japanese cohort study conducted from 2010 to 2013. Maternal serum vitamin D concentrations determined in the 2nd trimester of pregnancy were negatively associated with epigenetic gestational age acceleration at birth, based on cord blood cell methylation analysis. In contract, there was no association with cord blood serum vitamin D. This study replicates the findings of previous publications reporting an association between low serum 25(OH)D levels and the fetal epigenetic clock, which suggests possible added benefits of securing an adequate vitamin D status among pregnant women.

The one-carbon metabolism as an underlying pathway for placental DNA methylation – a systematic review

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https://pubmed.ncbi.nlm.nih.gov/38484284/

Comments: Marjolein van Vliet and coworkers from the Erasmus Medical Center, Rotterdam, The Netherlands, performed a systematic review on the associations between one-carbon metabolism, modulated by the intake of one-carbon moieties or multivitamin supplements, and DNA methylation in human placenta cells. They evaluated a large number of 22 studies, including 16 observational and 3 interventional clinical studies, 2 in vitro studies on human placental cell lines, and one observational study that combined clinical and in vitro work. The exposures were intakes of folate and folic acid, homocysteine, choline, S-adenosylmethionine and S-adenosylhomocysteine, combination supplements, as well as dietary patterns reflecting differences in intake of one-carbon moieties. Most clinical studies used a gene-specific approach. Overall, one-carbon moieties were not associated with global methylation, although conflicting outcomes were reported for choline. With genome-wide approaches, few differentially methylated sites were associated with S-adenosylmethionine, S-adenosylhomocysteine, or dietary patterns. Most studies taking a gene-specific approach found site-specific relationships, specifically in genes involved in growth and development, but the overlap among studies was limited. Generalizable conclusions that can be drawn are limited due to the considerable heterogeneity among studies with respect to exposures, outcomes, sample size, and study design, as well as observed differences in DNA methylation between female and male offspring, the part of placenta that was sampled, timing of exposure, and underlying genotype, all of which may influence the results obtained. Moreover, most available studies are of observational nature and did not adequately adjust for potential confounders, which is important since dietary habits and the use of supplements tend to be associated with other lifestyle patterns that may affect DNA methylation, for example, smoking, physical activity, and body mass, as well as socioeconomic status.

Cognitive benefits of folic acid supplementation during pregnancy track with epigenetic changes at an imprint regulator

Hilman L[1], Ondičová M[1,2], Caffrey A[3], Clements M[3], Conway C[1], Ward M[3], Pentieva K[3], Irwin RE[1], McNulty H[3], Walsh CP[1,4]

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Comments: Luke Hilman et al. from the Ulster University, Northern Ireland, analyzed samples from a randomized controlled trial (RCT). Enrolled in the trial were women with singleton pregnancies who took 400 µg of folic acid per day during the first trimester. They were randomly assigned to receive from the end of their first pregnancy trimester until the end of pregnancy either 400 µg/day of FA (n = 96) or placebo (n = 94). The authors analyzed methylation at the ZFP57 region in cord blood cells. The ZFP57 gene encodes a zinc finger protein containing a KRAB domain, which appears to

function as a transcriptional repressor and may also drive DNA methylation. Fully methylated alleles of an alternative upstream promoter of ZFP57 were associated with lower results in a subtest of the Wechsler Intelligence Scale for Children at the age of 11 years, the Symbol Search and Cancellation subtest. Although the randomized controlled design of this study is a particular strength, the sample size of this study is not large and the results would need replication. Nevertheless, the findings are impressive and point to a possible epigenetic mechanism through which an added folic acid supply during the second and third trimesters of pregnancy could benefit later offspring cognition at later school age.

Improvements in lung function following vitamin C supplementation to pregnant smokers are associated with buccal DNA methylation at 5 years of age

Shorey-Kendrick LE[1], McEvoy CT[2], Milner K[3], Harris J[3], Brownsberger J[3], Tepper RS[4], Park B[5], Gao L[5], Vu A[6], Morris CD[6], Spindel ER[1]

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https://pubmed.ncbi.nlm.nih.gov/38413986/

Correction: *https://pubmed.ncbi.nlm.nih.gov/38664854/*

Comments: Lyndsey Shorey-Kendrick from the Oregon Health and Science University, Beaverton, OR, USA, and coworkers performed epigenome-wide association studies based on buccal cell DNA methylation in 5-year-old children whose mothers were smokers during pregnancy and participated in a randomized controlled trial. They were assigned to supplementation with 500 mg of vitamin C/day (78 children included in this follow-up study) or placebo (80 children). Prenatal vitamin C treatment was linked to 457 differentially methylated CpGs in the offspring at age 5 years ($q < 0.05$ after FDR correction). Current wheeze was associated with 782 candidate differentially methylated CpG sites, and 19 differentially methylated regions ($p < 0.001$). Although the number of subjects in the included sample is limited, the impact of the randomized vitamin C supply in pregnancy on buccal DNA methylation on children followed-up at 5 years after birth is impressive and likely to have originated prenatally. The shown link to lung function at early school age is an additional important finding, suggesting a relevant impact of vitamin C supply for smoking pregnant women for offspring health.

Epigenetic signature of very low birth weight in young adult life

Kuula J[1,2], Czamara D[3], Hauta-Alus H[1,4,5,6], Lahti J[7], Hovi P[1], Miettinen ME[1], Ronkainen J[8], Eriksson JG[9,10,11], Andersson S[5], Järvelin MR[8,12], Sebert S, Räikkönen K[7], Binder EB[3], Kajantie E[1,5,13,14]

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Comments: Very low birthweight has previously been associated with epigenetic alterations in the neonatal period and infancy. In contrast, information on persistent changes at later ages is limited. Juho Kuula from the University of Helsinki, Finland, and coworkers assessed DNA methylation in peripheral venous blood cells in a discovery cohort at a mean age of 22 years, including 157 subjects born with very low birthweight (VLBW) and 161 controls born at full term. They found 66 differentially methylated CpGs associated with VLBW ($p < 0.05$, FDR-corrected). The authors performed meta-analyses to assess whether these 66 CpG sites could be validated in subjects from four other cohort studies. They identified 5 hypermethylated CpGs that were significantly associated with VLBW and with low birth weight. The consistency of these results is stunning and suggests that the well-known relationship of being born with VLBW or low birth weight with a variety of adverse later health outcomes could in part be mediated by epigenetic mechanisms.

Parental epigenetic age acceleration and risk of adverse birth outcomes: the Norwegian mother, father and child cohort study

Magnus MC[1], Lee Y[1], Carlsen EØ[1], Arge LA[1], Jugessur A[1,2], Kvalvik LG[2], Morken NH[1,3], Ramlau-Hansen CH[4], Myrskylä M[5,6,7], Magnus P[1], Håberg SE[1,2]

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Comments: There is little information on associations between maternal epigenetic age acceleration and adverse outcomes at birth, and no studies on the impact of paternal epigenetic age acceleration. Maria Magnus from the Norwegian Institute of Public Health, Oslo, Norway, and coworkers assessed parental epigenetic age with 7 epigenetic clocks in a very large sample of 2,198 mothers and 2,193 fathers participating in the Mother, Father, and Child Cohort Study in Norway. They found higher epigenetic age acceleration of mothers – but not of fathers – associated with significantly lower length of gestation with 5 of the 6 epigenetic clocks used. In line with these findings, higher epigenetic age acceleration also tended to be associated with an increased risk of preterm birth across most clocks, although the confidence intervals were wide, and a significant risk increase for spontaneous preterm birth was found with two clocks. The important results from this very large study suggest that an accelerated biological age of the mother, in addition to her chronological age, can increase the risk for preterm delivery.

Epigenetic clock at birth and childhood blood pressure trajectory: a prospective birth cohort study

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Comments: Jie Hu, from the Harvard T.H. Chan School of Public Health, Boston, USA, and collaborators explored cord blood DNA methylation data and blood pressure at 3–15 years of age in 500 boys and 440 girls participating in the Boston Birth Cohort study. The authors found that systolic and diastolic blood pressure percentiles based on repeated measures tended to be inversely associated with epigenetic methylation age acceleration at birth. Systolic blood pressure percentiles were significantly inversely associated with methylation age acceleration in all children and in boys, but not in girls, but statistical significance was lost after adjusting for cord blood cell composition. Subgroup analyses showed interactions with both preterm birth and sex. These novel findings add further indications to the previously reported indications for developmental origins of high blood pressure and the influence of both preterm birth and sex, which can impact on later cardiovascular disease risk.

Is exposure to pesticides associated with biological aging? A systematic review and meta-analysis

Zuo S[1,2], Sasitharan V[3], Di Tanna GL[4], Vonk JM[2], De Vries M[2], Sherif M[5], Ádám B[5], Rivillas JC[6], Gallo V[1]

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Ageing Res Rev 2024:99:102390

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Comments: Shanshan Zuo, University of Groningen, The Netherlands, and collaborators performed a systematic review exploring whether exposure to pesticides is associated with biological effects, given that pesticide exposure has been linked to the risk of various adverse health outcomes such as birth defects, asthma, diabetes, neurologic diseases, and cancers. They included a large number of 20 studies with 10,368 individuals, of which 16 reported on telomere length and 4 on epigenetic clocks. The authors found that no significant effects were found on either epigenetic clocks or telomere length. However, telomere length was shorter in higher-exposed populations after removing influential effect sizes or low-quality studies. This appears to be the first systematic review evaluating the available evidence on the association between pesticide exposure and biological aging. The results show considerable heterogeneity between available studies, which includes different exposures mostly to pesticide mixtures and not defined individual substance, and a predominance of cross-sectional studies, which limit the level of available evidence. Nonetheless, the results suggest possible adverse effects of high pesticide exposure on accelerated aging, which could be related to reported adverse health outcomes.

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

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

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Comments: In this paper, Ines Verlinden from the Catholic University Leuven, Belgium, and collaborators report on a follow-up study including 818 individuals who were former pediatric intensive care unit (PICU) patients at an age between 0 and 17 years and had participated in a randomized clinical trial comparing earlier or later use of parenteral nutrition. At follow-up visits 2 and 4 years after PICU treatment, anthropometric measurements were performed and buccal mucosal cells were collected at the 2-year visit for DNA methylation measurements, as well as in a reference group of 392 matched healthy children. The former PICU patients grew less in height, but gained more weight than matched healthy children over the 4-year follow-up. Compared to the group of healthy children, former PICU children showed a significantly lower epigenetic age, with the deviation becoming apparent from a mean chronological age of about 8 years or older. In adults, a lower epigenetic age is associated with health benefits and a lesser risk of age-related diseases, but less is known on the possible health impact in children and a potential impact on lesser growth. The reasons for the observed difference of epigenetic age changes in younger and older children, respectively, remain to be explored. Also, it would be valuable to know whether the observed differences were present immediately after PICU discharge, and how they evolved over time.

Abnormal DNA methylation within HPA-axis genes years after paediatric critical illness

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

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Comments: In this paper, Grégoire Coppens from the Catholic University Leuven, Belgium, reports on further analyses of the data reported in the publication by Ines Verlinden et al. cited above. Based on the observation that stress during critical illness can activate the hypothalamus-pituitary-adrenal (HPA) axis with an acute rise in total and free cortisol, the authors explored whether DNA methylation in buccal mucosa cells is altered within genes encoding key proteins within the different levels of the HPA axis and glucocorticoid signaling, and whether this may be modulated by glucocorticoid treatment during intensive care. The results in former PICU patients show different DNA methylation of 26 CpG sites, which were mostly hypomethylated, compared to health controls. These differences were not sex-dependent, while age at PICU treatment affected 4 differentially methylated CpG sites where the degree of hypomethylation increased with age at treatment. Glucocorticoid therapy during PICU was associated with a small increase in methylation difference in 5 CpG sites, with a mean difference of about 3%. Methylation in the gene loci FKBP5 and AKR1D1 were associated with cognitive and behavioral outcomes 2 years after PICU treatment. The observations reported here support long-term surveillance of children after PICU

treatment and also call for caution regarding the use of glucocorticoids in these patients. Future research exploring underlying mechanisms as well as cross-tissue validation could help inform therapeutic strategies that contribute to mitigating the epigenetic and long-term health impact of intensive care treatment.

Developmental origins of psycho-cardiometabolic multimorbidity in adolescence and their underlying pathways through methylation markers: a two-cohort study

Choudhary P[1], Ronkainen J[1], Carson J[2,3], Karhunen V[1,4], Lin A[2,5], Melton PE[3,6], Jarvelin MR[7,8,9,10], Miettunen J[1,10], Huang RC[2,11,12], Sebert S[1]

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Comments: Priyanka Choudhary and coworkers from the University of Oulu, Finland; the University of Western Australia, Perth, WA, Australia; and the Imperial College, London, UK, explored how prenatal exposures may influence psycho-cardiometabolic multimorbidity in adolescence, mediated through epigenetic biomarkers. They evaluated data from two cohorts, the Northern Finland Birth Cohort 1986 (490 subjects) and the Raine Study from Australia (995 individuals). The authors applied factor analysis to group prenatal exposures into three latent factors (body mass index, socio-obstetric profile [SOP], and lifestyle), and adolescent psycho-cardiometabolic traits into four latent factors (anthropometric, insulin-triglycerides, blood pressure, and mental health). The results show prenatal BMI having the strongest positive direct effect on psycho-cardiometabolic multimorbidity, whereas the socio-obstetric profile showing a modest negative direct effect, which points to protective factors such as marital status or parity. The lifestyle latent factor exerted indirect effects via a DNA methylation score reflecting maternal smoking during pregnancy, and an epigenetic age estimate capturing phenotypic aging, especially in the Raine Study and modestly in the Norwegian cohort. Overall, this is an elegant, hypothesis-driven cross-cohort study demonstrating that prenatal adversities – particularly maternal body mass index and lifestyle exposures – are associated with adolescent psycho-cardiometabolic multimorbidity, partly via epigenetic pathways. Importantly, these relationships are consistent across two culturally and genetically diverse cohorts. The authors' approach is both methodologically innovative and biologically plausible.

Epigenetic timing effects on child developmental outcomes: a longitudinal meta-regression of findings from the Pregnancy and Childhood Epigenetics Consortium

Neumann A[1], Sammallahti S[2,3], Cosin-Tomas M[4,5,6], Reese SE[7], Suderman M[8], Alemany S[9,10,11], Almqvist C[12], Andrusaityte S[13], Arshad SH[14], Bakermans-Kranenburg MJ[15], Beilin L[16], Breton C[17], Bustamante M[4,5,6], Czamara D[18], Dabelea D[19], Eng C[20], Eskenazi B[21], Fuemmeler BF[22], Gilliland FD[23], Grazuleviciene R[13], Håberg SE[24], Herberth G[25], Holland N[26], Hough A[27], Hu D[28], Huen K[26], Hüls A[29,30,31], Jarvelin MR[32,33,34,35], Jin J[36], Julvez J[37], Koletzko B[38], Koppelman GH[39], Kull I[40], Lu X[41], Maitre L[42,43,44], Mason D[27], Melén E[45], Merid SK[45], Molloy PL[46], Mori TA[16], Mulder RH[47], Page CM[48], Richmond RC[8], Röder S[25], Ross JP[49], Schellhas L[50], Sebert S[51], Sheppard D[52], Snieder H[41], Starling AP[53], Stein DJ[54], Tindula G[55], van IJzendoorn MH[56,57,58], Vonk J[59,60], Walton E[61], Witonsky J[62], Xu CJ[63,64], Yang IV[65], Yousefi PD[8], Zar HJ[66], Zenclussen AC[25], Zhang H[67], Tiemeier H[1,68], London SJ,[69] Felix JF[70,71], Cecil C[1,72,73]

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Comments: Alexander Neumann from the Erasmus Medical Center, Rotterdam, The Netherlands, and coworkers used longitudinal meta-regression models to explore previously published meta-analyses from the Pregnancy and Childhood Epigenetics Consortium to examine DNA methylation data at birth as well as cross-sectionally in childhood associated with child health outcomes, specifically attention deficit hyperactivity, psychopathology, sleep duration, body mass index, and asthma. They found epigenetic associations with child health outcomes highly developmental-stage specific. DNA methylation markers at birth did not reliably align with markers identified during childhood. They further report that the CpG sites associated with health outcomes that varied across timepoints were enriched for neural pathways, suggesting potential particular relevance to neurodevelopmental programming. By applying meta-regression across multiple cohorts, the study provides robust insights across diverse populations, enhancing the reliability and generalizability of the findings. The authors' emphasis on DNA methylation's developmental timing is conceptually refreshing and addresses a growing concern: that biomarkers found at one life stage may lack relevance at another and hence may undermine the generalizability of findings across developmental stages. Thereby, the study underlines the necessity of longitudinal epigenetic studies with repeated DNA methylation assessments to better understand the dynamic interplay between epigenetics, development, and long-term health and to enable the creation of more accurate, generalizable epigenetic biomarkers.

Conflict of Interest Statement

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

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Nutrition and Growth in Preterm and Term Infants

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Introduction

During this year's review period, we will highlight several studies exploring growth in preterm infants and its relationship to nutrition and later outcomes. Advances range from updated growth charts that better identify suboptimal growth to AI-driven systems for personalized nutritional support. In addition, the importance of standardized reporting in nutrition research, early phosphate monitoring, and sustained nutritional support beyond infancy has been increasingly recognized. Furthermore, recent work reinforces the critical value of breastfeeding support – particularly for overlooked populations such as late preterm infants – and the impact of family-integrated care strategies, including kangaroo mother care. Together, these findings underscore the need for a multifaceted approach to optimizing nutrition in preterm infants, integrating technological innovation, systematic quality improvement, and family-centered care. For term infants, this year's highlighted research is on the topics breastfeeding, food allergy, and breastfeeding substitutes. These studies question routine iron supplementation in breastfed infants from low-risk populations, reveal breastfeeding's protective effects against certain autoimmune diseases, and demonstrate that extended breastfeeding can mitigate risks associated with rapid infant growth. Additionally, new insights into human milk composition beyond 6 months support extended milk donation policies, while reviews of specialized formulas for functional gastrointestinal disorders and formulas supplemented with manufactured human-identical milk oligosaccharides call for more rigorous evidence before widespread adoption.

Key articles reviewed for this chapter

Preterm Infants

Fenton third-generation growth charts of preterm infants without abnormal fetal growth: a systematic review and meta-analysis
Fenton TR, Elmrayed S, Alshaikh BN
Paediatr Perinat Epidemiol 2025;39:543–555

Measures of nutrition intake and growth reported in preterm nutrition studies: a scoping review
Meiliana M, Bloomfield FH, Harding JE, Lin L
JPEN J Parenter Enteral Nutr 2025 May 7. doi: 10.1002/jpen.2768. Online ahead of print

Associations between growth and childhood body composition in very preterm, late preterm and term children
Nyakotey DA, Gamble GD, McKinlay CJD, Bloomfield FH, Harding JE, on behalf of the Neonatal Nutritional Interventions Early School-Age Outcomes Studies (NIEOS) Collaboration
Acta Paediatr 2025;114:1030–1042

Early hypophosphataemia and refeeding syndrome in extremely low birthweight babies and outcomes to 2 years of age: secondary cohort analysis from the ProVIDe trial
Ford N, Bloomfield FH, Jiang Y, Cormack BE
Arch Dis Child Fetal Neonatal Ed 2025;110:157–164

Postnatal growth and neurodevelopment at 2 years' corrected age in extremely low birthweight infants
Nyakotey DA, Clarke AM, Cormack BE, Bloomfield FH, Harding JE, on behalf of the ProVIDe Study Group
Pediatr Res 2024;96:436–449

Early nutritional influences on brain regions related to processing speed in children born preterm: a secondary analysis of a randomized trial
Bando N, Sato J, Vandewouw MM, Taylor MJ, Tomlinson C, Unger S, Asbury MR, Law N, Branson HM, O'Connor DL
JPEN J Parenter Enteral Nutr 2024;48:778–786

Early postnatal weight loss and its association with outcomes in very preterm neonates: a systematic review and meta-analysis
Kothapally S, Rath C, Gowda BB, Sharma J, Patole SK, Rao S
Neonatology 2025;122:477–494

Mother's own milk provision during the first 12 weeks of life by gestational age
Patel AL, Wilson J, Holmes M, Johnson TJ
JAMA Netw Open 2025;8:e250024

Differences between neonatal units with high and low rates of breast milk feeding for very preterm babies at discharge: a qualitative study of staff experiences
McLeish J, Aloysius A, Gale C, Quigley M, Kurinczuk JJ, Alderdice F
BMC Pregnancy Childbirth 2024;24:863

The relationship of early expressed milk quantity and later full breastmilk feeding after very preterm birth: a cohort study
Levene I, O'Brien F, Fewtrell M, Quigley MA
Matern Child Nutr 2025;21:e13719

Effect of kangaroo mother care in low birth weight infants on human milk intake: a randomized controlled trial
Sinha B, Mazumder S, Thakur A, Devi S, More D, Ashorn P, Sommerfelt H, Kurpad A, Bhandari N
Am J Clin Nutr 2025;121:1109–1116

AI-guided precision parenteral nutrition for neonatal intensive care units
Phongpreecha T, Ghanem M, Reiss JD, Oskotsky TT, Mataraso SJ, De Francesco D, Reincke SM, Espinosa C, Chung P, Ng T, Costello JM, Sequoia JA, Razdan S, Xie F, Berson E, Kim Y, Seong D, Szeto MY, Myers F, Gu H, Feister J, Verscaj CP, Rose LA, Sin LWY, Oskotsky B, Roger J, Shu CH, Shome S, Yang LK, Tan Y, Levitte S, Wong RJ, Gaudillière B, Angst MS, Montine TJ, Kerner JA, Keller RL, Shaw GM, Sylvester KG, Fuerch J, Chock V, Gaskari S, Stevenson DK, Sirota M, Prince LS, Aghaeepour N
Nat Med 2025;31:1882–1894

Term Infants

Breastfeeding

Effect of low-dose iron supplementation on early development in breastfed infants: a randomized clinical trial
Svensson L; Chmielewski G, Czyżewska E, Domellöf M, Konarska Z, Pieścik-Lech M, Späth C, Szajewska H, Chmielewska A
JAMA Pediatr 2024;178:649–656

Effect of iron supplementation in healthy exclusively breastfed infants: a systematic review and meta-analysis
Tian K, Liu W, Huang Y, Zhou R, Wang Y
Front Pediatr 2025;13:1587457

Association between breastfeeding and the risk of autoimmune diseases: a systematic review and meta-analysis
Li WJ, Gao YC, Hu X, Tan YT, Deng JJ, Pan HF, Tao FF
Autoimmunity Rev 2025;24:103801

Breastfeeding and infant growth in relation to childhood overweight – a longitudinal cohort study
Leth-Møller M, Kampmann U, Hede S, Ovesen PG, Hulman A, Knorr S
Am J Clin Nutr 2025;121:835–842

Macronutrient concentrations in human milk beyond the first half year of lactation: a cohort study
Muts J, Lukowski JIA, Twisk JWR, Schoonderwoerd A, van Goudoever JB, van Keulen BJ, van den Akker CHP
Arch Dis Child Fetal Neonatal Ed 2025;110:248–252

Food Allergy

Probiotics in infants for prevention of allergic disease
Wang HZ, Hayles EH, Fiander M, Sinn JKH, Osborn DA
Cochrane Database Syst Rev 2025;6(6):CD006475

Growth, safety and tolerance in infants fed rice protein hydrolysate formula: the GRITO randomised controlled trial
Lemoine A, Nieto-García A, Nieto-Cid M, Espín-Jaime B, Mazón A, Salhi H, Salamouras D, Kalach N, de Castellar-Sansó R, Delgado Ojeda J, Navas-López VM
Nutrients 2025;17:162

Breast Milk Substitutes

Infant formulas for the treatment of functional gastrointestinal disorders: a position paper of the ESPGHAN Nutrition Committee
Haiden N, Savino F, Hill S, Kivelä L, De Koning B, Köglmeier J, Luque V, Moltu SJ, Norsa L, Saenz De Pipaon M, Verduci E, Bronsky J
J Pediatr Gastroenterol Nutr 2024;79:168–180

Technical review by the ESPGHAN special interest group on gut microbiota and modifications on the health outcomes of infant formula supplemented with manufactured human milk oligosaccharides
Hojsak I, Dinleyici EC, van den Akker CHP, Domellöf M, Haiden N, Szajewska H, Vandenplas Y, the ESPGHAN Special Interest Group on Gut Microbiota and Modifications
J Pediatr Gastroenterol Nutr 2025 Mar 24. Online ahead of print

Preterm Infants

We begin with a discussion of the updated Fenton preterm growth charts [1], followed by a review of how growth and nutrition are reported in the literature [2]. We then examine several cohort studies, ranging in size and scope, that assess the associations between growth, nutrition, and various clinical outcomes [3–7].

Fenton third-generation growth charts of preterm infants without abnormal fetal growth: a systematic review and meta-analysis

Fenton TR[1], Elmrayed S[2], Alshaikh BN[1,3]

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Measures of nutrition intake and growth reported in preterm nutrition studies: a scoping review

Meiliana M, Bloomfield FH, Harding JE, Lin L

Liggins Institute, University of Auckland, Auckland, New Zealand
JPEN J Parenter Enteral Nutr 2025 May 7. doi: 10.1002/jpen.2768. Online ahead of print
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https://pubmed.ncbi.nlm.nih.gov/40342174/

Associations between growth and childhood body composition in very preterm, late preterm and term children

Nyakotey DA[1], Gamble GD[1], McKinlay CJD[2,3], Bloomfield FH[1], Harding JE[1], on behalf of the Neonatal Nutritional Interventions Early School-Age Outcomes Studies (NIEOS) Collaboration

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https://pubmed.ncbi.nlm.nih.gov/39652519/

Early hypophosphataemia and refeeding syndrome in extremely low birthweight babies and outcomes to 2 years of age: secondary cohort analysis from the ProVIDe trial

Ford N[1], Bloomfield FH[1], Jiang Y[2], Cormack BE[1,3]

[1]Liggins Institute, University of Auckland, Auckland, New Zealand; [2]Department of Statisitics, University of Auckland, Auckland, New Zealand; [3]Starship Child Health, Auckland City Hospital, Auckland, New Zealand
Arch Dis Child Fetal Neonatal Ed 2025;110:157–164
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https://pubmed.ncbi.nlm.nih.gov/39122562/

Postnatal growth and neurodevelopment at 2 years' corrected age in extremely low birthweight infants

Nyakotey DA[1], Clarke AM[1], Cormack BE[1,2], Bloomfield FH[1], Harding JE[1], on behalf of the ProVIDe Study Group

[1]Liggins Institute, University of Auckland, Auckland, New Zealand; [2]Starship Child Health, Auckland City Hospital, Auckland, New Zealand
Pediatr Res 2024;96:436–449
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https://pubmed.ncbi.nlm.nih.gov/38337041/

Early nutritional influences on brain regions related to processing speed in children born preterm: a secondary analysis of a randomized trial

Bando N[1,2], Sato J[3,4,5], Vandewouw MM[4,5,6,7], Taylor MJ[3,4,5,8,9], Tomlinson C[1,8,10], Unger S[1,8,10,11], Asbury MR[1,2], Law N[2], Branson HM[4,9], O'Connor DL[1,2,11]

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Early postnatal weight loss and its association with outcomes in very preterm neonates: a systematic review and meta-analysis

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Comments: The third version of the well-known Fenton Growth Charts for Preterm Infants has now been published [1]. This comprehensive systematic review and meta-analysis encompass data from 4.8 million births, including approximately 175,000 infants born before 30 weeks gestation, from 15 countries over the last 2 decades. It represents the most robust dataset ever assembled for both fetal and preterm growth assessment, and includes nomograms for length and head circumference alongside weight. Besides the substantially higher number of assessed infants, another major change compared to the previous version is that these new charts are now prescriptive (also called normative) growth charts rather than descriptive ones. This means that rather than simply describing observed growth patterns in preterm populations, they prescribe optimal growth by focusing exclusively on infants without abnormal fetal growth. The researchers excluded infants born to mothers with hypertension, diabetes, or other conditions affecting fetal development, as well as those delivered through provider-initiated preterm birth. As a result, the weights corresponding to all percentiles are now slightly higher, especially for infants below 30 weeks gestation.

Clinically, these charts will likely identify more infants as small-for-gestational-age, which reflects a more accurate assessment of which infants may have experienced suboptimal fetal growth. At the same time, the charts maintain harmonization with World Health Organization (WHO) growth standards at 50 weeks gestational age and support precise daily growth plotting once an infant is born preterm and admitted to the neonatal intensive care unit (NICU). It would represent a significant improvement if these updated curves are widely implemented in daily clinical care and scientific research, as this would facilitate benchmark comparisons and improve interclinical comparability.

Researchers from the Auckland group in New Zealand were particularly productive last year. First, in a comprehensive scoping review, they assessed 250 publications on nutrition and growth in preterm infants published over 5 recent years and evaluated how accurately and precisely nutritional intake and growth were reported [2]. The authors revealed concerning inconsistencies in research reporting that have important implications for the field. Only 4% of studies explained how nutrition intake was calculated, despite this being fundamental to study interpretation and reproducibility. Weight reporting showed dramatic variability, with five different measurement methods and 13 different ways of calculating weight gain across multiple timepoints being used. Additionally, 26% of studies failed to specify their weight gain calculation methods at all, while those that did provide this information used five different approaches. This variability severely limits our ability to compare findings across studies and to develop robust evidence-based clinical guidelines. The researchers emphasize the urgent need again for standardized reporting frameworks, particularly for documenting actual nutrition intake and for reporting growth outcomes using both absolute values and Z-scores, which would significantly improve research utility and clinical translation. Previously, attempts to standardize these outcomes apparently failed [8, 9].

A New Zealand study involving 1,125 children examined how birth timing affects long-term body composition outcomes [3]. The researchers compared children born very preterm (VPT; 23–31 weeks), late preterm (LPT; 35–37 weeks), and at full-term, measuring their growth and body composition at both 2 and 6 years of age using bioelectrical impedance analysis. The key findings revealed that VPT children remained smaller with lower fat mass and fat-free mass indices at both 2 and 6 years compared to term children, suggesting incomplete catch-up growth. However, LPT children showed no significant differences from term peers at either timepoint, which suggests successful catch-up growth in this group. Importantly, weight growth from 2 to 6 years emerged as the strongest predictor of childhood body composition across all groups – this was more influential than early postnatal growth. This finding highlights the critical importance of continued nutritional support and monitoring beyond infancy for optimizing long-term outcomes in preterm children.

From a secondary analysis of data from the New Zealand ProVIDe randomized controlled trial (RCT) published a few years ago, the authors have now assessed the relationship between refeeding syndrome and hypophosphatemia in the first week of life with risks of death or neurodisability at 2 years of age [4]. Among the 352 extremely low birthweight infants (<1,000 g) assessed, those who experienced refeeding syndrome had nearly double the odds of poor outcomes (adjusted OR 1.96). Severe hypophosphataemia (<0.9 mmol/L) was particularly concerning, being associated with a 167% higher risk of death and 131% increased risk of neurodisability. The dose-response relationship observed suggests that cellular energy failure in developing brains may explain the worse neurodevelopmental outcomes. These findings

support the need for enhanced phosphate monitoring during the critical first week of life and highlight the importance of optimized parenteral nutrition protocols with attention to both macronutrients as well as micronutrients to prevent these potentially serious nutrition-related complications in extremely vulnerable infants.

In another secondary analysis from the same ProVIDe RCT, the authors examined associations between faltering growth and developmental delay in 327 preterm infants with birth weights below 1,000 g [5]. The period between birth and 2 years' corrected age was divided into several epochs, after which it became apparent that growth faltering between the fourth postnatal week and 36 weeks postmenstrual age was more strongly associated with developmental delay (particularly motor delay) than growth faltering in the periods before or after this timeframe. However, it is important to note that overall postnatal growth still remains a relatively poor predictor of developmental delay at 2 years (AUC $\leq$ 0.62), suggesting that many other factors contribute to neurodevelopmental outcomes.

Canadian research from last year assessed correlations between early life nutritional intakes and brain MRI scans at age 5 years in a cohort of 40 preterm-born infants with birth weights below 1,500 g [6]. In brief, there were no associations found between first month macronutrient intakes (parenteral plus enteral) and brain region sizes. However, the relative intake of mother's own milk during the first month of life, as opposed to donor human milk or preterm formula, appeared to be associated with greater volumes of several brain regions. These included total cortical gray matter, cingulate gyri, and occipital gyri, and these associations persisted even after adjusting for maternal educational level, which may be an important confounder.

Kothapally and colleagues published a systematic review examining the amount of early postnatal weight loss and its association with outcomes in very preterm neonates [7]. They analyzed 18 cohort studies including more than 25,000 infants in total. Although meta-analysis on adjusted odds ratios was only possible for 2 or 3 studies per outcome, the authors described important associations for both excessive (defined as >15%) and inadequate (defined as <5%) postnatal weight loss. Excessive weight loss significantly increased risks of mortality (OR 1.39), severe intraventricular hemorrhage (OR 1.37), and necrotizing enterocolitis (OR 2.05). Surprisingly, inadequate weight loss was also associated with adverse outcomes, including mortality and chronic lung disease. These findings suggest that optimal early postnatal weight loss exists within a relatively narrow range (5%–15%), with both extremes being potentially harmful. The results highlight the need for careful fluid and nutritional management in the first days of life for very preterm infants to achieve this balance.

In the next section, we will describe recent research that has revealed critical insights into breastfeeding patterns among vulnerable infant populations, highlighting both concerning disparities and promising interventions for improvement [10–13].

Mother's own milk provision during the first 12 weeks of life by gestational age

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Differences between neonatal units with high and low rates of breast milk feeding for very preterm babies at discharge: a qualitative study of staff experiences

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The relationship of early expressed milk quantity and later full breastmilk feeding after very preterm birth: a cohort study

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Effect of kangaroo mother care in low birth weight infants on human milk intake: a randomized controlled trial

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Comments: In a comprehensive analysis of nearly 30,000 births from the United States, published in *JAMA Network Open*, researchers assessed whether initiation and duration of mother's own milk (MOM) feeding varied by gestational age at birth [10]. The findings reveal a concerning and somewhat paradoxical disparity: late preterm infants (34–36 weeks) had the lowest rates of both MOM initiation (82%) and continuation at 12 weeks (61%), which were slightly but significantly lower than rates for extremely preterm infants (90% initiation, 63% continuation), moderately preterm infants (88% initiation, 59% continuation), and term infants (88% initiation, 72% continuation). After adjusting for maternal characteristics, late preterm infants were 4.4% points less likely to initiate MOM feeding and 6.7% points less likely to continue at 12 weeks compared to term infants. No significant differences were found between extremely/moderately preterm and term groups. This paradoxical finding is particularly concerning given that late preterm infants represent the largest preterm subgroup, accounting for 6.7% of all births. The authors suggest that these infants may be overlooked for lactation support due to their relatively healthier appearance and shorter NICU stays, highlighting the need for targeted interventions that address both initiation and continuation barriers in this vulnerable yet often underserved population.

A recent qualitative study comparing four English neonatal units with either low or high rates of breast milk feeding at discharge reveals striking differences in how effectively they support mothers of very preterm babies (born before 32 weeks) with breast milk feeding [11]. While national rates show that only 60% of very preterm infants receive their mother's milk at discharge, some units achieve much higher success rates. The high-performing units had full-time infant feeding specialists who could build relationships with mothers throughout their entire journey, from antenatal counseling through to discharge. These units also fostered a "whole team" approach where every staff member understood their role in supporting feeding, and this was backed by regular training specific to preterm feeding challenges. In contrast, lower-performing units relied on overstretched specialists with minimal protected time for this work, leading to missed opportunities and inconsistent information being provided to mothers. Critical gaps included poor coordination between maternity and neonatal staff, inadequate facilities for mothers to stay with their babies, and pressure to move to bottle-feeding rather than taking time to establish direct breastfeeding. The authors concluded that effective breastfeeding support requires dedicated feeding specialists, strong leadership that champions breast milk feeding and breastfeeding within Family Integrated Care models (even in the absence of rooming-in facilities), and multidisciplinary team training that encourages and enables every staff member to take an appropriate share of responsibility for consistently informing and assisting mothers with expressing and breastfeeding.

Related to these findings was a recent study from the United Kingdom published in *Maternal & Child Nutrition* by Levene and colleagues, which provided valuable insights into the relationship between early expressed breast milk quantities and successful breastfeeding outcomes for 132 very preterm infants [12]. The findings suggest that the quantity of milk mothers can express in the first days and weeks after very preterm birth may serve as an important predictor of future breastfeeding success. For example, mothers who were able to express more than 250 mL at postnatal day 4 had a high probability of providing full breast milk at around term corrected age: 88% (95% CI: 72%–97%). By day 21, the amount needed to be at least 650 mL to reach similar probabilities of success. This has significant implications for how neonatal teams counsel families and structure their lactation support programs. The research underscores the importance of robust lactation support programs in NICUs, with particular

focus on the critical early period when milk production is being established. Early intervention strategies may be key to ensuring that more preterm infants can benefit from their mother's milk throughout their hospitalization and beyond.

One intervention examining how milk expression could be increased was assessed last year by researchers from India and published in *The American Journal of Clinical Nutrition* [13]. This randomized controlled trial of 550 low birth weight infants (1,500–2,250 g) investigated whether promoting and supporting kangaroo mother care (KMC) in home settings would enhance human milk intake and quality. Participants were randomized to receive either intensive KMC support (which included continuous skin-to-skin contact plus exclusive breastfeeding promotion through regular home visits) or standard care during the neonatal period at home. Using the deuterium dilution technique measured over 14 days, researchers found significantly higher human milk intake in the KMC group: 368 ± 135 g/d versus 331 ± 144 g/d in controls, representing a clinically significant difference of approximately 10%. The effect was particularly pronounced in preterm infants and small-for-gestational-age infants. Additionally, the percentage of exclusive breastfeeding increased dramatically from 56% to 90%. Of note, the composition of the milk remained largely unchanged between groups. Although this research took place outside the hospital setting, it again illustrates the importance of active parental involvement and participation in the care of vulnerable infants, as this also has a large influence on breastfeeding rates and success [14, 15].

Artificial intelligence (AI) is increasingly making its way into neonatal care, and a particularly interesting study was published in *Nature Medicine* where an artificial intelligence-driven system for compounding and ordering parenteral nutrition (PN) for preterm and critically ill neonates was developed [16].

AI-guided precision parenteral nutrition for neonatal intensive care units

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Comments: The formulation of PN is notoriously complex, time-consuming, and prone to variability and error, especially when it is individually compounded for each patient. By leveraging over a decade of electronic health record data, nearly 80,000 PN prescriptions from over 5,900 patients were combined with daily patient-specific parameters, such as laboratory values and fluid goals, to train a deep learning model [16]. The system identified an optimum of 15 clusters of different PN compositions, enabling personalized yet relatively standardized PN formulations. These formulas were not static but adapted dynamically to clinical changes, such as serum electrolyte imbalances or evolving nutritional needs. The model's performance was compelling: in both internal and external validations, the AI recommendations closely matched expert prescriptions (Pearson's $R \geq 0.91$) and were consistently rated higher in a blinded study by multidisciplinary clinicians. More importantly, deviations from the study's prescriptions were associated with significantly increased odds of adverse outcomes, including necrotizing enterocolitis, sepsis, and mortality. Crucially, the AI-driven PN system was not presented as a black box. A physician-in-the-loop architecture ensured that recommendations adhere to clinical guidelines and can be adjusted based on clinician input, thereby preserving clinical autonomy while enhancing safety and efficiency. Moreover, when physicians modified recommendations based on clinical judgment, the AI adapted and learned from these modifications. These developments could potentially improve nutritional care substantially in the coming years. On the other hand, it is worth noting that at least in Europe, there is a trend toward more standardized PN solutions, sometimes provided in all-in-one bags, for the majority of patients. This approach not only improves prescription ease but also enhances compounding and pharmaceutical quality in terms of stability and compatibility, while generally providing a more balanced composition that is closer to published guidelines [17, 18]. The 15 different proposed PN recipes in the discussed AI study are quite far from a single standardized bag approach, highlighting different philosophies in PN provision globally.

Term Infants

Breastfeeding

Effect of low-dose iron supplementation on early development in breastfed infants: a randomized clinical trial

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Effect of iron supplementation in healthy exclusively breastfed infants: a systematic review and meta-analysis

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Association between breastfeeding and the risk of autoimmune diseases: a systematic review and meta-analysis

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Breastfeeding and infant growth in relation to childhood overweight – a longitudinal cohort study

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Macronutrient concentrations in human milk beyond the first half year of lactation: a cohort study

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Comments: Exclusive breastfeeding is recommended by WHO and many national authorities for 6 months after birth. However, since the iron content in human milk is low and iron intake from complementary foods is often limited, breastfed infants may be at risk of iron deficiency (ID). Iron is essential for normal brain development. There are few data on the impact of iron supplementation on child development, and current guidelines in breastfed infants after age 4 months are divergent. The American Academy of Pediatrics (AAP) recommends initiating iron supplementation (1 mg/kg/d) in all full-term infants receiving more than 50% breast milk at age 4 months until the iron needs are met by their diet [19]. Conversely, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition (CoN) concluded that there is no convincing evidence that iron supplements should be provided to all normal birthweight, exclusively breastfed infants during the first 6 months of life in populations with a low prevalence of iron deficiency anemia (IDA) among 6-month-olds [20]. Svensson et al. [21] conducted a randomized, double-blind, placebo-controlled trial (the Supplemental Iron and Development in Breastfed Infants (SIDBI) trial) in an outpatient setting in Poland and Sweden. Their objective was to assess whether an iron supplementation of 1 mg/kg/day between 4 and 9 months in exclusively or predominantly breastfed infants improves psychomotor development at 12 months. Participants (n = 221) were healthy singleton infants born at term with birth weight >2,500 g who were exclusively or predominantly breastfed (>50%) and did not have anemia (hemoglobin >10.5 g/dL) at age 4 months. They received iron (micronized microencapsulated ferric pyrophosphate), 1 mg/kg, or placebo once daily from age 4–9 months. The primary outcome was psychomotor development assessed by motor score of Bayley Scales of Infant and Toddler Development III at 12 months, adjusted for gestational age, sex, and maternal education. Secondary outcomes included cognitive and language scores at 12 months; motor, cognitive, and language scores at 24 and 36 months; ID (serum ferritin <12 ng/mL) and IDA (ID and hemoglobin <10.5 g/dL) at 12 months. Compared to placebo, iron supplementation had no significant effect on psychomotor development, cognitive score, or language score at 12 months. There were no significant differences at 24 and 36 months. The intervention did not reduce the risk for ID or IDA at 12 months. These results are in line with the ESPGHAN CoN recommendation. They may seem in contradiction with the results of the systematic review and meta-analysis of randomized controlled trials (RCTs) on the effects of daily iron supplementation on

health in children aged 4–23 months from Pasricha et al. [22]. In children aged 4–23 months receiving iron supplements, the risk ratio (RR) for anemia was 0.61 (95% confidence interval (CI): 0.50–0.74), for ID was 0.30 (95% CI: 0.15–0.60), and for IDA was 0.14 (95% CI: 0.10–0.22). No statistical difference in mental or psychomotor development was identified. However, populations with a high risk of anemia were included in this systematic review, thereby preventing any comparison with the study of Svensson et al. performed in a low-risk anemia setting. The study of Svensson et al. has limitations. The iron status of pregnant and postpartum women was not assessed, and IDA in pregnancy was not an exclusion criterion for the trial. However, even though iron supplementation is beneficial for mothers, it has been shown to not improve the occurrence of low birthweight, preterm delivery, infant mortality, or impaired psychomotor development [23, 24]. It would have been optimal to obtain blood samples directly after the intervention period, i.e., at 9 months of age. However, even if Svensson et al. were not able to observe a transient difference in iron status between the groups, the effect of iron supplementation on psychomotor development was still absent, and the conclusions of their article are still valid.

Tian et al. [25] performed a systematic review and meta-analysis of studies assessing the effect of iron supplementation in healthy exclusively breastfed infants. This study included eight RCTs with a total of 685 participants assessing the effects of daily iron supplementation on iron status, growth, and neurodevelopment. The iron supplement intervention during the exclusively breastfeeding period lasted between 2 and 5 months. At 6 months of age, compared to infants who were exclusively breastfed without iron supplementation, those who received oral iron supplementation showed an increase in hemoglobin (Hb) levels (mean difference [MD]: 0.42; 95% CI: 0.19–0.66, $p < 0.001$) and a reduction in the incidence of ID (RR: 0.38; 95% CI: 0.15–1.00, $p = 0.050$) and IDA (RR: 0.58; 95% CI: 0.40–0.84, $p = 0.004$). However, by 12 months of age, the supplementation had no effect on Hb levels, the incidence of ID or IDA, or mental development index. Iron supplementation appeared to reduce weight gain (MD = −0.04; 95% CI: −0.07 to −0.01, $p = 0.004$) and head circumference gain (MD: −0.14, 95% CI: −0.18 to −0.09, $p < 0.001$). Limited available evidence suggests that iron supplementation may be beneficial for hematologic parameters and the incidence of IDA in healthy exclusively breastfed infants. However, it may delay weight gain and head circumference growth. In addition, the heterogeneity of included studies with respect to iron supplementation sources and dose, age at and duration of supplement intervention, as well as geographic, economic, and social background of infants should be highlighted. To conclude on the need for iron supplementation in breastfed infants living in low-risk anemia settings, available data seem too limited to recommend iron supplementation in all healthy exclusively/predominantly breastfed full-term infants from the age of 4 months.

Human milk has a sophisticated immunoregulatory system and is full of bioactive substances [26]. Immunoglobulins, cytokines, and other immunologically active molecules in human milk, such as TGF-β and IL-10, may influence the immune system of the infant. Through regulating gene expression and epigenetic changes (such as DNA methylation), breastfeeding can control the immune system's long-term growth and function, hence reducing the likelihood of autoimmunity. Some studies have explored the association between breastfeeding and several autoimmune diseases, but the findings remain inconsistent. No meta-analysis has yet simultaneously addressed multiple autoimmune diseases or examined how the duration of breastfeeding may influence the risk of developing autoimmune diseases. Li et al. [27] performed a systematic review and meta-analysis of studies on the association

between breastfeeding and rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ulcerative colitis (UC), Crohn's disease (CD), multiple sclerosis (MS), and type 1 diabetes mellitus (T_1D). Of the 40 included studies (35 case-control studies and 5 cohort studies), 12 were stratified by the duration of breastfeeding. There was a protective association between breastfeeding and a reduced risk of autoimmune diseases (odds ratio (OR) = 0.80; 95% CI: 0.72–0.89, $p < 0.001$). A protective impact was significant for RA (OR: 0.66; 95% CI: 0.46–0.93, $p = 0.018$), MS (OR: 0.78; 95% CI: 0.63–0.98, $p = 0.030$) and T_1D (OR: 0.80; 95% CI: 0.66–0.98, $p = 0.028$), and was more pronounced with breastfeeding duration of at least 4 months (OR: 0.81; 95% CI: 0.72–0.90, $p < 0.001$). No protective impact of breastfeeding was found for UC, CD, and SLE. Li et al. concluded that (1) breastfeeding provides an overall protective effect against autoimmune diseases and a significant protective effect on RA, MS, and T_1D; (2) this protective effect appears stronger with breastfeeding duration of at least 4 months, which is more accessible than the 6-month recommendation. However, this study has limitations: (1) the existing literature on the association between breastfeeding and autoimmune diseases is limited; (2) there is an imbalance in the types of study design included in this meta-analysis, with a predominance of case-control studies and a relative scarcity of cohort studies. This may introduce biases, thereby limiting the broader applicability of the findings of Li et al.

Both breastfeeding and infant growth have been shown to be important regarding later weight. Rapid growth is associated with later overweight in both childhood and adulthood [28]. Longer duration of breastfeeding has been associated with slower growth in infancy [29] and has been extensively investigated in relation to overweight. In a recent meta-analysis of 159 studies, there were 27% lower odds of overweight or obesity in breastfed infants compared to nonbreastfed infants [30]. However, there are few data on the interplay between longitudinally infant growth and breastfeeding in relation to later overweight. In addition, it remains unknown if rapid weight gain is always a risk factor for overweight, regardless of the mode of feeding. The aim of the study from Leth-Møller et al. [31] was to investigate how breastfeeding duration interacts with patterns of infant growth and how this is associated with later childhood overweight. They hypothesized that the risk of being overweight in childhood is increased in infants with rapid growth but that breastfeeding can attenuate the risk. They collected data on duration of exclusive breastfeeding and child growth from Aarhus Municipality, Denmark and on maternal health from the patient records at Aarhus University Hospital, 2008–2013. Infant growth was estimated using latent class analysis. Duration of exclusive breastfeeding was grouped as never, ≤4 months, and >4 months. Childhood overweight was defined as a body mass index Z-score >1 at age 5–9 years. Among 7,074 infants, three growth patterns were identified: average, accelerated, and decelerated. No or ≤4 months of breastfeeding was associated with being overweight at 5–9 years (adjusted OR: 1.61; 95% CI: 1.27–2.03 and aOR: 1.54; 95% CI: 1.28–1.85, respectively) compared to >4 months of breastfeeding. Compared with average infant growth, accelerated infant growth was associated with childhood overweight (aOR: 1.35; 95% CI: 1.01–1.79). Accelerated infant growth showed no evidence of being associated with overweight if infants were exclusively breastfed >4 months (aOR: 1.20; 95% CI: 0.68–2.10). Decelerated growth was not associated with overweight regardless of exclusive breastfeeding duration. After investigating the interplay, Leth-Møller et al. concluded that breastfeeding had an impact on the risk of overweight, especially in those with accelerated infant growth, whereas longer duration of exclusive breastfeeding abolished this risk. This suggests that rapid infant weight gain due to

exclusive breastfeeding is not a risk factor for overweight, but rapid infant weight gain due to other forms of feeding, such as with formula, could pose a risk for overweight. Health care professionals should take not only infant growth but also breastfeeding duration into consideration when consulting children with or at risk of overweight.

Human milk is not a uniform body fluid but a secretion of the mammary gland of changing composition [32]. The composition of human milk is adapting to fulfill the nutritional needs of infants and young children and ensure normal growth and development. Foremilk differs from hindmilk, and colostrum is strikingly different from transitional and mature milk. Milk composition also changes with time of day and during the course of lactation [32]. It has been shown that protein concentrations decrease during the first 6 months post-birth while fat content may increase. However, there is limited knowledge about the composition of human milk beyond the first 6 months of lactation. When a mother's milk is unavailable or insufficient, donated human milk becomes the preferred alternative to preterm formula for very preterm infants. Currently, there is no consensus or established guidelines from the European Milk Bank Association (EMBA) or the Human Milk Banking Association of North America (HMBANA) regarding the duration a woman should be allowed to donate milk to a bank during extended lactation or whether this milk, even with multinutrient fortification, is nutritionally less suitable for preterm infants. The study of Muts et al. [33] aimed to assess the macronutrient composition of human milk during extended lactation. A retrospective longitudinal cohort study was performed within the Dutch National Human Milk Bank. Donors who had provided milk donations at least once after the 6-month postpartum mark were selected. The Miris Human Milk Analyzer was used to analyze macronutrient concentrations in the milk samples. A total of 820 milk samples from 86 women were collected between 5 weeks and 28 months postpartum and divided into six different lactation periods: 0–2 months, 2–4 months, 4–8 months, 8–12 months, 12–18 months, and >18 months. On beginning their donations, the women had a mean age of 37.4 years (SD: 3.7) and a mean BMI of 25.0 kg/m^2 (SD: 4.7). Mean gestational age was 38.1 weeks (SD: 3.7). Protein concentrations followed a U-shaped path. They dropped over the first 8 months of lactation (difference: −0.19 g/dL, $p < 0.001$) and stabilized between 8 and 18 months before increasing again by 0.21 (95% CI: 0.06–0.21) g/dL. The carbohydrate concentration remained stable throughout the 28-month study period. The fat concentration stayed consistent for the initial 8 months but showed a substantial rise from the 8th month of lactation through the end of the study. Post 18 months, the fat content showed a rise of 1.90 (95% CI: 1.59–2.21) g/dL. Given the high caloric density of fat, the energy content also started increasing after 8 months of lactation, continuing to rise even after 2 years of lactation. Muts et al. concluded that (1) the macronutrient content of human milk does not decrease significantly after 6 months of lactation; (2) human milk banks may accept donations from mothers up to 2 years post-birth; (3) future research should also examine bioactive components crucial for infant immunity and growth (e.g., antibodies, enzymes and hormones) in human milk beyond the initial breastfeeding months.

Food Allergy

Probiotics in infants for prevention of allergic disease

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Growth, safety and tolerance in infants fed rice protein hydrolysate formula: the GRITO randomised controlled trial

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Comments: The prevalence of allergic diseases is increasing, and it is estimated that 30%–40% of the population worldwide suffers from one or more allergic diseases. Up to 10% of the population may experience food allergy, which is more frequently reported in infancy and childhood [34]. The colonization of the intestine by the microbiota begins before birth and matures slowly, until it reaches the adult state at around 3 years of age. The intestinal microbiota plays a key role in the development of the human immune system, especially in the first years of life. Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [35]. It has been hypothesized that probiotics given early in life may have a preventive effect on the risk of allergy as immunomodulatory agents and activators of host defense pathways. Wang et al. [36] updated the 2007 Cochrane review entitled "Probiotics in infants for prevention of allergic disease and food hyperactivity". Eligible studies were RCTs comparing a probiotic to a control, or a

probiotic added to a prebiotic ("synbiotic"). Probiotics were added to human milk or infant formula, added in the manufacturing process or given separately. Health outcomes were infant incidence by 2 years of age and childhood incidence (up to 10 years of age or up to the age of latest report between 2 and 10 years) of specific allergic diseases, including asthma, eczema, allergic rhinitis, immunoglobulin E (IgE)-mediated food allergy, and IgE-mediated cow's milk protein allergy. Adverse effects were also assessed. A total of 24 studies (7,077 mother-infant pairs) mostly performed in Europe and published between 2000 and 2020 were included. Probiotics may result in little to no difference in asthma (RR: 0.96; 95% CI: 0.65–1.44; low-certainty evidence), allergic rhinitis (RR: 0.89; 95% CI: 0.45–1.77; low-certainty evidence) and IgE-mediated cow's milk protein allergy (RR: 0.99; 95% CI: 0.82–1.20; low-certainty evidence) by 2 years of age. Probiotics may result in a slight reduction in eczema by 2 years of age (RR: 0.87; 95% CI: 0.78–0.97; low-certainty evidence). Probiotic supplementation may have little to no effect on the incidence of food allergy by 2 years (RR: 1.12; 95% CI: 0.57–2.20; very low-certainty evidence). The evidence is also very uncertain about the effect of synbiotics on eczema by 2 years of age (RR:0.88; 95% CI: 0.52–1.47). Synbiotics may result in little to no difference in food allergy by 2 years of age (RR: 1.06; 95% CI: 0.55–2.07; low-certainty evidence). There were no data for the effect of synbiotics on asthma, allergic rhinitis, and IgE-mediated cow's milk protein allergy by 2 years of age. There were no serious adverse events related to probiotics or synbiotics reported. These findings are consistent with reviews indicating some reduction in eczema by 2 years of age with probiotic supplementation, but minimal impact on other allergic outcomes such as food allergy, allergic rhinitis, and asthma. Although there were no serious adverse events reported for the use of probiotics in infants, Wang et al. concluded that incorporating probiotics and synbiotics into routine practice requires further information to support their use. There is a discrepancy between claims made on the preventive effect of probiotics on the risk of allergy later in life and the paucity of scientific data supporting these claims.

Managing cow's milk protein allergy (CMPA) involves the strict avoidance of cow's milk protein and related products while ensuring adequate nutrition, typically achieved through specialized infant formulas. These include extensively hydrolyzed cow's milk protein formulas (eHF), amino acid formulas, and plant-based infant formulas (hydrolyzed rice formulas (HRFs) and soy protein infant formulas). According to current practice guidelines from the ESPGHAN [37], cow's milk-derived eHF is the first choice for CMPA management, but HRF is considered as a first-line alternative. Amino acid formulas are reserved for infants with impaired nutritional status, anaphylaxis, and eosinophilic esophagitis. As the amino acid content of rice proteins differs from that of human milk proteins, the protein quality of HRFs is improved by supplementation with certain amino acids that may be lacking in rice, typically lysine, threonine, and tryptophan [38]. Although initial concerns had been raised regarding the possible lower protein quality of HRFs, both healthy infants and infants with CMPA fed with HRF exhibit normal growth and development [38]. Native rice has a high arsenic content. However, the content of arsenic is strictly regulated for foods intended for children under 3 years of age, according to Directive EU 2013/46 of August 28, 2013 amending Directive 2006/141. Manufacturers are required to respect safety limits. Since 2016 (Directive EU 2015/1006 of June 25, 2015), the maximum

level of inorganic arsenic for rice intended to produce foodstuffs for children under 3 years of age is 0.10 mg/kg (a limit twice as low as that for white rice). Acquiring tolerance to cow's milk proteins is also an important goal in CMPA management. However, very few studies have evaluated tolerance acquisition for HRFs. The study from Lemoine et al. [39] was initiated to compare outcomes between infants with CMPA fed with HRF and those fed with an eHF. The primary objective was to compare growth at 6, 9, and 12 months after inclusion into the study between the two randomized groups. Secondary objectives were to evaluate anthropometrics, protein status, safety, and acquisition of tolerance to cow's milk proteins. A total of 105 children were enrolled. The weight-for-length Z-scores were −0.01 (HRF) and −0.29 (eHF) at baseline and 0.29 and 0.05, respectively, at the last visit, with no significant between-group difference. Other anthropometric variables indicated normal growth, with no significant between-group differences. The frequency of reported adverse events (AEs) was comparable between the two groups. One infant in the eHF group exhibited clinical intolerance to the product, as evidenced by an immediate allergic reaction, whereas no infant showed an allergic reaction to HRF. Sixteen serious AEs were reported in both groups, occurring in three infants in the HRF group and four infants in the eHF group. None of these serious AEs were deemed related to the study treatment by the investigators. At the end of the 12-month follow-up, 72.2% of infants in the HRF group and 53.7% of those in the eHF group acquired cow's milk protein tolerance (defined by a negative oral food challenge and subsequent tolerance to standard cow's milk), with no significant difference between groups. Acquisition of tolerance was faster in the HRF group (median age: 16.3 months) compared to the eHF group (median age: 20.4 months), but the difference was not significant. Lemoine et al. concluded that HRF demonstrated appropriate growth, acquisition of tolerance, and a good safety profile in infants with CMPA, with no significant difference *versus* eHF. HRF could be considered as an appropriate option in the management of CMPA. This is in line with the World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update where HRF is considered as equivalent to eHF [40]. The French Society of Pediatrics CoN also stated that HRF can be considered as an alternative to eHF as a first-line treatment for infants with CMPA because of their effectiveness, in terms of allergic symptoms and nutritional adequacy, their palatability, and their lower cost [38].

Infant formulas for the treatment of functional gastrointestinal disorders: a position paper of the ESPGHAN Nutrition Committee

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Technical review by the ESPGHAN special interest group on gut microbiota and modifications on the health outcomes of infant formula supplemented with manufactured human milk oligosaccharides

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Comments: Functional gastrointestinal disorders (FGIDs), such as infant regurgitation, infant colic, and functional constipation, are common and physiological phenomena during the early months of life, generally not requiring any medical intervention or treatment.

The diagnosis of FGIDs relies on the symptom-based Rome criteria that were revised for infants/toddlers and for children and adolescents in 2016 [41]. The infant food industry provides a wide range of formulas for managing these FGIDs. These formulas are heavily marketed, potentially creating misconceptions among healthcare providers and parents about their effects. The Committee on Nutrition (CoN) of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) conducted a review of the available evidence concerning the safety and efficacy of formulas specifically formulated for addressing infant regurgitation, infant colic, and functional constipation [42]. This ESPGHAN Position paper did not primarily focus on the safety and efficacy of prebiotics and probiotics, synthetic human milk components, such as human-identical milk oligosaccharides, or synbiotics, as these ingredients are also used in standard formulas. Instead, the paper concentrated on formulas specifically designed for the treatment of FGIDs. A total of 72 papers were included in the review. In the absence of evidence, recommendations reflected the authors' combined expert judgment. Final consensus was obtained by multiple e-mail exchange and meetings of the ESPGHAN CoN. Their conclusions were the following: (1) Whether an infant is breastfed or formula-fed, parents need to be informed that FGIDs typically do not necessitate treatment or change to a special formula. Therefore, reassurance of parents and family should be the first-line recommendation. (2) Breastfeeding should never be discontinued in favor of formula feeding in infants experiencing any or several FGIDs. In majority of formula-fed infants, no specific formulas are indicated. (3) In formula-fed infants, thickened infant formulas often referred to as "antireflux or AR formulas" or formulas with appropriately added thickeners can be considered under medical guidance in specific cases of profound regurgitation. There is currently no conclusive evidence to recommend one thickening agent over another due to a lack of comparative trials. (4) There is a lack of clinical evidence of formulas for infants with colic, i.e., formulas with low-lactose, partially hydrolyzed protein, extensively hydrolyzed protein, pre- or probiotics, β-palmitate, or soy protein-based formulas. (5) In case of infant constipation, considering formulas with high β-palmitate and increased magnesium content may be an option to soften stool consistency. Formulas for use in combined FGIDs are not recommended. In any case, formulas designed for feeding infants presenting with FGIDs should be used under proper medical guidance and supervision. The ESPGHAN CoN recommendations will help health care providers in managing infants with FGIDs.

Human milk oligosaccharides (HMOs) are complex carbohydrates composed of five different monosaccharides as potential building blocks: glucose, galactose, N-acetylglucosamine, fucose, and sialic acid [43]. Concentration of HMOs is around 2.0 g/dL in colostrum and approximately 1.0–1.5 g/dL in mature human milk, with around 150–200 distinct HMOs. They do not provide direct nutritional value to infants. Instead, they function as prebiotics, promoting a "healthy" gut microbiota. Some HMOs specifically nourish beneficial bacteria such as *Bifidobacterium infantis* in the gastrointestinal tract. Several strains of the species *Bifidobacterium bifidum* and *Bifidobacterium breve* may also metabolize certain HMOs. These bacteria, in turn, help maintain a "balanced" gut microbiota and reduce the risk of diseases, particularly gastrointestinal infections. In addition to their prebiotic role, HMOs prevent pathogens from adhering to epithelial cells. They also contribute to immune function by enhancing the maturation of the intestinal mucosa, strengthening the intestinal epithelial barrier, and acting as immunomodulators to influence the immune system.

The technical review developed by the ESPGHAN special interest group (SIG) on gut microbiota and modifications (GMM), supports the creation of a position paper on the use of human-identical milk oligosaccharides (HiMOs) produced through chemical synthesis or microbial biotechnology [44]. The ESPGHAN SIG-GMM conducted a systematic review to evaluate the clinical outcomes of HiMO-supplemented infant formulas in healthy infants (0–12 months). Six RCTs and two mechanistic substudies investigated different combinations of HiMOs added to the formula. The limited number of RCTs that have been conducted so far evaluating HiMOs supplemented to healthy infant formulas are heterogeneous because of differences in study design, including HiMOs combinations and durations of interventions. The majority of studies were powered only to assess parameters of growth. For other outcomes like infections and specific adverse events, studies were underpowered to assess them adequately. Furthermore, three studies had a high risk of bias due to incomplete outcome data and four studies for selective reporting. All studies were industry initiated and sponsored, and none of them was investigator-initiated. The HiMOs studied so far show no difference compared to the control formula in the following outcomes: anthropometric data, regurgitation-related symptoms, crying, fussiness, or colic. A specific combination of five HiMOs (2′-fucosyllactose [FL], 3-FL, lacto-N-tetraose [LNT], 3′-sialyllactose [SL], and 6′-SL) suggest a softer stool consistency and more frequent defecation in healthy infants, but these studies also used the highest amount of HiMOs. The clinical relevance of this finding remains uncertain. Regarding infection prevention, no clear conclusion can be drawn. There was no difference in tolerability and no safety concerns were raised with the HiMOs. Overall, high-quality, well-powered, investigator-initiated RCTs focused on clear outcomes are needed before routine addition of HiMOs to infant formulas can be recommended. This technical report will serve for the formulation of recommendations by the ESPGHAN Committee on Nutrition on the use of HiMOs-supplemented infant formula in healthy infants.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscript.

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Cognition

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Introduction

Maternal and early-life nutrition, in critical periods such as preconception, pregnancy, infancy, and early childhood, plays a fundamental role in both anatomical and functional brain development. This year's review covers the period from July 1, 2024, to June 30, 2025, focusing on the interplay between nutrient adequacy, environmental exposures, and maternal dietary patterns in shaping cognitive outcomes.

Three major thematic areas have been identified:

(1) Long-chain polyunsaturated fatty acids (LC-PUFAs) and micronutrients. New studies address both expected associations and unresolved questions, concerning the effects of specific fatty acid profiles and other micronutrients (vitamin D, iodine, selenium) on cognition. The results on LC-PUFA supplementation and status in pre- and perinatal periods show positive results, while contrasting evidence is still reported based on parental genetic patterns. Of note, no associations between iron status and neurodevelopment in high- and middle-income countries have been reported by a systematic review.

(2) Toxicants and pollutants. The study that we have selected underlines the detrimental impact of environmental contaminants on neurodevelopment, further emphasized in case of nutrient deficiencies. These observations have a double relevance, not just at individual level, but as markers of the worsening status of the planet too.

(3) Maternal nutrition and dietary patterns. Studies highlight how overall diet quality during pregnancy shapes cognitive outcomes. Special attention is given to plant-based diets, clarifying the difference between "plant-based" and vegan patterns to prevent unjustified alarmism and to distinguish risks linked to poorly planned veganism from the generally low-risk, nutrient-sufficient, plant-based approach.

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," "iodine," "selenium," "fatty acids," "metals," "microbiome," "obesity," "pregnancy," "gestation," "infancy," "childhood," "infants," "children," and "offspring."

Key articles reviewed for this chapter

LC-PUFAs and Micronutrients – Pregnancy and Early Life

Maternal omega-6/omega-3 concentration ratio during pregnancy and infant neurodevelopment: the ECLIPSES study
Shahabi B, Hernández-Martínez C, Jardí C, Aparicio E, Arija V
Nutrients 2025;17:170

The impact of long-chain omega-3 polyunsaturated fatty acid supplementation in pregnant women toward the intelligence status of early childhood: protocol for a systematic review and meta-analysis
Lim HY, Mohammad Fadzil MA, Mustar S, Abdul Shukor IH, Mohamed WAS
JMIR Res Protoc 2025;14:e60417

Patterns of perinatal exposure to PUFAs and child neurodevelopment: evidence from Mendelian randomization using *FADS* cluster variants
Abou Assi A, Armand M, Sarté C, Tafflet M, Yuan WL, Peyre H, Charles MA, Heude B, Bernard J
Am J Clin Nutr 2025;122:235–243

Testing maternal effects of vitamin-D and omega-3 levels on offspring neurodevelopmental traits in the Norwegian mother, father and child cohort study
Wootton RE, Dack K, Jones HJ, Riglin L, Madley-Dowd P, Borges C, Pagoni P, Roth C, Brantsæter AL, Corfield EC, Stoltenberg C, Øyen AS, Davey Smith G, Ask H, Thapar A, Stergiakouli E, Havdahl A
Psychol Med 2024;54:1–11

Gestational vitamin D concentration and child cognitive development: a longitudinal cohort study in the environmental influences on child health outcomes program
Melough MM, McGrath M, Palmore M, Collett BR, Kerver JM, Hockett CW, Schmidt RJ, Kelly RS, Lyall K, Zhao Q, Hipwell AE, Korrick SA, Gilbert-Diamond D, Weiss ST, Chu SH, Mirzakhani H, Porter JM, Sathyanarayana S for the ECHO Cohort Consortium
Am J Clin Nutr 2025;122:571–581

The effects of prenatal iron supplementation on offspring neurodevelopment in upper middle- or high-income countries: a systematic review
Moumin NA, Shepherd E, Liu K, Makrides M, Gould JF, Green TJ, Grzeskowiak LE
Nutrients 2024;16:2499

Resurgence of iodine deficiency in the United States during pregnancy: potential implications for cognitive development in children
Daniel KS, Mangano KM
Nutr Rev 2025 Mar 17;83:1944–56

The association between prenatal maternal selenium concentration and neurodevelopment in early childhood: results from a mother–child cohort study
Ranjitkar S, Kvestad I, Chandyo RK, Strand TA, Bakken KS, Ulak M, Huber S, Averina M, Shrestha M, Hysing M
J Nutr 2025;155:1962–9

The effects of early childhood probiotic intake on the association between prenatal micronutrient supplementation and neurobehavioral development in preschool children: a four-way decomposition analysis
Ding L, Zhang M, Strodl E, Yin X, Wen G, Sun D, Xian D, Zhao Y, Zheng Y, Liu F, Hu R, Zhao L, Yang W, Chen W
Front Nutr 2025;12:1614820

Toxicants and Pollutants – Pregnancy and Early Life

Thyroid-stimulating hormone (TSH) mediates the associations between maternal metals and neurodevelopment in children: a prospective cohort study
Yu L, Zhang H, Liu J, Cao S, Li S, Li F, Xia W, Xu S, Li Y
Environ Pollut 2024;363(pt 1):125150

Effects of prenatal exposure to multiple heavy metals on infant neurodevelopment: a multi-statistical approach
Kou X, Millán MP, Canals J, Moreno VR, Renzetti S, Arija V
Environ Pollut 2025;367:125647

Associations of prenatal metal exposure with child neurodevelopment and mediation by perturbation of metabolic pathways
Xie Y, Xiao H, Zheng D, Mahai G, Li Y, Xia W, Xu S, Zhou A
Nat Commun 2025;16:2089

Seafood and neurocognitive development in children: a systematic review
O'Connor LE, Spill MK, Saha S, Balalian A, Davis JS, MacFarlane AJ
Adv Nutr 2025;16:100391

Association between prenatal mercury exposure and pediatric neurodevelopment: the Japan environment and children's study
Kuraoka S, Oda M, Ohba T, Mitsubuchi H, Iwai-Shimada M, Tatsuta N, Kamijima M, Nakamura K, Katoh T; Japan Environment and Children's Study (JECS) Group
Sci Total Environ 2024;957:177489

Prenatal and postnatal exposure to PCBs and neurodevelopment of preschoolers living in the PCB-contaminated region
Fábelová L, Wimmerová S, Šovčíková E, Čonka K, Drobná B, Hertz-Picciotto I, Trnovec T, Palkovičová Murínová Ľ
Environ Res 2025;282:122044

Impact of prenatal phthalate exposure on newborn metabolome and infant neurodevelopment
Hoffman SS, Tang Z, Dunlop A, Brennan PA, Huynh T, Eick SM, Barr DB, Rushing B, McRitchie SL, Sumner S, Taibl KR, Tan Y, Panuwet P, Lee GE, Eatman J, Corwin EJ, Ryan PB, Jones DP, Liang D
Nat Commun 2025;16:2539

Associations of prenatal glyphosate exposure with child neurodevelopment in a Canadian pregnancy cohort study
Hall M, Ashley-Martin J, Till C, Hu J, Lanphear B, Curl C, Arbuckle TE, Boivin M, Booij L, Muckle G, Fisher M, Asztalos E, Bouchard MF, MacFarlane AJ, Hyland C
Environ Int 2025;199:109480

Prenatal endocrine-disrupting chemicals exposure and impact on offspring neurodevelopment: a systematic review and meta-analysis
Yang Z, Zhang J, Wang M, Wang X, Liu H, Zhang F, Fan H
Neurotoxicology 2024;103:335–57

Systematic review on endocrine disrupting chemicals in breastmilk and neuro-behavioral development: insight into the early ages of life
Brambilla MM, Perrone S, Shulhai AM, Ponzi D, Paterlini S, Pisani F, Rollo D, Pelosi A, Street ME, Palanza P
Neurosci Biobehav Rev 2025;169:106028

Maternal Nutrition and Dietary Patterns – Pregnancy and Early Life

A western dietary pattern during pregnancy is associated with neurodevelopmental disorders in childhood and adolescence
Horner D, Jepsen JRM, Chawes B, Aagaard K, Rosenberg JB, Mohammadzadeh P, Sevelsted A, Vahman N, Vinding R, Fagerlund B, Pantelis C, Bilenberg N, Pedersen CT, Eliasen A, Brandt S, Chen Y, Prince N, Chu SH, Kelly RS, Lasky-Su J, Halldorsson TI, Strøm M, Strandberg-Larsen K, Olsen SF, Glenthøj BY, Bønnelykke K, Ebdrup BH, Stokholm J, Rasmussen MA
Nat Metab 2025;7:586–601

Maternal dietary patterns, breastfeeding duration, and their association with child cognitive function and head circumference growth: a prospective mother–child cohort study
Horner D, Jepsen JRM, Chawes B, Vinding R, Rosenberg JB, Mohammadzadeh P, Luo Y, Fagerlund B, Flensborg-Madsen T, Wood TR, Felix JF, Monnerup L, Glenthøj BY, Bønnelykke K, Ebdrup BH, Stokholm J, Rasmussen MA
PLoS Med 2025;22:e1004454

Socioeconomic adversity, maternal nutrition, and the prenatal programming of offspring cognition and language at two years of age through maternal inflammation
Gogos A, Thomson S, Drummond K, Holland L, O'Hely M, Dawson S, Marx W, Mansell T, Burgner D, Saffery R, Sly P, Collier F, Tang ML, Symeonides C, Vuillermin P, Ponsonby AL; BIS Investigator Group
Brain Behav Immun 2024;122:471–82

Anthropometric and sociodemographic variables, but not preconception or prenatal maternal nutrition supplementation, predict neurodevelopment in offspring of the "Women First" trial
Waldrop S, Chowdhury D, Westcott JE, Biasini F, Garcés A, Figueroa L, Tshefu A, Lokangaka A, Bauserman M, Saleem S, Ali SA, Goldenberg RL, Goudar SS, Dhaded SM, Derman RJ, Kemp JF, Koso-Thomas M, Das A, Hambidge M, Krebs NF; Women First Preconception Nutrition Trial Study Group
Matern Child Nutr 2024;20:e13703

Nutritional supplementation in pregnant, lactating women and young children following a plant-based diet: a narrative review of the evidence
Herrero Jiménez MP, Del Pozo de la Calle S, Cuadrado Vives C, Escobar Sáez D
Nutrition 2025;136:112778

Impact of maternal health and stress on steroid hormone profiles in human milk: implications for infant development
Ten-Doménech I, Moreno-Giménez A, Campos-Berga L, Zapata de Miguel C, López-Nogueroles M, Parra-Llorca A, Quintás G, García-Blanco A, Gormaz M, Kuligowski J
J Lipid Res 2024;65:100688

The mediating effect of maternal gut microbiota between prenatal psychological distress and neurodevelopment of infants
Fan X, Zang T, Wu N, Liu J, Sun Y, Slack J, Bai J, Liu Y
J Affect Disord 2024;362:893–902

Maternal prepregnancy obesity and offspring intelligence quotient at 5 years: a multicohort analysis
Dow C, Lorthe E, Bernard JY, Galera C, Marchand-Martin L, Tafflet M, Ancel PY, Charles MA, Heude B
Paediatr Perinat Epidemiol 2025;39:162–74

Dietary glycemic index and load during pregnancy and offspring behavioral outcomes: exploring sex differences
Cendra-Duarte E, Canals J, Becerra-Tomás N, Mateu-Fabregat J, Bulló M, Arija V
Eur J Pediatr 2025;184:178

Is maternal diabetes during pregnancy associated with neurodevelopmental, cognitive and behavioral outcomes in children? Insights from individual participant data meta-analysis in ten birth cohorts
Pretorius RA, Avraam D, Guxens M, Julvez J, Harris JR, Nader JT, Cadman T, Elhakeem A, Strandberg-Larsen K, Marroun HE, Defina S, Yang TC, McEachan R, Wright J, Ibarluzea J, Santa-Marina L, Delgado JM, Rebagliato M, Charles MA, Vainqueur C, Maritano S, Zugna D, Yuan WL, Heude B, Huang RC
BMC Pediatr 2025;25:76

LC-PUFAs and Micronutrients – Pregnancy and Early Life

Maternal omega-6/omega-3 concentration ratio during pregnancy and infant neurodevelopment: the ECLIPSES Study

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Nutrients 2025;17:170
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https://pubmed.ncbi.nlm.nih.gov/39796604/

Setting: Spain
Study: Longitudinal birth cohort study
Association/effect: Higher omega-6/omega-3 and arachidonic acid/docosahexaenoic acid (ARA/DHA) ratios in 3rd trimester associated with poorer motor development in infants

Treatment/methods: Maternal serum long-chain omega-3 polyunsaturated fatty acids (LC-PUFAs) in 1st and 3rd trimester; Bayley Scales of Infant Development-III (BSID-III) at early infancy

Age-related associations: Early infancy (first weeks of life)

Key message: Optimize omega-6/omega-3 balance late in pregnancy; focus on ARA/DHA ratio

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The impact of long-chain omega-3 polyunsaturated fatty acid supplementation in pregnant women toward the intelligence status of early childhood: protocol for a systematic review and meta-analysis

Lim HY[1], Mohammad Fadzil MA[1], Mustar S[1], Abdul Shukor IH[2], Mohamed WAS[1]

[1]Nutrition, Metabolic and Cardiovascular Research Centre, Institute for Medical Research, National Institutes of Health, Shah Alam, Malaysia; [2]Environmental Health Research Centre, Institute for Medical Research, National Institutes of Health, Shah Alam, Malaysia

JMIR Res Protoc 2025;14:e60417

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https://pubmed.ncbi.nlm.nih.gov/40245394/

Setting: International countries

Study: Protocol for a systematic review and meta-analysis of randomized controlled trials

Association/effect: Not yet applicable (evidence synthesis planned to estimate the causal effect of prenatal omega-3 LC-PUFA on early-childhood intelligence outcomes)

Treatment/methods: PRISMA-guided systematic review and meta-analysis of randomized controlled trial (RCT) of omega-3 LC-PUFA in pregnancy; outcomes include cognition, language, motor, behavior, attention, vision, hearing, and neurodevelopment up to 8 years

Age-related associations: Early childhood (≤8 years)

Key message: High-certainty synthesis in progress; will clarify heterogeneity by dose, timing, and population and provide a more definitive estimate of effects

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Patterns of perinatal exposure to PUFAs and child neurodevelopment: evidence from Mendelian randomization using *FADS* cluster variants

Abou Assi A[1], Armand M[2], Sarté C[2], Tafflet M[1], Yuan WL[1], Peyre H[3,4,5], Charles MA[1,6], Heude B[1], Bernard J[1]

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Am J Clin Nutr 2025;122:235–243

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https://pubmed.ncbi.nlm.nih.gov/40610128/

Setting: France
Study: Cohort study (EDEN cohort)
Association/effect: Beneficial pattern (high omega-3 LC-PUFAs, low omega-6 LC-PUFAs) linked to higher intelligence quotient (IQ); Mendelian Randomization supports the benefit of colostrum LC-PUFAs and harm of high linoleic acid/dihomo-γ-linolenic acid (LA/DGLA)
Treatment/methods: Erythrocyte/colostrum PUFAs; fatty acid desaturase (*FADS*) variants; IQ at 5–6 years
Age-related associations: 5–6 years
Key message: Quality and source/timing of LC-PUFAs matter; excess LA/DGLA could be detrimental

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Testing maternal effects of vitamin-D and omega-3 levels on offspring neurodevelopmental traits in the Norwegian mother, father and child cohort study

Wootton RE[1,2,3,4,5], Dack K[2,3], Jones HJ[2,3,6,7], Riglin L[8], Madley-Dowd P[2,3,7], Borges C[2,3], Pagoni P[2,3], Roth C[1], Brantsæter AL[9], Corfield EC[1,5], Stoltenberg C[10], Øyen AS[1], Davey Smith G[2,3], Ask H[5,11], Thapar A[8], Stergiakouli E[2,3], Havdahl A[1,5,11]

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Psychol Med 2024;54:1–11.
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https://pubmed.ncbi.nlm.nih.gov/39248077/

Setting: Norway
Study: Mother, Father and Child Cohort Study (MoBa)
Association/effect: No evidence for causal maternal effects of vitamin D or DHA on attention deficit hyperactivity disorder (ADHD)/autism-related traits after genetic control
Treatment/methods: Maternal genetic variants as instruments; child neurodevelopmental trait assessments
Age-related associations: 5 years
Key message: Interpret observational associations with caution; genetics confound some nutrient-neurodevelopment links

Gestational vitamin D concentration and child cognitive development: a longitudinal cohort study in the environmental influences on child health outcomes program

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Setting: United States

Study: Longitudinal multicohort (ECHO Program)

Association/effect: Higher gestational 25-OH-vit D associated with better overall/fluid cognition; strongest when exposure is early in pregnancy

Treatment/methods: Maternal vitamin D levels; standardized cognition at school-age

Age-related associations: 7–12 years

Key message: Vitamin D sufficiency should be supported preconception and in the first trimester. This may help reduce disparities

The effects of prenatal iron supplementation on offspring neurodevelopment in upper middle- or high-income countries: a systematic review

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Nutrients 2024;16:2499

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https://pubmed.ncbi.nlm.nih.gov/39125379/

Setting: Spain and Australia

Study: Systematic review of RCTs

Association/effect: Little to no benefit on cognition in nonanemic women; one RCT signals possible behavioral harm at 4 years

Treatment/methods: MEDLINE/CINAHL/EMBASE/Cochrane to May 2023

Age-related associations: Infancy to 4 years

Key message: In high- and middle-income countries settings, target iron deficiency; avoid routine prophylaxis in iron-replete women

Resurgence of iodine deficiency in the United States during pregnancy: potential implications for cognitive development in children

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Nutr Rev 2025 Mar 17;83:1944–1956

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https://pubmed.ncbi.nlm.nih.gov/40096706/

Setting: United States

Study: Narrative review

Association/effect: Declining urinary iodine concentration (UIC) in women of reproductive age; pregnant women often have <150 µg/L; low UIC linked to reduced IQ

Treatment/methods: PRISMA-guided search 2010–2024

Age-related associations: Childhood IQ outcomes

Key message: Reinforce iodine adequacy policies and prenatal supplementation where needed

The association between prenatal maternal selenium concentration and neurodevelopment in early childhood: results from a mother–child cohort study

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J Nutr 2025;155:1962–1969

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https://pubmed.ncbi.nlm.nih.gov/40222584/

Setting: Nepal (Bhaktapur)

Study: Prospective mother-child cohort

Association/effect: No association between maternal Se concentration and BSID-III total or domain scores across timepoints

Treatment/methods: Maternal plasma Se measured by inductively coupled plasma-mass spectrometry at <15 weeks' gestation; BSID-III assessments at 6, 12, and 24 months; linear mixed models adjusted for maternal age and socioeconomic status

Age-related associations: 6, 12, and 24 months

Key message: Despite ~36% Se deficiency, no detectable effects on early neurodevelopment; nonlinear/threshold effects cannot be excluded

The effects of early childhood probiotic intake on the association between prenatal micronutrient supplementation and neurobehavioral development in preschool children: a four-way decomposition analysis

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Front Nutr 2025;12:1614820

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https://pubmed.ncbi.nlm.nih.gov/40469665/

Setting: China (Shenzhen)
Study: Cohort study
Association/effect: Prenatal multivitamin supplementation associated with lower neurobehavioral developmental disorder risk; early-childhood probiotic intake enhanced the protective effect
Treatment/methods: Maternal questionnaire on prenatal supplementation; probiotic intake during 0–3 years; neurobehavior assessed by Ages & Stages Questionnaires-3 (ASQ-3)
Age-related associations: Preschool (3–7 years); strongest benefits observed for gross motor, fine motor, and personal-social domains
Key message: Pairing prenatal multivitamins with early-life probiotics may yield additive neurobehavioral benefits

Comments on LC-PUFAs and micronutrients:

LC-PUFAs and key micronutrients (vitamin D, iodine) remain central for neurodevelopment. Balance matters: higher n–6/n–3 and ARA/DHA ratios in late pregnancy associate with poorer motor outcomes (ECLIPSES). Genetic analyses (MoBa MR) caution against over-interpreting observational associations for DHA/vitamin D.

A particularly important contribution is the systematic review on iron supplementation and neurodevelopment in high- and middle-income countries. In these settings, routine prenatal iron in iron-replete women shows limited cognitive benefit, and one RCT even signaled possible behavioral harm at 4 years. These findings reinforce a targeted, status-guided approach to iron supplementation, while still recognizing the need to detect and correct iron deficiency wherever it occurs.

Evidence from the ECHO Program suggests benefits of adequate gestational vitamin D, especially when sufficiency is achieved early in pregnancy, with potential to reduce disparities. Yet, effects remain heterogeneous across study designs, and vitamin D adequacy should be prioritized before or early in gestation.

Signs of a resurgence of iodine deficiency during pregnancy even in high-income countries argue for renewed public health attention and supplementation policies where intake or urinary iodine concentration are low.

A large Chinese cohort reported that prenatal multivitamin supplementation was associated with a lower risk of neurobehavioral developmental disorders, and early-life probiotic intake enhanced this protective effect, highlighting prenatal-postnatal synergy along the gut-brain axis.

Take-home: The balance of LC-PUFAs and key micronutrients (vitamin D, iodine) is crucial for neurodevelopment. Effective strategies include optimizing the omega-6/omega-3 ratio, ensuring early sufficiency of vitamin D and iodine, adopting status-guided iron supplementation, and integrating pre- and postnatal interventions, such as multivitamins with probiotics, to support the gut-brain axis.

Thyroid-stimulating hormone (TSH) mediates the associations between maternal metals and neurodevelopment in children: a prospective cohort study

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Setting: China

Study: Prospective cohort study

Association/effect: V, Mn, and Pb linked to higher risk of cognitive/motor delay; TSH mediates part of the association

Treatment/methods: Maternal plasma metals; weighted quantile sum model; BSID-China Revision, mental development indexes/psychomotor development indexes (MDIs/PDIs) at 2 years; mediation by neonatal TSH

Age-related associations: 2 years

Key message: Metal mixtures impair development via thyroid axis-nutrient-toxicant interplay is key

Effects of prenatal exposure to multiple heavy metals on infant neurodevelopment: a multi-statistical approach

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Environ Pollut 2025;367:125647

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https://pubmed.ncbi.nlm.nih.gov/39761717/

Setting: Spain
Study: Prospective cohort study (ECLIPSES)
Association/effect: Mixture adversely affects expressive language; Cd and Ni main contributors; Pb shows nonlinear language effect
Treatment/methods: Maternal urinary Cd, Ni, Hg, and Pb; Bayley at 40 days
Age-related associations: Newborn
Key message: Language appears especially sensitive to early-life metal mixtures

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Associations of prenatal metal exposure with child neurodevelopment and mediation by perturbation of metabolic pathways

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Nat Commun 2025;16:2089
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https://pubmed.ncbi.nlm.nih.gov/40025012/

Setting: China (Wuhan)
Study: Prospective cohort study
Association/effect: Metal mixture inversely associated with MDIs/PDIs; aluminum contributed the most; mediation via amino acid, purine/pyrimidine pathways
Treatment/methods: 11 maternal urinary metals; cord blood untargeted metabolomics; Bayley at 2 years
Age-related associations: 2 years
Key message: Mechanistic evidence links metal exposure to neurotransmitter-related metabolic disruption

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Seafood and neurocognitive development in children: a systematic review

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Setting: Northern Europe
Association/effect: Higher seafood intake likely improves cognition in 0–18 years; evidence graded low certainty

Study: Systematic review
Treatment/methods: ROBINS-E/ROB2; GRADE
Age-related associations: Infancy to adolescence
Key message: Benefits of seafood (especially fatty fish) within recommended intakes likely outweigh contaminant risks

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Association between prenatal mercury exposure and pediatric neurodevelopment: the Japan environment and children's study

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Setting: Japan
Study: Prospective cohort study
Association/effect: No significant associations with developmental scores at 2 and 4 years; bonito-tuna highest dietary correlate
Treatment/methods: Cord blood mercury speciation; Kyoto Scale of Psychological Development tests
Age-related associations: 2 and 4 years
Key message: Null findings at typical exposure ranges; species choice still relevant for risk mitigation

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Prenatal and postnatal exposure to PCBs and neurodevelopment of preschoolers living in the PCB-contaminated region

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Setting: Slovakia
Study: Cohort study
Association/effect: Prenatal dioxin-like polychlorinated biphenyls (DL-PCBs) lower Verbal Intelligence Quotient/Performance Intelligence Quotient/Full-Scale Intelligence Quotient (VIQ/PIQ/FSIQ); postnatal DL-PCBs lower VIQ/FSIQ; nondioxin-like polychlorinated biphenyls (NDL PCBs) postnatally lower VIQ/FSIQ
Treatment/methods: High-resolution gas chromatography for congeners; Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) at 6 years
Age-related associations: 6 years
Key message: Both prenatal and postnatal PCB burdens matter; verbal domains notably affected

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Impact of prenatal phthalate exposure on newborn metabolome and infant neurodevelopment

Hoffman SS[1], Tang Z[2], Dunlop A[3], Brennan PA[4], Huynh T[2], Eick SM[2], Barr DB[2], Rushing B[5,6], McRitchie SL[6], Sumner S[5,6], Taibl KR[2], Tan Y[2], Panuwet P[2], Lee GE[2], Eatman J[2], Corwin EJ[7], Ryan PB[2], Jones DP[8], Liang D[1,2]

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Setting: African American (Atlanta)
Study: Prospective cohort study
Association/effect: Phthalates perturb tyrosine/tryptophan/thyroxine pathways; links to NICU Neonatal Neurobehavioral Scale neurobehavioral profiles
Treatment/methods: Urinary phthalate metabolites at 8–14 and 24–30 weeks; newborn DBS metabolomics
Age-related associations: Newborn
Key message: Biologically plausible neurotransmitter pathway disruption with prenatal phthalates

Associations of prenatal glyphosate exposure with child neurodevelopment in a Canadian pregnancy cohort study

Hall M[1], Ashley-Martin J[2], Till C[1], Hu J[2], Lanphear B[3], Curl C[4], Arbuckle TE[2], Boivin M[5], Booij L[6,7], Muckle G[5,8], Fisher M[2], Asztalos E[9], Bouchard MF[10], MacFarlane AJ[11,12], Hyland C[13,14]

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https://pubmed.ncbi.nlm.nih.gov/40344873/

Setting: Canada

Study: Prospective cohort study

Association/effect: No significant associations for IQ/social/behavioral outcomes; non-significant inverse trend for aminomethylphosphonic acid (AMPA) with PIQ

Treatment/methods: 1st trimester urinary glyphosate and AMPA; WPPSI-III, Social Responsiveness Scale-2, Assessment System for Children-2 at 3–4 years

Age-related associations: 3–4 years

Key message: At low background exposure, clear neurotoxicity signals not observed; continue monitoring

Prenatal endocrine-disrupting chemicals exposure and impact on offspring neurodevelopment: a systematic review and meta-analysis

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Neurotoxicology 2024;103:335–357

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https://pubmed.ncbi.nlm.nih.gov/39013523/

Setting: International countries
Study: Systematic review and meta-analysis
Association/effect: Prenatal metals and phthalates impair cognition/motor; polyfluoroalkyl substances (PFAS) linked to language deficits; some sex-specific effects
Treatment/methods: Studies ≤3 years; domain-based evaluation; pooled β estimates
Age-related associations: 0–3 years
Key message: Consistent small adverse effects across multiple endocrine-disrupting chemical (EDC) classes

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Systematic review on endocrine disrupting chemicals in breastmilk and neuro-behavioral development: insight into the early ages of life

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Setting: Systematic review
Association/effect: Negative associations between breastmilk EDCs and mental/psychomotor and sociocommunicative outcomes (heterogeneous results)
Study: Systematic review
Treatment/methods: Focus on breastmilk as exposure matrix
Age-related associations: First 6 years of life
Key message: Breastmilk is optimal nutrition, but can reflect environmental exposures – reduce maternal EDC burden

Comments on toxicants and pollutants:	Toxicants may exert small but consistent adverse effects on early cognition, language, and motor domains, with mixtures (metals, phthalates, PFAS/PCBs) emerging as more informative than single-chemical approaches. Mechanistic work points to thyroid disruption (TSH mediation) and perturbation of amino-acid, purine/pyrimidine pathways. Nutrient-toxicant interactions seem to have additional effects. Accordingly, micronutrient insufficiency (e.g., iodine, iron) may heighten the susceptibility to metals and EDCs; this underscore integrated strategies, exposure mitigation + nutrient adequacy. Seafood provides neuroprotective effects of LC-PUFAs but may also contain methylmercury. The latest evidence suggests that, within recommended intakes and choosing low-mercury species, benefits likely outweigh risks. Large cohorts at typical exposure ranges (e.g., JECS; glyphosate in MIREC) sometimes show null effects; heterogeneity by dose, species, and co-exposures is expected.

Breastfeeding remains the optimal form of infant nutrition; however, breast milk may reflect the maternal burden of EDCs. Public health policies should therefore aim to reduce environmental EDC exposure for the benefit of both mother and child, while continuing to strongly promote breastfeeding.
Take-home: Measures such as reducing exposures where feasible (air quality, low-mercury fish choices, safer product use), strengthening nutritional buffers (iodine, iron, DHA), and promoting mixture-aware, mechanism-anchored analyses should be supported, consistent with the emerging concept of sustainability.

Maternal Nutrition and Dietary Patterns – Pregnancy and Early Life

A western dietary pattern during pregnancy is associated with neurodevelopmental disorders in childhood and adolescence

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Dietary pattern: Western versus varied diets
Setting: Denmark
Study: Cohort study
Association/effect: Western pattern associated with attention deficit hyperactivity disorder and autism diagnoses; early-mid pregnancy most sensitive
Treatment/methods: Food frequency questionnaire (FFQ)-derived patterns; maternal and fetal metabolomes; clinical diagnoses and trait measures
Age-related associations: 10 years
Key message: Early pregnancy is a critical window – target dietary quality improvements before/early in gestation

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Maternal dietary patterns, breastfeeding duration, and their association with child cognitive function and head circumference growth: a prospective mother–child cohort study

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PLoS Med 2025;22:e1004454
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https://pubmed.ncbi.nlm.nih.gov/40208849/

Dietary pattern: Western versus varied diets
Setting: Denmark
Study: Prospective cohort study
Association/effect: Western pattern linked with lower cognition at 2.5 years; also reduced head circumference growth; breastfeeding considered

Treatment/methods: FFQ patterns; sparse partial least square metabolite scores; BSID (2.5 years) and Wechsler Intelligence Scale for Children (10 years); head circumference trajectories

Age-related associations: 2.5 years, 10 years

Key message: Diet quality and duration of breastfeeding jointly influence growth and cognition trajectories

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Socioeconomic adversity, maternal nutrition, and the prenatal programming of offspring cognition and language at two years of age through maternal inflammation

Gogos A[1,2], Thomson S[1], Drummond K[1,2], Holland L[1,2], O'Hely M[3,4], Dawson S[3,4], Marx W[4], Mansell T[3], Burgner D[3], Saffery R[3], Sly P[5,6], Collier F[6], Tang ML[3], Symeonides C[3], Vuillermin P[4,7], Ponsonby AL[1,2,3]; BIS Investigator Group

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Brain Behav Immun 2024;122:471–482

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https://pubmed.ncbi.nlm.nih.gov/39163911/

Dietary pattern: "Modern wholefoods" versus "Processed"

Setting: Australia

Study: Prospective cohort study

Association/effect: Diet patterns associated with glycoprotein acetylation/high-sensitivity C-reactive protein (GlycA/hsCRP) and BSID-III cognition/language; partial mediation via GlycA

Treatment/methods: Validated FFQ; modern "wholefoods" and "processed" dietary patterns; GlycA and hsCRP at 28 wks; Bayley-III at 2 years

Age-related associations: 2 years

Key message: Nutrient-dense wholefoods may buffer socioeconomic risk via lower maternal inflammation

Anthropometric and sociodemographic variables, but not preconception or prenatal maternal nutrition supplementation, predict neurodevelopment in offspring of the "Women First" trial

Waldrop S[1], Chowdhury D[2], Westcott JE[1], Biasini F[3], Garcés A[4], Figueroa L[4], Tshefu A[5], Lokangaka A[5], Bauserman M[6], Saleem S[7], Ali SA[7], Goldenberg RL[8], Goudar SS[9], Dhaded SM[9], Derman RJ[10], Kemp JF[1], Koso-Thomas M[11], Das A[2], Hambidge M[1], Krebs NF[1]; Women First Preconception Nutrition Trial Study Group

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Matern Child Nutr 2024;20:e13703

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https://pubmed.ncbi.nlm.nih.gov/39044360/

Dietary pattern: Supplementation versus environment

Setting: Guatemala, Democratic Republic of the Congo, Pakistan, India (low- and middle-income countries)

Study: Randomized preconception nutrition trial

Association/effect: Preconception/prenatal supplements did not predict BSID-III; maternal education, birthweight, linear growth, and home stimulation

Treatment/methods: BSID-III at 24 months; family care indicators; linear growth ΔLAZ 6–24 months

Age-related associations: 24 months

Key message: Nurturing care, growth, and education drive development more than generic supplementation in these low- and middle-income country settings

Nutritional supplementation in pregnant, lactating women and young children following a plant-based diet: a narrative review of the evidence

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Nutrition 2025;136:112778

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https://pubmed.ncbi.nlm.nih.gov/40373355/

Dietary pattern: Plant-based
Setting: Europe and United States
Study: Narrative review
Association/effect: Plant-based diets are generally adequate with appropriate supplementation (B12, iodine, DHA/EPA [eicosapentaenoic acid], choline, creatine)
Treatment/methods: Scoping of deficiencies and supplementation guidance
Age-related associations: Pregnancy, lactation, early childhood
Key message: Plant-based ≠ vegan: emphasize planned supplementation; avoid unjustified alarmism for well-planned plant-based diets

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Impact of maternal health and stress on steroid hormone profiles in human milk: implications for infant development

Ten-Doménech I[1,2], Moreno-Giménez A[1,3], Campos-Berga L[1,3], Zapata de Miguel C[1,3], López-Nogueroles M[4], Parra-Llorca A[1,5], Quintás G[6,7], García-Blanco A[2,3], Gormaz M[1,5], Kuligowski J[1,2]

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J Lipid Res 2024;65:100688
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https://pubmed.ncbi.nlm.nih.gov/39490927/

Setting: Spain
Study: Prospective cohort study
Association/effect: Cortisone/pregnenolone relate to maternal weight gain/well-being and infant growth; pasteurization may reduce steroid levels
Treatment/methods: 14 steroids in human milk/donor human milk; maternal/infant questionnaires
Age-related associations: Newborn to 6 months
Key message: Support maternal mental and physical health; prefer own mother's milk; optimize milk bank practices

The mediating effect of maternal gut microbiota between prenatal psychological distress and neurodevelopment of infants

Fan X[1], Zang T[2], Wu N[2], Liu J[2], Sun Y[2], Slack J[3], Bai J[4], Liu Y[1,2]

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J Affect Disord 2024;362:893–902

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https://pubmed.ncbi.nlm.nih.gov/39013520/

Setting: China

Study: Prospective cohort study

Association/effect: *Roseburia* mediates the effect of distress on total neurodevelopment; inflammatory cytokines correlate with poorer fine motor/problem-solving

Treatment/methods: 16S rRNA + liquid chromatography-mass spectrometry short-chain fatty acids; maternal cytokines; infant ASQ/BSID-like scales at 6–8 months

Age-related associations: 6–8 months

Key message: Psychological well-being and microbiota may be the intervention targets alongside diet

Maternal prepregnancy obesity and offspring intelligence quotient at 5 years: a multicohort analysis

Dow C[1], Lorthe E[1,2,3], Bernard JY[1], Galera C[4,5,6], Marchand-Martin L[1], Tafflet M[1], Ancel PY[1], Charles MA[1], Heude B[1]

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Paediatr Perinat Epidemiol 2025;39:162–174

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https://pubmed.ncbi.nlm.nih.gov/39777691/

Setting: France
Study: Cohort study
Association/effect: Lower IQ more prevalent with maternal obesity; analyses adjust for socioeconomic status and paternal body mass index
Treatment/methods: WPPSI at ~5 years
Age-related associations: 5 years
Key message: Address preconception weight and metabolic health as part of neurodevelopment prevention strategies

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Dietary glycemic index and load during pregnancy and offspring behavioral outcomes: exploring sex differences

Cendra-Duarte E[1,2], Canals J[1,3,4], Becerra-Tomás N[1,3], Mateu-Fabregat J[3,5,6], Bulló M[3,5,6,7], Arija V[1,2,3]

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Eur J Pediatr 2025;184:178
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https://pubmed.ncbi.nlm.nih.gov/39909936/

Dietary pattern: Glycemic load (GL) and glycemic index (GI)
Setting: Spain
Study: Prospective cohort study
Association/effect: Highest GL tertile in 1st trimester linked to internalizing/externalizing and autism spectrum disorder/attention problems; stronger in girls; no 3rd-trimester effect
Treatment/methods: FFQ; GL/GI computed; Child Behavior Checklist 1.5–5 at age 4
Age-related associations: 4 years
Key message: Limit high-GL diets in early pregnancy; possible sex-specific vulnerability

Is maternal diabetes during pregnancy associated with neurodevelopmental, cognitive and behavioral outcomes in children? Insights from individual participant data meta-analysis in ten birth cohorts

Pretorius RA[1,2,3], Avraam D[4,5], Guxens M[6,7,8], Julvez J[6,9], Harris JR[10], Nader JT[11], Cadman T[5,12], Elhakeem A[13], Strandberg-Larsen K[5], Marroun HE[14], Defina S[8,15], Yang TC[16], McEachan R[16], Wright J[16], Ibarluzea J[17], Santa-Marina L[18,19], Delgado JM[20,21], Rebagliato M[20,22], Charles MA[23,24], Vainqueur C[23], Maritano S[25,26], Zugna D[25], Yuan WL[23], Heude B[23], Huang RC[1,27]

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https://pubmed.ncbi.nlm.nih.gov/39885386/

Setting: Europe and Australia

Study: Two-stage IPD meta-analysis

Association/effect: Gestational diabetes mellitus associated with higher ADHD symptoms at 7–10 years and externalizing problems at 4–6 years; preexisting diabetes signals attenuated after full adjustment

Treatment/methods: Cohort harmonization; confounder-adjusted regression
Age-related associations: 4–10 years
Key message: Optimize glycemic control and diet quality in pregnancy to mitigate externalizing/ADHD risk

Comments on maternal nutrition and dietary patterns:	Dietary quality in early-mid pregnancy consistently aligns with cognitive advantages and head growth; Western/processed patterns are found to be associated with higher risk of ADHD/autism traits. High glycemic load in the first trimester relates to internalizing and externalizing problems (stronger in girls); window of susceptibility matters. As for plant-based/vegan diets, a genuine plant-based pattern (where small amounts of animal foods are allowed by definition, as it happens to lacto-ovo vegetarian diets) is generally safe when well planned; vegan diets indeed require supplementation (B12, iodine, DHA/EPA, choline, creatine). Avoid unjustified alarmism for plant-based diets; focus on education and supplementation where appropriate. GDM and pre-pregnancy obesity relate to behavioral symptoms or lower IQ in several cohorts. Optimize weight, glycemic control, and overall diet quality preconception/early pregnancy. Socioeconomic adversity impacts child cognition partly via maternal diet and inflammation (e.g., GlycA); maternal mental health and gut-microbiota profiles may mediate risk; supportive care and stress reduction complement nutrition. Human milk endocrine profile varies with maternal health/stress; prioritize own mother's milk and optimize milk bank practices while maintaining breastfeeding support. **Take-home: Elevated overall diet quality, ensuring targeted supplementation for restrictive patterns, and integrating metabolic and psychosocial care all cooperate to support child neurodevelopment**.

Overview

The studies reviewed this year highlight how both single nutrients and broader dietary patterns contribute to shaping neurodevelopment across sensitive life stages. Evidence reinforces the role of balanced LC-PUFAs and selected micronutrients (vitamin D, iodine, iron) in cognitive outcomes, with the additional insight that supplementation strategies should be adapted to single settings rather than universal. Environmental toxicants consistently emerge as significant modifiers of neurodevelopment, underscoring the importance of integrating exposure reduction with nutritional adequacy to build resilience.

Maternal dietary quality, particularly during early pregnancy, appears to influence later cognitive and behavioral trajectories, while plant-based dietary patterns are generally safe if well planned and supplemented. Emerging findings on the gut-brain axis suggest that combining prenatal multivitamins with early-life probiotics may enhance neurodevelopmental protection.

Overall, an integrated view is needed: maternal health, environmental exposures, and nutrition interact in complex ways that cannot be disentangled by a single-nutrient perspective. Future research should further embrace mixture-aware and mechanism-based approaches, coupled with machine learning and artificial intelligence tools, to disentangle the multifactorial drivers of cognitive outcomes. This integrative perspective, consistent with the concept of sustainability, may guide more effective public health policies and individualized strategies to support optimal brain development.

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Author Contributions

Both authors have read and commented on the reviewed manuscripts.

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Nutrition and Growth in Chronic Diseases

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Introduction

Children living with chronic illness face a range of challenges that compromise nutritional status and linear growth, from increased metabolic demands and systemic inflammation to feeding difficulties, malabsorption, and the side effects of long-term therapies. The result is often impaired weight gain, impaired linear growth, altered body composition, and micronutrient imbalances. Advances in medical care and supportive therapies have improved survival for many chronic pediatric conditions, shifting attention to the quality life as well as growth and nutritional health. Monitoring growth and nutritional status has therefore become more than a supportive measure – it is a sensitive marker of health, of disease control and treatment adequacy, as well as a modifiable target for intervention. This chapter highlights recent evidence on nutrition and growth across several chronic diseases of childhood, including celiac disease, inflammatory bowel disease, intestinal failure, cystic fibrosis, chronic kidney disease, and congenital heart disease. We have reviewed and summarized new studies that shed light on the mechanisms of impaired growth, the evolving impact of therapies, and the ongoing need for individualized nutritional strategies. These insights emphasize that growth and nutrition must remain at the core of pediatric chronic disease management.

Key articles reviewed for this chapter

Celiac Disease

Short- and long-term nutritional status in children and adolescents with celiac disease following a gluten-free diet: a systematic review
Papoutsaki M, Katsagoni CN, Papadopoulou A
Nutrients 2025;17:487

Dietary challenges in children with gluten-related disorders: a study on food neophobia
Nogueira Firme J, Dos Santos EB, Zandonadi RP, Nakano EY, Botelho RBA
Nutrients 2024;16:3924

BMI status of children with celiac disease has changed in the last decades: a 30-year retrospective study
Monzani A, Marcolin S, Medina F, Valentino K, Rabbone I
Nutrients 2024;16:2729

Inflammatory Bowel Disease

Anthropometric trajectories in children prior to development of inflammatory bowel disease
Brusco De Freitas M, Poulsen GJ, Jess T
JAMA Netw Open 2025;8:e2455158

Clinical risk factors for body composition deficits in children with inflammatory bowel disease
Alexander E, Stein R, Rudra S, Albenberg L, Zemel B
J Pediatr Gastroenterol Nutr 2025;81:266–274

Investigating sarcopenia in pediatric Crohn's disease with magnetic resonance enterography: an observational study
Calia M, Rebora P, Gandola D, Norsa L, Maino C, Romanchuk A, Sansotta N, Panceri R, Valle C, Valsecchi MG, Biondi A, Ippolito D, Zuin G
Clin Nutr ESPEN 2025;68:14–21

Intestinal Failure

Vitamin and trace element status and growth in children with short bowel syndrome being weaned off parenteral nutrition
Tuokkola J, Olkkonen E, Gunnar R, Pakarinen M, Merras-Salmio L
J Pediatr Gastroenterol Nutr 2025;80:318–325

Retrospective review of growth in pediatric intestinal failure after weaning from parenteral nutrition
Nucci AM, Bashaw H, Kirpich A, Rudolph J
Nutr Clin Pract 2025;40:176–187

Cystic Fibrosis

Effects on growth, weight and body composition after CFTR modulators in children with cystic fibrosis
López Cárdenes CM, Merino Sánchez-Cañete A, Vicente Santamaría S, Gascón Galindo C, Merino Sanz N, Tabares González A, Blitz Castro E, Morales Tirado A, Garriga García M, López Rozas M, Ramos Riesgo T, Álvarez Beltrán M, Gutiérrez Martínez JR, Suárez González M, García Romero R, De la Mano Hernández A, Muñoz Codoceo MR, Martín Fernández C, Tutau Gómez C, Torcuato Rubio E, Ortiz Pérez P, Loverdos Eseverri I, García Volpe C, Salcedo Lobato E, Martín Rivada A, Castro Millan AM, Del

Brio Castillo R, Sierra San Nicolás S, Murray Hurtado M, Crehuá Gaudiza E, Medina Martínez M, González Jiménez D; y grupo de trabajo de FQ y páncreas de la SEGHNP
Pediatr Pulmonol 2024;59:3632–3640

Growth, body composition, and strength of children with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor (ETI)
Boat T, Hossain MM, Nakamura A, Hjelm M, Hardie W, Wackler M, Amato A, Dress C
Pediatr Pulmonol 2025;60:e27463

Chronic Kidney Disease

Factors associated with statural growth in pediatric kidney transplant recipients with focus on metabolic acidosis
Prytuła A, Reynders D, Goetghebeur E, Krupka K, Bacchetta J, Kanzelmeyer N, Guzzo I, Labbadia R, Benetti E, Shenoy M, Sellier-Leclerc AL, Oh J, Litwin M, Rubik J, Awan A, Bilge I, Weber LT, Müller D, Simon T, Pape L, Tönshoff B; on behalf of the ESPN Transplantation and CKD-MBD working group and the CERTAIN Research Network
Pediatr Nephrol 2025;40:2059–2070

Congenital Heart Disease

Role of leptin and insulin like growth factor-1 in regulation of growth in children with congenital cyanotic heart disease
Elsharkawy AA, El-Hawary AK, AlSawah GA, AboElenin HM, Awad MH
Growth Factors 2024;42:198–204

Celiac Disease

Short- and long-term nutritional status in children and adolescents with celiac disease following a gluten-free diet: a systematic review

Papoutsaki M[1,2], Katsagoni CN[1,2], Papadopoulou A[3]

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Nutrients 2025;17:487
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Comments: Celiac disease (CeD) is an immune-mediated enteropathy, triggered by gluten ingestion in genetically predisposed individuals. In children, CeD may present with signs of malabsorption, growth faltering, micronutrient deficiencies, and reduced bone mineral density [1]. Adherence to a gluten-free diet (GFD) results in mucosal healing and improved growth, yet maintaining both high-quality and strict GFD can be challenging, and full nutritional adequacy is not always achieved. The reliance on commercially available gluten-free products, which are frequently low in fiber, protein, and micronutrients, further contributes to dietary imbalance [2]. In addition, psychosocial and behavioral barriers complicate dietary management [3].

International guidelines emphasize that CeD management should go beyond gluten elimination, incorporating regular nutritional counseling, growth monitoring, and bone health assessment [4, 5].

This current systematic review [6] synthesized evidence from observational and interventional studies on nutritional status in pediatric CeD after GFD initiation, and included 15 observational studies with over 2,000 pediatric patients. The review confirmed that although growth and weight indices generally improve after diagnosis, nutritional adequacy remains a significant concern.

A consistent finding across studies was excessive protein intake compared to recommendations, observed in both short- and long-term follow-up. Conversely, carbohydrate and fiber intake tended to be insufficient, reflecting the limited diversity and quality of gluten-free products. Long-term data indicated a shift toward higher fat intake, particularly saturated fats. Micronutrient intake and biochemical assessments highlighted persistent deficiencies in iron, calcium, vitamin D, folate, and B-vitamins. Interestingly, vitamin C and iodine intake showed improvement in some prospective studies, but these were exceptions to the majority of studies.

The review's strength lies in its broad scope, but heterogeneity in study designs and outcome measures limited meta-analytic conclusions. Nonetheless, the synthesis provides robust evidence that nutritional recovery in pediatric CeD is incomplete, even with good dietary compliance. This paper reinforces the role of pediatric gastroenterologists and dietitians in providing long-term multidisciplinary care to children with CeD.

Dietary challenges in children with gluten-related disorders: a study on food neophobia

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https://pubmed.ncbi.nlm.nih.gov/39599710/

Comments: The nutritional imbalances highlighted in the systematic review by Papoutsaki et al. raise the question of why children with CeD continue to fall short of recommended intakes. One important behavioral factor is food neophobia (FN), defined as the reluctance or refusal to try unfamiliar foods. FN is common in childhood but may be intensified in the context of chronic diseases requiring restrictive diets, where both children and caregivers may adopt cautious or avoidant attitudes toward new foods for fear of gluten contamination.

Nogueira Firme and colleagues [7] investigated FN in 209 Brazilian children on GFD (58% females, mean age of 7.2 ± 2.3 years), using a validated questionnaire for FN. Most children (43.1%) presented moderate FN, followed by high FN in 29.2%, and low FN in 27.7%, with general and vegetable neophobia being most pronounced. Interestingly, FN did not decline with age, suggesting persistence throughout childhood in this population, and higher socioeconomic status was paradoxically associated with greater vegetable neophobia. These findings underscore that restrictive

feeding practices, protective caregiver behaviors, and heightened concerns over food safety may perpetuate limited food acceptance. The study further emphasizes the need for a holistic approach in nutritional management of CeD and other restrictive diets, to focus not only on gluten elimination but also on achieving a nutrient-rich, diversity-rich diet.

BMI status of children with celiac disease has changed in the last decades: a 30-year retrospective study

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Comments: This retrospective cohort study [8] examined BMI at diagnosis in nearly 500 children with CeD over a 30-year period, at a single Italian center. Comparing those diagnosed between 1990–2011 ($n = 250$) and 2012–2022 ($n = 243$), the authors found a shift in nutritional phenotype at presentation. The proportion of underweight children at diagnosis decreased by half (24.4% vs. 12.7%, $p < 0.001$), while rates of overweight and obesity more than doubled (4.4%–13.2%, $p < 0.05$). These findings reflect a major change from the classical presentation of CeD as a disease of malnutrition and growth failure to one increasingly recognized in children with normal or even excessive weight.

In addition, gastrointestinal symptoms were paradoxically more common in overweight/obese children than in underweight ones, suggesting that symptom may be misleading in overweight/obese children with CeD. Furthermore, the rising prevalence of overweight and obesity at diagnosis challenges the traditional nutritional paradigm of CeD, as patients may face the dual burden of micronutrient deficiencies (as demonstrated by Papoutsaki et al. [6]) alongside risks related to excessive adiposity, such as metabolic complications.

Together, these studies show that pediatric CeD now presents with a wide nutritional spectrum – from persistent micronutrient deficiencies to behavioral barriers limiting dietary diversity, and even increasing rates of overweight. This highlights the need for ongoing, individualized nutritional follow-up that addresses both deficiency and excess.

Inflammatory Bowel Disease

Children with inflammatory bowel disease (IBD) are at risk of growth failure and altered body composition due to chronic inflammation, reduced nutrient intake, malabsorption, and treatment effects [9]. Although growth impairment is common and well-studied, lean body mass and sarcopenia are increasingly recognized as major complications that often remain undetected when relying on BMI alone [10].

Anthropometric trajectories in children prior to development of inflammatory bowel disease

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Comments: The population-based study from Denmark by Brusco De Freitas et al. [11] followed 1,522 children born 1997–2015 who developed IBD, with anthropometric data available up to 10 years before and 3 years after diagnosis. By leveraging national birth and child health registers, the investigators constructed Z-score trajectories for weight, height, and BMI, comparing IBD patients against the general population and unaffected siblings. In Crohn's disease (CD), weight faltering was evident up to 3 years before diagnosis (mean difference in weight Z-score −0.21, 95% CI −0.34 to −0.08), and height and BMI declined most sharply in the year prior. In ulcerative colitis (UC), deviations appeared later and were less pronounced. After diagnosis, impairments persisted, with incomplete catch-up mainly in CD. Sibling comparisons showed no similar pattern, confirming disease-specific effects. This study highlights that growth faltering precedes clinical onset, particularly in CD, making longitudinal growth monitoring an important potential tool for earlier detection.

Clinical risk factors for body composition deficits in children with inflammatory bowel disease

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Investigating sarcopenia in pediatric Crohn's disease with magnetic resonance enterography: an observational study

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Comments: Expanding beyond growth faltering or underweight, the study by Alexander et al. [12] focuses on body composition analysis in 516 children with IBD (45% females, median age 13.1 years, 70% with CD), followed at the Children's Hospital of Philadelphia, USA. This study showed that lean body mass deficits are frequent at presentation despite normal BMI. Using DXA within 6 months of diagnosis, 26% had low appendicular lean soft tissue mass index, while only 4% were underweight by BMI and none had fat mass index deficits. Independent predictors of low lean body mass included CD (OR 2.3, $p = 0.01$), active disease (OR 2.1, $p = 0.008$), thrombocytosis (OR 2.2, $p = 0.01$), glucocorticoid exposure (OR 1.9, $p = 0.04$), and Asian ethnicity (OR 6.4, $p < 0.001$). This study demonstrates that BMI substantially underestimates suboptimal nutrition status in pediatric IBD and reinforces the importance of routine body composition assessment.

The recent Italian two-center retrospective study by Calia et al. [13], used magnetic resonance enterography (MRE) to assess muscle mass in 74 children (mean age 13.2 years; 25 girls) with newly diagnosed CD. Sarcopenia, defined as total psoas muscle area (tPMA) <3rd percentile, was present in 46%. Despite lower BMI in the sarcopenic group (BMIz −1.49 vs. −0.36, $p = 0.001$), 56% of sarcopenic patients had BMIz > −2. Sarcopenia was associated with higher clinical and endoscopic activity of the disease at baseline. Over a median 35-month follow-up, composite adverse outcomes did not differ significantly, yet sarcopenic children had more relapses (0.258 vs. 0.132 per person-year, $p = 0.068$) and more steroid treatment cycles. Practically, adding tPMA to standard MRE reads provides a no-extra-burden screen for high-risk children who may warrant targeted nutrition and tighter inflammation control.

Together, these studies emphasize the nutritional risk in pediatric IBD, from growth faltering before diagnosis, through lean mass deficits and frequent sarcopenia. These publications demonstrate that BMI alone is insufficient, and that systematic monitoring of growth, body composition, and muscle status should be an integral part of IBD care.

Vitamin and trace element status and growth in children with short bowel syndrome being weaned off parenteral nutrition

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Retrospective review of growth in pediatric intestinal failure after weaning from parenteral nutrition

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Comments: Pediatric intestinal failure (IF) is a complex condition defined by reduced intestinal mass and/or function below the minimum needed to maintain adequate hydration, nutrient, and energy absorption for growth, thereby requiring parenteral nutrition (PN) to sustain life and development. The most common pediatric cause is short bowel syndrome (SBS) (either as a result of necrotizing enterocolitis in premature infants, or due to congenital intestinal malformations), followed by congenital enteropathies and severe dysmotility disorders [14]. IF outcomes have improved with multidisciplinary intestinal rehabilitation programs and standardized monitoring. However, although PN is lifesaving, the quality of life is substantially affected by this treatment, and there are major PN-related complications. Particularly in SBS, one of the most important goals of care is to promote enteral adaptation and achieve enteral autonomy; however, nutritional risks can persist even after PN weaning [15]. The recent study by Tuokkola et al. [16] describes a Finnish cohort of 59 children with SBS, focused on weaning window – defined as the months immediately before and after PN cessation, representing a period of maximal biochemical vulnerability. During this phase, deficiencies in fat-soluble vitamins (D, A, K) and trace elements (selenium, zinc) were common, with blood vitamin D levels being low in 58% and blood vitamin A levels in 37% at the time of transition. Growth outcomes were determined largely by residual bowel anatomy, with children lacking ileum and colon

continuity showing significantly poorer height trajectories. This study underlines the need for intensified laboratory monitoring during and after PN weaning, coupled with tailored supplementation strategies.

Complementing the micronutrient data, this two-center US registry by Nucci et al. [17] analyzed long-term growth patterns of 150 IF patients weaned from PN. Over the following 5 years, most non-transplanted children maintained growth within ~0.5 Z-score of their PN-weaning baseline, indicating stability but limited catch-up. Diagnosis mainly influenced the outcomes: children with small bowel atresia demonstrated some linear recovery, while those with midgut volvulus or gastroschisis often had later decelerations. These results demonstrate that achieving enteral autonomy does not guarantee nutritional recovery, and highlight the heterogeneity of growth outcomes depending on underlying diagnosis and treatment course.

Together, these studies show that after PN cessation, children with IF remain at risk: micronutrient deficiencies peak around weaning, while growth tends to stabilize with limited catch-up. The findings emphasize that PN weaning should mark a new phase of nutritional rehabilitation and surveillance.

Cystic Fibrosis

Effects on growth, weight and body composition after CFTR modulators in children with cystic fibrosis

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Growth, body composition, and strength of children with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor (ETI)

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Comments: Cystic fibrosis (CF) is a congenital disease caused by mutations in the CFTR gene encoding the cystic fibrosis transmembrane conductance regulator protein. Dysfunction leads to thick secretions, recurrent infections, exocrine pancreatic insufficiency, malabsorption, and impaired growth. Traditional therapy focused mostly on symptom control – airway clearance, pancreatic enzyme replacement, antibiotics, and nutritional support. In the past decade, CFTR modulators – particularly the triple therapy elexacaftor/tezacaftor/ivacaftor (ETI) – have transformed the clinical course of the disease [18, 19]. Early evidence shows better linear growth in children starting modulators at a young age, raising the possibility of normalizing growth trajectories and reducing long-term complications.

These two recent pediatric studies illustrate how modulators reshape the nutritional profile of CF. A large Spanish multicenter study by López Cárdenes et al. [20] evaluated 234 children (median age 13.6 years) initiating CFTR modulators, including both dual and triple therapies. After 12 months, both groups showed significant improvements in weight and BMI Z-scores. Body composition analysis in a subgroup on ETI ($n = 62$) revealed an increase in fat mass at 6 months ($p = 0.04$), which attenuated by 12 months, while fat-free mass rose significantly at both 6 and 12 months ($p < 0.05$). Triceps skinfold thickness also increased, indicating increased fat mass. These findings confirm that modulators improve nutritional status but raise new concerns regarding excessive fat gain.

The US prospective study by Boat et al. [21] followed 27 children (ages 6–11) on ETI over a 12-month period, and reported stable weight, height, and BMI Z-scores, matching healthy US peers. However, composition analysis revealed a 12% rise in fat mass index ($p = 0.007$) and a significant increase in fat-free mass index (+0.44 kg/m^2/year, $p < 0.001$). Skeletal muscle mass index rose by +0.33 ($p < 0.001$), accompanied by a 47% improvement in handgrip strength ($p = 0.001$). However, some already overweight children accumulated fat mass, again, raising new concerns about metabolic health.

Factors associated with statural growth in pediatric kidney transplant recipients with focus on metabolic acidosis

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Comments: Children with chronic kidney disease (CKD) are at high risk for growth failure, malnutrition, and micronutrient imbalance. Growth impairment in pediatric CKD is multifactorial: chronic inflammation, metabolic acidosis, bone-mineral disturbances, inadequate intake, and altered growth hormone–IGF-1 axis. Despite advances in renal replacement therapy and nutritional support, many children fail to reach normal height potential, both before and after kidney transplantation [22, 23].

Prytuła et al. [24] reported a large multinational registry analysis, from the Cooperative European Paediatric Renal Transplant Initiative (CERTAIN) Research Network, that included 2,147 pediatric kidney transplant recipients with up to 5 years of follow-up. Median age at transplantation was 10.2 years, and median baseline height-for-age Z-score was −1.73, reflecting significant pre-transplant growth impairment.

The study specifically examined the role of metabolic acidosis, present in 31%–39% of children post-transplant. The study showed that there was no significant association between plasma bicarbonate levels and linear growth ($p = 0.21$), and alkali supplementation did not improve height velocity ($p = 0.73$). Instead, the strongest

determinants of growth were glucocorticoid exposure ($p < 0.001$), allograft rejection ($p = 0.04$), and reduced graft function (higher eGFR associated with better growth, $p < 0.001$). Younger age at transplant, living donor transplantation ($p = 0.04$), and use of recombinant growth hormone ($p = 0.04$) were also linked to improved catch-up. Overall, despite modern transplant care, many children did not achieve full normalization of height, underscoring the persistent impact of CKD and its treatments on growth.

Congenital Heart Disease

Role of leptin and insulin like growth factor-1 in regulation of growth in children with congenital cyanotic heart disease

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Comments: Children with congenital heart disease (CHD) are at high risk of growth failure and malnutrition, particularly in the first years of life. The mechanisms are multifactorial and include increased metabolic demands, feeding difficulties, impaired nutrient absorption, and the impact of chronic hypoxemia and heart failure [25]. Poor growth has been associated with worse surgical outcomes, neurodevelopmental delays, and higher mortality [26]. Even after corrective surgery, nutritional risk can persist, and careful growth monitoring with individualized nutritional support remains a cornerstone of management.

This case-control study by Elsharkawy et al. [27] compared 39 children with cyanotic congenital heart disease (CCHD) (mean age ~2.9 years) to 47 healthy controls. Anthropometric data confirmed significant growth impairment in the CCHD group: both height and weight were lower, with corresponding BMI reduction. The biochemical profile showed that serum leptin levels were less than half of controls (2.07 vs. 3.94 ng/mL, $p < 0.001$) and IGF-1 was markedly reduced (35 vs. 110 ng/dL, $p < 0.001$).

Within the patient group, leptin correlated positively with BMI ($r = 0.36$, $p = 0.021$), suggesting that reduced adipose tissue and lower energy reserves directly explain leptin deficiency. In contrast, IGF-1 correlated with arterial oxygen saturation ($r = 0.347$, $p = 0.04$), supporting hypoxemia as a driver of impaired GH–IGF-1 axis activity. Importantly, leptin did not correlate with oxygen saturation or IGF-1, indicating independent mechanisms: leptin reflects nutritional status and fat mass, while IGF-1 reflects oxygenation and endocrine regulation.

The findings underscore the multifactorial nature of growth impairment in cyanotic CHD. While surgical correction may help restore oxygen delivery and IGF-1 activity, ensuring adequate energy intake and addressing feeding difficulties are critical for improving leptin levels and weight gain.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

Both authors have read and commented on the reviewed manuscripts.

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

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Introduction

Early nutrition plays a pivotal role in shaping lifelong health by influencing growth patterns, body composition, and the risk of developing obesity and related metabolic disorders. The first years of life represent a critical window during which nutritional exposures can exert lasting effects through mechanisms such as metabolic programming and hormonal regulation. Breastfeeding (BF), timing of complementary feeding, and dietary quality are important for these outcomes. Moreover, early-life nutrition interacts with environmental factors as discussed in one of the selected papers.

We conducted a nonsystematic literature search using PubMed with the terms "breastmilk [or] human milk [or] complementary [and] growth [or] body composition [or] adiposity" published between July 1, 2024, and June 30, 2025. We also employed Elicit using the research query "papers published between July 1, 2024, and June 30, 2025, on the topics of early nutrition and its effect on growth, body composition, and later obesity."

We have selected 10 publications based on their relevance to the research within this field, novelty, and overall quality. While most studies were conducted in high-income countries, we also included three studies from low- and middle-income countries (LMICs) that investigated the effect of various nutritional supplementations. We have grouped the articles into four thematic categories: Human milk composition and growth (two studies), Impact of breastfeeding and complementary feeding on later adiposity (three studies), Nutritional supplementation in LMICs (three studies), and Maternal characteristics, breastfeeding and offspring growth (two studies).

Key articles reviewed for this chapter

Human Milk Composition and Growth

Poly- and perfluoroalkyl substances (PFAS) in the first 1000 days reduce linear growth, lean body mass and bone mineral density at age 3 years
van Beijsterveldt IALP, Dorrepaal DJ, van Zelst BD, van den Berg SAA, Hokken-Koelega ACS
Clin Nutr 2025;50:175–182

Breastfeeding and health outcomes for infants and children: a systematic review
Patnode CD, Henrikson NB, Webber EM, Blasi PR, Senger CA, Guirguis-Blake JM
Pediatrics 2025;156:e2025071516

Impact of Breastfeeding and Complementary Feeding on Later Adiposity

Infants' dietary pattern characterized by ultraprocessed foods is associated with rapid weight gain and overweight/obesity risk: national health and nutrition examination survey 2009–2018
Neri D, Martínez Steele E, Rauber F, Santos Costa CD, D'Aquino Benicio MH, Bertazzi Levy R
J Acad Nutr Diet 2024;124:841–850

An infant diet score based on health records is associated with BMI: a nationwide mother-child cohort study in Iceland (ICE-MCH)
Jonsdottir J, Thorisdottir B, Einarsdottir K, Thorsdottir I
Matern Child Nutr 2025;21:e70010

Childhood nutritional factors and cardiometabolic outcomes at 9–11 y of age: findings from the ROLO longitudinal birth cohort study
Callanan S, Delahunt A, Phillips CM, Wilson Z, Foley H, McNestry C, Douglass A, Cody D, McDonnell CM, Twomey PJ, Crowley RK, McAuliffe FM
Am J Clin Nutr 2024;120:891–906

Nutritional Supplementation in Low- and Middle-Income Countries

Impact of high- and moderate-protein supplementation on early-life obesity and body composition: a randomized controlled trial in India
Manapurath R, Chowdhury R, Upadhyay RP, Kurpad AV, Bose B, Devi S, Dwarkanath P, Bhandari N, Taneja S, Strand TA
Am J Clin Nutr 2025;121:1380–1386

Maternal multiple micronutrient supplementation in rural Pakistan increased some milk micronutrient concentrations, but not infant growth, at three-months postpartum: a randomized controlled trial substudy
Baxter JB, Wasan Y, Daniel AI, Begum K, Hussain A, Iqbal J, Aufreiter S, Beggs MR, Duan L, Greco A, Huang C, Soofi S, Bandsma RH, Bhutta ZA, O'Connor DL
Am J Clin Nutr 2025;122:174–184

Predictors of stunting and pathway analysis for linear growth among children aged two to three years after a trial of small-quantity lipid-based nutrient supplements and home-installed growth charts in three districts in Zambia
Locks LM, Chembe M, Billima-Mulenga T, Lauer JM, Sizakawe D, Henderson S, Rockers PC, Parkerson D, Fink G
J Nutr 2025;155:589–601

Maternal Characteristics, Breastfeeding and Offspring Growth

Maternal physical activity and its relationship to the human milk metabolome and infant body composition

Lu C, Dreyfuss JM, Hua T, Wolfs D, Nagel EM, Peña A, Lock EF, Seburg E, Pierce S, Kyere-Davies G, Johnson KE, Uniyal A, Tu J, Gale CA, Blekhman R, Kiebish M, Aristizabal-Henao JJ, Short KR, Rudolph MC, Demerath EW, Fields DA, Isganaitis E

J Clin Endocrinol Metab 2025 May 26:dgaf296. doi: 10.1210/clinem/dgaf296. Online ahead of print

Maternal mediterranean diet during lactation and infant growth

Grabowski A, Baylin A, Ellsworth L, Richardson J, Kaciroti N, Sturza J, Miller AL, Gearhardt AN, Lumeng JC, Gregg B

Breastfeed Med 2024;19:848–856

Human Milk Composition and Growth

Poly- and perfluoroalkyl substances (PFAS) in the first 1000 days reduce linear growth, lean body mass and bone mineral density at age 3 years

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Comments: Human milk (HM) is widely recognized as the optimal source of nutrition for infants. The World Health Organization (WHO) recommends exclusive breastfeeding (EBF) for the first 6 months of life, with continued BF up to 2 years of age or beyond. BF has been associated with several health benefits for the infants, including reduced weight gain in early life, lower incidence of respiratory and gastrointestinal infections, and decreased levels of blood pressure and insulin [1]. However, HM may also serve as a route of exposure to environmental contaminants, such as per- and polyfluoroalkyl substances (PFAS). These substances are synthetic compounds widely used in industrial processes and consumer products. Their persistence in the environment has led to widespread human exposure and has been associated with adverse health outcomes, including cancer in adults [2]. In children, PFAS exposure might interfere with the neuro- and metabolic development especially during critical windows of early development. Nevertheless, current knowledge regarding the long-term effects of early-life PFAS exposure remains limited. The authors have previously reported 2–3 times higher PFAS levels in exclusively breastfed (EBF) infants compared to exclusively formula fed (EFF) suggesting that BF constitutes a significant pathway for infant PFAS exposure [3].

In the present study, the associations between plasma PFAS levels measured in early life and subsequent growth, body composition, and bone mineral density (BMD) at

3 years of age were investigated in a cohort of 237 Dutch term-born infants. Among these, 99 were EBF for at least 3 months, 55 were EFF, and 81 received mixed feeding. EBF infants had higher PFAS levels both at 3 months (7.16 ng/mL) and 2 years (5.61 ng/mL) compared to EFF (2.35 ng/mL and 2.64 ng/mL, respectively) and mixed-fed children (4.32 ng/mL and 3.13 ng/mL, respectively). Over time, PFAS levels showed a slight decline in EBF and mixed-fed infants, potentially reflecting the long biological half-life of PFAS compounds. In contrast, PFAS concentrations remained stable in EFF infants. Higher PFAS levels in early life seem to have unfavorable effects on overall growth affecting linear growth, body composition, and bone mineralization. The authors have found that higher PFAS levels at 3 months and 2 years were associated with reduced linear growth (−0.069 SDS linear growth per ng/mL PFAS and −0.105 SDS linear growth per ng/mL PFAS, respectively), and lower height SDS (−0.063 and −0.099 height SDS per ng/mL PFAS, respectively) at 3 years of age. Furthermore, higher PFAS at 2 years were associated with lower lean body mass (LBM) and reduced BMD SDS at 3 years.

Given the elevated PFAS concentrations observed in EBF infants, an important question arises as to whether PFAS exposure may attenuate the well-established benefits of BF. As the authors write, a limitation is that an ideal comparison would involve a cohort of EBF infants unexposed to PFAS; however, such a scenario is not feasible due to the ubiquitous nature of these compounds. Instead, they found that EBF children had 0.408 SDS higher LBM and 0.547 SDS BMD at 3 years of age compared to EFF children indicating opposite effects of EBF for 3 months and PFAS levels at 2 years.

The study underlines the growing concerns of environmental pollutants that may interfere with growth and developments during critical periods in early life.

Despite the presence of PFAS, major health organizations like WHO emphasize that the benefits of BF outweigh potential risks. However, due to the environmental persistence and long biological half-life of PFAS, early-life exposure may have cumulative effects over time. The findings presented here suggest that PFAS in HM could potentially diminish the beneficial impact of early BF growth trajectories, bone development, and body composition – factors that may influence the risk of obesity and related health outcomes later in life. These results underscore the need for further investigation into the long-term health effects of PFAS exposure, and they call for longitudinal studies with extended follow-up periods to better understand these associations.

Breastfeeding and health outcomes for infants and children: a systematic review

Patnode CD[1], Henrikson NB[2], Webber EM[1], Blasi PR[2], Senger CA[1], Guirguis-Blake JM[3]

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Comments: The general understanding of how BF and intake of HM may improve specific infant outcomes, and the magnitude of these benefits, develops as new knowledge develops over time. Therefore, the aims of this systematic review were to synthesize the current

knowledge and evidence on the associations between BF and consumption of HM and several health outcomes in infants and children in high-income countries. The outcomes of interest were infectious diseases, allergic conditions including asthma, oral health, autoimmune gastrointestinal conditions, diabetes, growth and obesity, cardiovascular diseases, childhood cancer, cognitive development, and infant mortality. In this systematic review, the authors evaluated the evidence on associations between BF and child health outcomes by reviewing articles published in English from 2006 to August 14, 2024. Published systematic reviews as well as primary studies comparing various BF exposures and child health outcomes among term infants from high-income countries were selected from relevant databases. Twenty-nine systematic reviews and 145 primary studies were included in this systematic review. Meta-analyses were not conducted for any outcome. The included studies had very variable sample sizes ranging from 139 to about 13 million individuals.

Generally, definition of BF exposures was poorly reported and very heterogeneous. Most data on BF were collected using point-in-time measures by maternal report during the infant's first year of life, while others were based on one time point measurement typical with recall at about age 1 year. Exposure indicators for BF were often expressed as more versus less BF that could refer duration, ever versus never BF, or exclusive BF versus mixed feeding or no BF. Very few studies discussed the mode of HM delivery, such as feeding at the breast or bottle-feeding with HM.

The outcomes of interest were collected using various methods, including direct measurement by study teams or clinicians or collected data from medical or social records. Outcomes were assessed at different ages from infancy to young adulthood, and some studies followed individuals to mid- or late adulthood. Overall, the review confirms that BF compared to no BF or less BF reduced the risk of many different adverse health outcomes. However, the evidence in many cases suffers from the risk of bias, including possible confounding, reverse causation, missing data, recall bias, and selection bias.

The results indicate a reduced risk of or several health outcomes for more BF compared to less BF. The most consistent and precise evidence of an association of ever BF and longer duration of any or exclusive BF was found for lower risk of acute otitis media, asthma, obesity, and childhood leukemia. However, there was consistent evidence that BF for 12 months or longer was associated with an increased risk of dental caries in early childhood. Evidence showed a possible protective association between BF and lower risk of moderate-to-severe respiratory and gastrointestinal infections (in infants and younger children), allergic rhinitis, malocclusion, inflammatory bowel disease, type 1 diabetes, rapid weight gain and growth, blood pressure, and infant mortality. No clear associations were found between BF and atopic dermatitis, celiac disease, or cognitive ability. It was not possible to draw a clear conclusion on the relation between BF and risk of food allergy or type 2 diabetes.

Although this systematic review with updated data published until August 2024 shows consistent evidence of reduced risk for several health outcomes for more versus less BF, it was not possible to identify clear thresholds of BF duration required to achieve beneficial effect for any of the outcomes.

It would be important for improving future guidelines if clearer evidenced-based thresholds could be identified. It will, among other things, require improved and internationally standardized methods for registration of BF practices. Furthermore, this review covers high-income countries. Similar knowledge for LMICs is needed.

Infants' dietary pattern characterized by ultraprocessed foods is associated with rapid weight gain and overweight/obesity risk: national health and nutrition examination survey 2009–2018

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Comments: Globally, obesity in children has become a major public health problem. In the United States, 19.7% of children and adolescents had obesity according to the 2017–2020 Nation Health and Nutrition Examination Survey (NHANES), and the prevalence increases with age [4]. It is well established that overweight and obesity often tracks into adulthood with higher risk to develop diseases such as type 2 diabetes and cardiovascular disease. While genetic and lifestyle factors are key determinants of obesity, factors acting early in life also influence the risk of later obesity. Concurrently, there has been a global shift from minimally processed foods to ultra-processed foods (UPF), including complementary feeding and children's diet. However, the extent of UPF consumption and its association with overweight in infancy is not yet well described. According to the Nova food classification system, UPF contains little or no whole food and typically include added sugars, salt, saturated fat, and various additives [5]. These components may negatively affect taste preferences and dietary habits formed in early life, which can persist into adulthood.

In this study by Neri et al., infants' dietary patterns were assessed, and their associations with weight outcomes were investigated. Data were drawn from the NHANES survey, including 744 US infants aged 6–12 months with normal birth weight and at least one 24-h dietary recall record. Dietary patterns were analyzed using principal component analysis based on energy intake from NOVA food subgroups. The outcomes were rapid weight gain, defined as >0.67 SD change in weight-for-age Z-score from birth to assessment and risk of overweight and/or obesity, defined as weight-for-height Z-score >+1.

Three distinct dietary patterns were identified: (1) the Natural or Minimally Processed Foods pattern: This pattern showed positive loadings for a variety of natural or minimally processed foods, including fruits, meat, eggs, and milk. It also included some processed culinary ingredients such as plant oils and animal fats, a few processed foods like cheese and commercial baby foods and certain UPF such as breads, soy products, and dressings. (2) Infant Formula pattern: Characterized by high positive loading for infant formula and breakfast cereals and negative loading for breast milk. (3) UPF pattern: This pattern had negative loadings for natural or minimally processed foods and processed culinary ingredients. It showed positive

loadings for other processed foods, such as salted or sweetened nuts, and for a variety of UPF, including salty snacks, French fries, and ready-to-eat hamburgers. Interestingly, it also had negative loadings for infant formula.

One-third of the infants were at risk of overweight and/or obesity, while 42% had experienced rapid growth. The majority (65.5%) were introduced to solid foods before 6 months of age, with a mean age of introduction at 4.6 months. Infants who experienced rapid growth or were at risk of overweight and/or obesity had a lower intake of calories from HM compared to those without rapid growth (56.5 kcal/d vs. 140 kcal/d) or not at risk of overweight and/or obesity (79.6 kcal/d vs. 120 kcal/d). Furthermore, adherence to the UPF pattern was positively associated with an increased risk of rapid weight gain (adjusted odds ratio (OR) [CI 95%] = 1.3 [1.1–1.5]) and overweight and/or obesity (adjusted OR 1.2 [1.0–1.4]). However, the distribution of infants across the three dietary patterns was not clearly described. Moreover, a standard reference value was used to assess intake and energy content of HM across all stages of lactation, which may lead to imprecise estimates. In addition, it was not possible to adjust for several relevant covariates, such as prepregnancy BMI and BF duration. Nevertheless, the findings suggest that the consumption of UPF may be linked to an increased risk of obesity not only in adults and older children [6, 7] but already during infancy.

This study underscores the importance of promoting BF and highlights the need for greater attention to the potential disadvantages of UPF consumption in infancy – not only in relation to growth and overweight risk, but also due to its potential influence on later taste preferences and dietary habits. This may indicate a need for stronger regulation of marketing practices and nutritional standards for foods targeted at infants.

An infant diet score based on health records is associated with BMI: a nationwide mother-child cohort study in Iceland (ICE-MCH)

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Comments: The diet during infancy undergoes significant changes – from exclusive milk feeding in the first 6 months to the gradual introduction of complementary foods. By 12 months, this transition is expected to result in a varied diet that includes all major food groups. This period is critical for ensuring adequate nutrition and introduce healthy diet habits to promote healthy growth and prevent the early onset of overweight [8]. Dietary patterns and Infant Diet Scores (IDS) offer valuable tools for assessing the overall quality of diets and alignment with dietary recommendation during this transitional period with rapid changes.

In the study by Jonsdottir et al., an IDS was created using data from a subgroup of infants (n = 12,848) with complete diet records, drawn from health records on all Icelandic infants born from January 2009 to June 2015 (n = 30,623). The feasibility of

the IDS was evaluated by examining its alignment with dietary guidelines and its associations with birth characteristics, sociodemographic factors, and infant BMI-for-age Z-score (BAZ) at 12 and 18 months. The IDS comprised six components reflecting key aspects of infant nutrition: (1) EBF, (2) any BF, (3) age at introduction of cow's milk, (4) age at introduction of complementary foods, (5) number of foods groups consumed to estimate food variety, and (6) use of vitamin D supplement. The total score ranged from 0 to 5 points with higher scores indicating greater adherence to dietary recommendations. The highest quintile of the IDS distribution was used as the reference category. The median IDS was 3.50 (interquartile range: 2.75–4.00), indicating that the majority of Icelandic infants in the study population followed the recommendation reasonably well, although only few infants followed the guidelines completely. The IDS was associated with several maternal and birth characteristics, showing positive associations with birth weight, maternal education, and maternal age, and negative associations with maternal prepregnancy obesity, multiple births, and rural residence. Furthermore, a lower IDS was associated with increased risk of having BAZ >+2 at both 12 and 18 months, compared to infants with highest IDS score (quintile 5). Overall, the found associations were in the expected direction, supporting the utility of the IDS as a valuable indicator of infant dietary quality.

The study is notable for its use of a large dataset derived from nationwide health records. It demonstrates the interesting use of IDS, which, unlike single-nutrient approaches, can capture the complexity of dietary intake, including food diversity, feeding practices, and alignment with dietary recommendations during infancy. Additionally, the negative associations with some maternal and sociodemographic characteristics may be valuable for identifying vulnerable groups and which IDS components received the lowest scores. This information could help to guide targeted nutritional support for these groups. As the authors also mention, the IDS can be adapted to reflect local dietary guidelines and food availability as national dietary recommendations differ as well as feeding practices across different settings.

Childhood nutritional factors and cardiometabolic outcomes at 9–11 y of age: findings from the ROLO longitudinal birth cohort study

Callanan S[1], Delahunt A[1], Phillips CM,[2] Wilson Z[1], Foley H[1], McNestry C[1], Douglass A[2], Cody D[3], McDonnell CM[4], Twomey PJ[5], Crowley RK[6], McAuliffe FM[1]

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Comments: Most research investigating HM consumption and infant outcomes is conducted from short-term perspectives, although some epidemiological studies exist using hard endpoints such as relevant diagnoses [9, 10]. Thus, the evidence on

whether the known benefits of HM persist into childhood, adolescence, and/or adulthood is sparse.

The study by Callanan and colleagues uses data from a longitudinal birth cohort with follow-up visits at 9 and 11 years of age. They aim to investigate how early feeding practice and childhood dietary quality are related to cardiometabolic outcomes in adolescence. For the purpose of this chapter, we will focus on the results related to HM consumption only. Specifically, they investigate whether exposure to HM (yes/no), duration of BF (months), and timing of introduction to complementary foods (continuously in weeks [wks] and categorically as early being introduced early, i.e., <17 wks postnatally vs. as recommended, i.e., ≥17 wks) are related to blood pressure, blood markers, anthropometric measurements, and body composition measured using dual energy X-ray absorptiometry. They invited participants enrolled in the Randomised cOntrol trial of LOw glycaemic diet (ROLO) in pregnancy longitudinal birth cohort of which $n = 399$ (52.5%) attended the 9- and 11-years follow-up and were included in their analyses. Information on HM consumption and duration of BF was collected at 6 months, and 2, 5, and 9–11 years postnatally, while information on introduction to complementary foods was collected at the 2-, 5-, and 9–11-years follow-up visits. They adjusted for several covariates including child sex, birthweight, age at follow-up, gestational age, preteen physical activity, maternal age at delivery, maternal ethnicity, early pregnancy body mass index (BMI), smoking, and preteen BMI.

Their main findings included a reduced body fat percentage of −2.86% for preteens who had received any HM compared to those who had never received HM. Further, longer durations of any BF were associated with lower plasma concentrations of C-reactive protein and interleukin-6 and tended to be related to lower systolic blood pressure percentile. However, the associations became nonsignificant after adjustment for confounding factors. They further observed that preteens who had been introduced to solid foods early had lower total cholesterol, which was only significant in crude models.

Although the findings are interesting, the results on blood markers are highly affected by lifestyle factors despite adjustment for confounding factors. In fact, these findings may highlight the remaining challenges within this area, in particular the methodological differences between short- versus long-term follow-up. In observational studies, it is crucial to adjust for possible confounding factors. However, in studies with a long follow-up, time-varying confounding factors such as smoking or physical activity may result in residual confounding. Thus, for the present findings, adjustment for lifestyle factors such as physical activity may not be sufficient to eliminate confounding. In addition, the authors adjust for covariates occurring after the exposure, i.e., competing exposures to the outcome, which may increase certainty and precision to the results/estimates. Yet, there is a risk of overadjustments, especially if the exposure may affect the covariate, such that it becomes a mediator. Importantly, observational studies testing a high number of hypotheses should be adjusted for multiple testing to reduce the risk of type I errors. This was not done in the present study, which tested 28 outcomes in relation to four different exposures. Consequently, there is a high risk of false-positive results, and their findings should be interpreted with caution.

Despite hereof, this study brings evidence of the importance of the early nutrition, particularly the benefits of HM consumption, in relation to cardiometabolic health in adolescence. Especially the long follow-up is novel, but brings certain limitations to the methodology, which should be considered. For future research, it could be of interest to investigate the influence of BF intensity, such that duration of EBF versus any BF would result in more pronounced associations with the outcomes of interest.

Nutritional Supplementation in Low- and Middle-Income Countries

Impact of high- and moderate-protein supplementation on early-life obesity and body composition: a randomized controlled trial in India

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Comments: In many low-income countries, the complementary feeding period is often characterized by introduction of nutritionally inadequate, monotonous diets that fail to meet the increasing energy and micronutrient needs of young children. Adequate protein intake is important for optimal growth during this critical period. Both protein quantity and especially quality are important for optimal growth, as low-quality protein is a major contributor to stunting and wasting in these settings. On the other hand, too high protein intake in early life has been associated with increased risk of obesity in later childhood. Avoiding high protein intake in early life has therefore been recommended as a preventive strategy for obesity [11, 12]. However, this field is still under considerable research, and this study investigates the balance between promoting healthy growth and preventing obesity in early life through appropriate protein intake.

In the randomized controlled trial with the primary aim to prevent stunting [13], a total of 1548 six-month-old infants from Delhi were randomized (1:1:1) to receive a daily packet of isocaloric high-protein milk-cereal (5.6 g protein), moderate-protein milk-cereal (2.5 g protein), or no supplementation for 6 months. The outcomes were overweight and/or obesity, defined as BMI-for-age Z-score (BAZ >+2 SD) assessed at 12 and 24 months of age. Furthermore, body composition was measured in a subgroup at 12 months. The prevalence of overweight/obesity was low for all groups at both 12 and 24 months, ranging from 0.4% to 0.8% and 0.2% to 0.6%, respectively, with no significant differences between groups at any time points. The BAZ increase from 6 to 12 months was slightly higher for the high-protein group compared to the

no-supplement group, whereas there was no difference at 24 months. For the moderate-protein group, there was no difference in BAZ at any time point compared to the no-supplement group. Notably, no difference in body composition was observed among the groups, suggesting that the small increase in BAZ at 12 months for the high-protein group was not accompanied by increased adiposity.

The results from the trial are interesting, as they provide new insights into how linear growth supported and stunting prevented without increasing the risk of later obesity through protein supplementation in LMICs. The high-protein supplement did not lead to increased adiposity or higher risk of overweight and/or obesity although the protein intake was increased but remained within recommended levels, but a limitation is the relatively short follow-up period. However, the effects of protein intake in high-income settings may differ from those in LMICs as the dietary context may be quite different, such as protein quality, digestibility, and absorption of amino acids. Additionally, the ratio between dairy and plant-based protein sources may be relevant to explore further, both in terms of sustainability, and to achieve the optimal protein composition for supporting linear growth. Even though the tested supplements did not appear to increase the risk of overweight, they had only minimal effect on reducing stunting [11]. This highlights the need for continued research in LMIC settings to develop affordable diets or supplements regarding protein quality, protein quantity, and protein sources aiming to prevent the dual burden of malnutrition and overweight.

Maternal multiple micronutrient supplementation in rural Pakistan increased some milk micronutrient concentrations, but not infant growth, at three-months postpartum: a randomized controlled trial substudy

Baxter JB[1,2], Wasan Y[3], Daniel AI[1,4], Begum K[3], Hussain A[3], Iqbal J[3], Aufreiter S[1,4], Beggs MR[1,4], Duan L[1], Greco A[1,4], Huang C[1], Soofi S[3], Bandsma RH[1,2,4,5], Bhutta ZA[1,2,3,6], O'Connor DL[1,4,7]

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Comments: Malnutrition during childhood remains a major challenge in many resource-limited countries. Close to 50% of children in resource-limited settings risk not to reach their full developmental potential mainly due to poor nutrition and its long-term consequences. EBF is recommended for the first 6 months postpartum and partly BF up to age 2 years or beyond. HM is considered unique and especially well-suited to secure optimal growth and development in infants. HM provides bioavailable and easily digestible nutrients, and furthermore, bioactive components that, among other effects, also reduce risk of infections. Micronutrients are an important part of HM nutrients. However, it is known that HM micronutrient composition can vary with the micronutrient status of the lactating mother. The first months of life are a period with rapid development and growth of, e.g., immune system, lean body mass, and the brain.

Several micronutrients are essential for these processes, and low maternal status may negatively affect infant and child development.

In Pakistan, the prevalence of stunting is high (length-for-age Z-score (LAZ) < −2). At the same time, BF is widely practiced and about 94% of children below 2 years of age receive HM. It is also known that multi-micronutrient deficiencies among females of reproductive age are widespread. Among young females in rural Pakistan, only 14% consume a diet that is likely to cover their needs for micronutrient.

It is not known how these factors affect mature HM composition and infant growth and whether multiple micronutrient supplementation (MMS) during pregnancy and lactation has a positive effect.

The aims of the study were therefore to examine the effects of maternal MMS postpartum compared to standard care in relation to: (1) HM macronutrient composition, and (2) infant growth at 3 months postpartum. Furthermore, associations between HM micronutrient composition and infant growth were analyzed.

The present substudy was nested in a district-based, two-arms, prospective, cluster-randomized, controlled trial where MMS was compared to standard care. A total of 25,447 females were enrolled and 4,163 life-birth observed. Mother-infant dyads were followed up to 12 months postpartum. At 3 months, mothers were invited to participate in the milk substudy if the following inclusion criteria were met: (1) Infant was term-born, (2) infant age 3 months ±30 days, (3) the mother willing to provide complete breast expression, and (4) exclusive or predominantly BF (using WHO definition).

The study enrolled 186 mother-infant dyads (97 in the MMS group and 89 in the standard care group), and the target sample size was not reached reducing the original planned power. There was a highly significant difference in HM concentration between the MMS and standard care groups for iodine. Furthermore, there was a significant difference for vitamin A (retinol). However, there was no difference between the two groups for vitamin B12, alpha-tocopherol and folate. In general, there were no differences between the groups for infant growth outcomes (LAZ, weight-for-age Z-score (WAZ), weight-for-length Z-score (WLZ), head circumference-for-age Z-score) except for alpha-tocopherol and LAZ.

It may seem surprising that supplementation with multi-micronutrients containing iodine, retinol, tocopherol, vitamin B12, and folate had so little influence on HM concentrations (except for iodine and vitamin A) in a group of females deficient in several micronutrients. Furthermore, the supplementation had almost no effect on infant growth. The authors speculate that a reason could be that the mothers might also be deficient in other micronutrients important for growth such as zinc. Another explanation could be that the supplementation generally did not raise the concentration of the added micronutrients above what the authors refer to as estimated adequate HM concentration. More research is needed on HM composition and how factors such as the lactating mother's diet influence the HM composition.

Predictors of stunting and pathway analysis for linear growth among children aged two to 3 years after a trial of small-quantity lipid-based nutrient supplements and home-installed growth charts in three districts in Zambia

Locks LM[1,2], Chembe M[3], Billima-Mulenga T[3], Lauer JM[1], Sizakawe D[4], Henderson S[5], Rockers PC[2], Parkerson D[5], Fink G[6,7]

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Comments:

Stunting is common among children in LMICs. It contributes to both morbidity and mortality and is associated with impaired child development and reduced educational achievement [14]. Low-quality diets and infectious diseases are the main causes of impaired growth; however, poor sanitation, inadequate infrastructure, and cultural barriers may also play a role. Despite global efforts, stunting remains a major public health challenge.

This study was based on a randomized controlled trial (RCT) conducted in Zambia, where 35% of children aged 6–59 months were stunted. The trial investigated the effect of installing growth charts in the home and/or receiving small-quantity lipid-based nutrients supplements (SQ-LNS) [15]. Though SQ-LNS resulted in 0.21 SD higher HAZ, over 40% of the children across all four intervention groups remained stunted. The aim was to identify predictors of stunting and HAZ among the children aged 27–36 months, who participated in the RCT.

Among others, the potential predictors included various sociodemographic characteristics, asset ownership (e.g., mobile phone, television, car, electricity, mosquito net), maternal and child characteristics, diet diversity, BF status, intervention group, household sanitation, and infections and diarrhea. They used multivariable models, including exposures with $p < 0.2$ in univariable models, to identify determinants of stunting and endline HAZ. Pathway analysis to explore underlying and modifiable risk factors was also conducted. Of the 1,911 children included in the study, 19.7% were stunted at baseline, when the children were between 2 and 11 months of age. Notably, at endline 2 years after the intervention, the prevalence of stunting was increased to 49.9%, indicating that this is a critical period for development of stunting and consequently also for preventing it. However, less than 1% of the children were wasted. Predictors of stunting and lower HAZ included being male, having lower baseline HAZ, lower asset ownership, shorter maternal height, lower maternal BMI and education, not being randomized to SQ-LNS, and using biomass instead of electricity. Furthermore, living in urban areas, more than one child under 5 years in the household, and episodes of diarrhea in the previous 2 weeks were also determinants for lower HAZ. Baseline HAZ was the strongest predictor. The pathway analysis supported these findings, as many of the same variables were associated with endline HAZ including not receiving SQ-LNS.

The study highlights the extent and complexity of stunting. Many of the identified determinants are related to socioeconomic status and poverty and may be

influenced by residual confounding. Nevertheless, randomization to SQ-LNS improved HAZ and lowered the risk of stunting. However, it is also evident that additional multisectoral strategies are needed to reduce the prevalence of stunting. These include poverty reduction, improved maternal education, better nutrition, control of infections, and broader health interventions.

Maternal Characteristics, Breastfeeding and Offspring Growth

Maternal physical activity and its relationship to the human milk metabolome and infant body composition

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Comments: Physical activity is recommended during pregnancy as it reduces the risk of pregnancy complications, such as preeclampsia and gestational diabetes mellitus, and by further reducing the risk of complicated births, including caesarean section [16, 17]. However, the evidence of the influence of physical activity during BF on HM composition and possibly infant outcomes is limited.

The study by Lu et al. investigated the influence of maternal physical activity on the HM metabolome and infant body composition. They used data from two different cohort studies: an acute exercise cohort and a habitual physical activity cohort. In the acute exercise cohort, 15 mothers completed a 3 × 10 min moderate-intensity walking on a treadmill 1 month postpartum and milk samples were collected before and after the exercise.

In the habitual exercise group, 119 mothers completed a Physical Activity Recall questionnaire at two time points (in third trimester of pregnancy and at 3 months postpartum) and completed an interviewer-based assessment of duration and intensity of physical activity during the last 7 days. Mothers were categorized as "cases" if they met the Centers for Disease Control and Prevention guidelines for physical activity at both timepoints; otherwise, they were categorized as "controls." Milk samples were collected as full expressions at 1 month postpartum, and infant body composition was assessed using both air displacement plethysmography (one and

3 months postpartum) and dual energy X-ray absorptiometry (6 months postpartum). The authors identified 101 milk metabolites, which were altered after the exercise cohort, while 45 metabolites differed between cases and controls in the cohort investigating habitual physical activity. Furthermore, 22 milk metabolites were associated with habitual physical activity after adjustment for confounding factors and 10 metabolites were associated with both acute and habitual physical activity. They were all inversely associated with habitual activity, while five increased and five decreased with acute physical activity. Interestingly, six of the 10 milk metabolites were positively associated with infant adiposity, such as fat mass index at 1 month and change in BMI Z-score from one to 3 months. All 10 metabolites were inversely associated with physical activity and positively associated with infant adiposity. Among others, the authors highlight β-hydroxybutyrate (BHB) as this is a byproduct of fatty acid oxidation occurring during exercise. Moreover, BHB can be conjugated with phenylalanine (Phe) to BHB-Phe, which has been related to reduced appetite, decreased food intake, and lower body weight in obese mice. Thus, the authors suggest that these metabolites in HM may contribute to the appetite regulation and energy intake, thus reducing the risk of later obesity in breastfed infants. However, in order to strengthen these hypotheses, evidence is needed to support the absorption of these metabolites in the infant gut.

In conclusion, as most current knowledge is from animal studies, these findings bring important and novel evidence of the benefits of physical activity during BF on HM composition. Yet, the influence on the infant is still uncertain and should be further investigated.

Maternal mediterranean diet during lactation and infant growth

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Comments: As mentioned earlier in this charter, HM is recommended as the primary source of infant nutrition, providing an ideal nutrient composition and important nonnutritive factors. However, HM composition is complex and dynamic and influenced by several factors such as maternal diet, health and genetics, and furthermore the sex of the infant. However, there is limited knowledge about if and how HM composition influences health in the offsprings.

The Mediterranean diet (MedDiet) has for many years been associated with better adult health and a reduced risk of several diseases such as cardiovascular disease and cancer. These positive effects are suggested to be related to its higher content of

monounsaturated fat, fiber, phytonutrients, whole grains, and omega-3 fatty acids, as well as lower content of omega-6 fatty acids, saturated fat, and sugar. During pregnancy, maternal MedDiet has been associated with lower maternal weight gain, lower risk of gestational diabetes, and lower risk of fetal growth restriction. For lactating mothers, higher MedDiet scores have been associated with, among other things, higher antioxidant and monosaturated fat content in HM, as well as higher infant urine antioxidant content. However, despite these positive health associations it is not known whether maternal MedDiet intake during lactation is associated with infant growth.

This study therefore aimed to examine if adherence to maternal MedDiet intake during lactation was associated to infant anthropometry and hypothesized that higher maternal MedDiet score would be associated with infant growth and lower adiposity. The substudy is based on data from the longitudinal observational cohort ABC Baby. It focuses on maternal diet during lactation and infant anthropometry at 6 months of age, (WAZ, LAZ, and WLZ) based on WHO standards and Flank skinfolds measurements. BF intensity was assessed at 2 months, defined as human milk feeds relative to the total number of liquids feeds (HM, formula, and cow's milk feeds). Maternal diet was assessed by Food Frequency Questionnaires and a MedDiet score was calculated reflecting adherence to MedDiet, ranging from 0 (minimal resemblances) to 8 (maximal resemblance).

A total of 167 mother-infant pairs were included in the analyses. Maternal mean age was 31.6 years. The mothers were predominantly white non-Hispanic and generally highly educated. Most mothers met the guidelines for vegetable and fruit intake but not for whole grain, fish, and nut intake. Compared to WHO standards, the infants were marginally shorter (LAZ mean −0.3) and heavier (WLZ mean 0.3). Linear models were used to assess associations of MedDiet with infant anthropometric outcomes adjusted for BF intensity, maternal BMI, and birth weight. Higher MedDiet score was associated with lower skinfold thickness. Higher intake of fruit and fish were associated with lower skinfold thickness, while higher nuts and seed intake was associated with higher WLZ. Higher intake of red meat and processed meat was associated with lower WAZ and LAZ. Higher intake of added sugar adjusted for energy intake was associated with lower WLZ.

Generally, the authors found associations between maternal diet during lactation and infant anthropometric outcomes at 6 months of age. Some of the associations may be expected such as higher MedDiet score related to lower skinfolds but other associations are difficult to explain, e.g., that nut and seed intake was associated to higher WLZ and red meat intake was associated to lower WAZ and LAZ. This underlines the limited understanding of how maternal diet influences HM composition and what constitutes a healthy milk composition. Furthermore, relatively few studies have evaluated the relation between HM composition and infant growth. A limitation in this study is the use BF intensity and did not measure the actual HM volume.

Future research will hopefully cover some of these gaps. It is especially important to know more about how maternal diet during lactation can improve both the health of the mother and infant, with long-term benefits for the offspring. In settings with undernourished mothers and children, this is especially relevant.

Conflict of Interest Statement

The authors report no conflict of interest.

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Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Pregnancy: The Impact of Maternal Nutrition on Intrauterine Fetal Growth

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Introduction

In this chapter of the 2026 edition of the yearbook on *Nutrition and Growth*, we review important manuscripts published between July 2024 and June 2025 addressing the association of maternal nutrition during pregnancy and intrauterine fetal growth. We selected 10 interesting studies, including both human and animal control studies, which gave us new insights through meticulous basic science. The new information presented here includes different types of diet composition during pregnancy and possible supplements taken and their possible effect on future children's health. We believe that this chapter enriches the reader, and hopefully will encourage further research and innovations to provide better care for our patients.

Key articles reviewed for this chapter

Human Studies

Maternal fatty acid intake and human embryonic growth: the Rotterdam Periconception Cohort
Rubini E, van Rossem L, Schoenmakers S, Willemsen SP, Sinclair KD, Steegers-Theunissen RPM, Rousian M
Eur J Epidemiol 2024;39:1379–1389
https://browzine.com/libraries/2584/journals/3203

Association between maternal folic acid supplementation in pregnancy and abnormal fetal growth: evidence from a birth cohort baseline survey
Zhang J, Wang M, Bai S, Lin S, Zhao X, Zhang F, Wang Z
Clin Nutr ESPEN 2025;66:135–141

Association of altered ratio of maternal folic acid and vitamin B12 during pregnancy with newborn birth weight, head circumference, and chest circumference
Ramijinni RR, Mahajan A, Sapehia D, Singh P, Suri V, Kaur J
J Am Nutr Assoc 2024;43:452–463

Maternal folate and vitamin B12 concentrations during pregnancy influence neonatal nutritional status and adiposity: results from the OBESO cohort
González-Ludlow I, Rodríguez-Cano AM, Mendoza-Ortega JA, Rodríguez-Hernández C, Suárez-Rico BV, Estrada-Gutierrez G, Tolentino-Dolores M, Parra-Hernández SB, Sánchez-Martínez M, Acevedo-Gallegos S, Perichart-Perera O
Nutrients 2025;17:372

The roles of maternal one-carbon metabolism and placental imprinted gene expression in placental development and somatic growth in a longitudinal birth cohort
Gutherz OR, Li Q, Deyssenroth M, Wainwright H, Jacobson JL, Meintjes EM, Chen J, Jacobson SW, Carter RC
Placenta 2025 Jun 26;167:109–121

Fish consumption and DHA supplementation during pregnancy: study of gestational and neonatal outcomes
Gualtieri P, Frank G, Cianci R, Dominici F, Mappa I, Rizzo G, De Santis GL, Bigioni G, Di Renzo L
Nutrients 2024;16:3051

What is the influence of maternal weight gain in different gestational clinical conditions on the prole weight in pre-school age?
Mariot MDM, Kretzer DC, Becker PC, Nunes IM, Goldani MZ, Bernardi JR, da Silva CH
Matern Child Nutr 2025;21:e13656

Maternal dietary patterns during pregnancy and birth weight: a prospective cohort study
Li T, He Y, Wang N, Feng C, Zhou P, Qi Y, Wang Z, Lin X, Mao D, Sun Z, Sheng A, Su Y, Shen L, Li F, Cui X, Yuan C, Wang L, Zang J, Zong G
Nutr J 2024;23:100

Animal Studies

Maternal adiponectin decreases placenta nutrient transport in mice
Samad M, Ulfenborg B, Soleimani Sani S, Bauzá Thorbrügge M, Mohan Shrestha M, Ohlsson C, Maliqueo M, Stener-Victorin E, Wernstedt Asterholm I, Benrick A
FASEB J 2025;39:e70556

Comparative impact of alternate-day fasting and time-restricted feeding on placental function and fetal development in maternal obesity
Liu S, Hua L, Mo X, Lei B, Zhang R, Zhou S, Jiang X, Fang Z, Feng B, Che L, Xu S, Lin Y, Wu D, Zhuo Y, Jin C
Nutrients 2024;17:25

Maternal fatty acid intake and human embryonic growth: the Rotterdam Periconception Cohort

Rubini E[1], van Rossem L[1,2], Schoenmakers S[1], Willemsen SP[1,3], Sinclair KD[4], Steegers-Theunissen RPM[1], Rousian M[1]

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Comments: Fetal neural development requires membrane phospholipids from essential polyunsaturated fatty acids (PUFAs), which are derived exclusively from the maternal diet. The authors of this study tried to evaluate the effect of fatty acids (FA) intake during the periconception period and early embryonic growth. In this prospective study, information was collected from the Rotterdam Periconception Cohort (Predict Study), a tertiary hospital-based birth cohort from The Netherlands. The study included 464 pregnant women who were <8 weeks pregnant during enrollment. Women completed food frequency questionnaire (FFQ), and longitudinal three-dimensional ultrasound examinations were performed during the 1st trimester. After adjusting for confounders, a higher dietary intake of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and other PUFAs was associated with a smaller head volume/embryonic volume ratio. Fish oil supplements alone were not associated with head volume (HV), embryonic volume (EV), or HV/EV ratio. Consumption of high dietary saturated FA was associated with a smaller HV/EV ratio, while low dietary EPA and/or DHA were associated with a larger HV/EV ratio. PUFA dietary pattern was inversely associated with HV/EV ratio. Several past studies demonstrated that asymmetric and higher head-to-body ratio is associated with adverse pregnancy outcomes. This correlates the study findings of the negative association between dietary DHA and PUFA to HV/EV ratio. The 2nd and 3rd trimesters are the key time for fetal neural programming, which might explain the lack of associations between PUFA intake and embryo HV during the 1st trimester. Several limitations to be mentioned – FA was evaluated by FFQ and not by collecting biological concentrations; the dose of fish oil supplements was not known; and furthermore, measurements of embryo HV and EV do not reveal possible cellular or molecular changes. To conclude, dietary intake of PUFAs could be associated with early embryonic development. Therefore, it should be encouraged during the periconceptional period in order to reduce risks of pregnancy complications.

Association between maternal folic acid supplementation in pregnancy and abnormal fetal growth: evidence from a birth cohort baseline survey

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Comments: Both fetal growth restrictions and overgrowth can cause labor complications and harm future health of the newborn. Folic acid (FA), vitamin B9, is a water-soluble vitamin that cannot be synthesized in the body and is recommended worldwide as a pre-pregnancy and 1st trimester supplement. The authors of the study tried to evaluate the association between abnormal fetal growth and FA supplementation during pregnancy. This is an observational study, a baseline survey of the Jinan birth cohort, performed between January 2018 and December 2019. Singleton healthy women of children without congenital anomalies were included. Women were recruited 1 month after delivery and completed health questionnaires. Out of 6,640 dyads, 6,501 pairs were included. FA supplementation of more than 4 months was found to have an OR of 0.76 for small for gestational age (SGA) (95% CI: 0.58–0.99) when the mother is <35 years of age and 0.73 (95% CI: 0.54–0.98) for primiparous women. As for large-for-gestational-age babies, FA supplementation during pregnancy had an OR of 0.69 (95% CI: 0.51–0.94) among mothers who had ≥13 years of education. Other studies also demonstrated FA supplementation as a protective factor for SGA. One possible explanation is that FA supplementation throughout pregnancy may lead to higher cord blood levels of RXRA methylation, which is associated with insulin sensitivity, adipogenesis, and metabolism. Some limitations to be mentioned – there is no information on pre-pregnancy maternal BMI or dietary habits, which may cause confounding bias. Furthermore, recall bias cannot be excluded. To conclude, cumulative FA supplementation during pregnancy is a protective factor for SGA, for nonelderly pregnant women, and primiparas. We still need to explore biological mechanisms in order to evaluate the optimal dose and timing of FA.

Association of altered ratio of maternal folic acid and vitamin B12 during pregnancy with newborn birth weight, head circumference, and chest circumference

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Comments: Water-soluble vitamins, like folic acid (FA) and vitamin B12, are key components in placental growth, DNA methylation, and cell metabolism during pregnancy. Today, neural tube defects (NTDs) related to FA deficiency decreased, but NTDs attributed to vitamin B12 deficiency have tripled. The aim of this study was to evaluate the effect of imbalance in FA and vitamin B12 ratios in pregnant women on anthropometric measurements of the newborn. In this prospective observational study performed in India between September 2018 and July 2019, 310 singleton pregnant women, who did not consume supplements, were included. Blood samples were taken after 37 weeks' gestation. Cord blood and placenta tissue were taken after delivery. High-ratio and low-ratio groups with altered maternal folate/maternal B12 (MRF/MB12) ratio were associated with reduced placental weight in comparison to the normal ratio group. Head circumference in neonates was significantly reduced in the B12-deficient group, and interestingly, it was normal size in the FA-deficient group. Both chest circumference and birthweight were reduced in the B12-deficient and FA-elevated and in the B12-normal and FA-deficient groups, but normal in the dual deficient group. In the high MRF/MB12 ratio group, there was also downregulation of one-carbon metabolism genes in the placenta (methionine synthase, glycine N-methyltransferase, and cystathionine β-synthase) compared to normal ratio. Others also demonstrated that FA and/or vitamin B12 deficiency increase the risk of preterm birth and low birthweight. Past studies also demonstrated that an increased FA with low vitamin B12 intake increases the risk for small-for-gestational-age neonates. Limitations to be mentioned are the small sample size, possible limited precision in the FA and B12 measurements, and no information on dietary supplementation. To conclude, it is important to maintain an optimal FA and B12 ratio during pregnancy. An altered ratio can influence fetal growth and development, thus highlighting the importance of balanced vitamin intake.

Maternal folate and vitamin B12 concentrations during pregnancy influence neonatal nutritional status and adiposity: results from the OBESO cohort

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Comments: One-carbon cycle generates methyl groups essential for various methylation processes and is crucial for cell division. Disruption in any step in these metabolic pathways, which is dependent also on folate and vitamin B12, may result in significant adverse fetal growth and development. The aim of this study is to evaluate maternal folate, B12, and homocysteine and their association with a newborn nutritional status profile and adiposity. This is a prospective study, part of the OBESO (Origen bioquimico y epigenetico del sobrepeso y la obesidad) cohort, which is

performed in Mexico City since 2017. The study included 90 healthy women with a singleton pregnancy who were evaluated during the 1st and 3rd trimesters with blood tests taken. Newborns were evaluated 24–72 h after delivery. Total B12 levels were deficient in 11.2% and 32.2% in the 1st and 3rd trimesters, respectively. Serum folate was elevated in 77.8% and 61.1% in the 1st and 3rd trimesters, respectively, with no case of folate deficiency. A high serum folate/low total B12 pattern was found in 5.6% and 18.9% of women in the 1st and 3rd trimesters, respectively. Higher waist circumference (WC) was correlated to higher total and active B12 levels. First trimester active B12 levels also correlated to neonate birthweight and higher levels were associated with a reduced risk of low birthweight. In the 3rd third trimester, higher folate concentrations correlated to higher WC and neonate fat mass percentage. Low maternal B12 levels were previously shown to be associated with lower birthweight. Unlike this study, several other studies demonstrated inverse or no association between B12 levels and anthropometric measurements at birth. Others demonstrated that lower maternal folate concentrations were associated with lower abdominal circumference. Several limitations to be mentioned are the small sample size, and that the results might be influenced by genetic polymorphisms. To conclude, this study highlights the interaction between B12, folate, and homocysteine and newborn nutritional status and adiposity markers.

The roles of maternal one-carbon metabolism and placental imprinted gene expression in placental development and somatic growth in a longitudinal birth cohort

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Comments: One-carbon metabolism provides the methyl groups needed for DNA methylation. Deficiency in nutrients essential for this process has been associated with adverse placental and fetal outcomes, as well as dysregulated DNA methylation. This study aims to examine the impact of maternal one-carbon nutrition on placental imprinted gene expression and fetal and postnatal growth. This is a secondary analysis from prenatally prospective longitudinal birth cohort study in Cape Town. Singleton healthy women were recruited and divided according to alcohol consumption. The study included 158 women who were interviewed and gave blood samples around conception, after 4, and 12 weeks. After delivery, placentas had gone through

pathology and mRNA evaluation. Children were evaluated for anthropometry measurements. Most women in the cohort consumed alcohol at conception (52.5%) and across pregnancy (58.2%). Serum vitamin B12 was negatively associated with placental weight. Erythrocyte folate was associated with larger head circumference at age 2 weeks. Plasma betaine was positively associated with placental weight-to-birthweight ratio. Plasma choline was associated with larger placental weight, larger neonatal BMI, and lower prevalence of maternal vascular underperfusion (MVU). Higher maternal plasma choline was associated with lower placental expression of 6 imprinted genes (*EPS15*, *IGF2R*, *LINC00657*, *SGCE*, *ZC3H12C*, *ZNF264*). According to the authors, this is the first study to identify potential roles of imprinted genes' effects of plasma choline on placental and fetal growth. Few studies also demonstrated a positive correlation between maternal choline and infant BMI. Another study demonstrated that women with higher choline consumption had differential placental gene expression patterns, which involved circulatory system development and blood circulation. Several limitations are the small sample size, and that the findings are limited to measure bulk tissue expression. Furthermore, the cohort is socioeconomically disadvantaged and mono-ethnic. To conclude, choline affects fetal development, with possibly beneficial effects on placental development and fetal and postnatal growth.

Fish consumption and DHA supplementation during pregnancy: study of gestational and neonatal outcomes

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Comments: Fish consumption during pregnancy is recommended by many medical organizations due to its high-quality protein and long-chain polyunsaturated omega-3 fatty acids (LCPUFA *n*-3). Nevertheless, fish may also contain pollutants like methylmercury and other heavy metals. There are conflicting results for associations between fish consumption and pregnancy outcomes. The authors of this study evaluated fish and docosahexaenoic acid (DHA) supplement intake and gestational and neonatal outcomes. In this observational survey, women who gave birth between November 2022 and July 2023 completed questionnaire for pregnancy outcomes and dietary and supplementation consumption. Only healthy, nonsmoker, singleton, omnivorous women were included. Out of 501 women, 404 were included in the statistical evaluation. Significant differences were found in gestational weight gain (GWG),

birthweight, and neonate length for those eating fish ≥3/week compared to non-consumers. Differences were also demonstrated between women who took DHA supplementation and women who did not for mode of delivery, GWG, and length of pregnancy. A negative correlation was observed between fish consumption, and DHA supplementation to GWG. DHA consumption was positively influencing birth length. A recent review, which showed positive correlations between consumption of 30 g/day of fatty fish and perinatal outcomes, supports the study findings. It has been proposed that *n*-3 could prolong gestation by decreasing prostaglandins F and E activity and enhancing eicosanoids activity, thus causing myometrial relaxation. Several limitations to be mentioned; there is no information about the type of fish consumed nor for intake of other micronutrients. Furthermore, due to the self-reported information there is potential for response bias. To conclude, this study supports the current recommendation for pregnant women to consume fish and seafood while limiting the intake of species with known high environmental pollutants. The study also supports the use of *n*-3 or fish oil supplements and thus diminishing the risk of mercury and toxin exposure.

What is the influence of maternal weight gain in different gestational clinical conditions on the prole weight in pre-school age?

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Comments: A high pregestational maternal body mass index (BMI), as well as excessive gestational weight gain (GWG), has been associated with an increased risk for future childhood overweight/obesity. Adverse intrauterine environments also affect offspring's future chronic diseases. The authors of this study aimed to evaluate the influence of maternal GWG among women with abnormal clinical conditions and future child's weight. This longitudinal observational study was performed in Brazil. The study included dyads of mothers to singleton pregnancies and children at the age of 3–6 years. Women were interviewed 48 h and 6 months after delivery, and children were evaluated at the age of 6 months and 3–6 years. Evaluation was performed according to maternal group: smoking, diabetes mellitus (DM), hypertension, with intrauterine growth restriction (IUGR) babies and controls. Women in the DM group, with adequate or excessive GWG, had children with increased BMI over time. In the hypertension group, women with GWG above the recommendations had children with increased BMI. In women in the IUGR group, with insufficient GWG, children showed an increased BMI at 6 months and a decrease between 3 and 6 years.

For those with excessive GWG, there was a decrease in BMI. Children to women in the control group with excessive GWG had increased BMI. As for the smoker's group, there was no significant correlation. Others already demonstrated that excessive GWG is associated with the prevalence of overweight children. Another study found that among children born with high birthweight, genes regulating glycemic control and appetite were altered. Limitations of the study to be mentioned are the sample loss from the first to the second phase and the lack of assessment of the GWG trajectory during pregnancy. To conclude, the study reinforces the importance of adequate GWG, especially in the presence of hypertension and DM, to prevent future children from being overweight.

Maternal dietary patterns during pregnancy and birth weight: a prospective cohort study

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Comments: Plant-based diets among Asians, have been associated with larger birth sizes, compared to inverse associations among Europeans. However, most information is based on Western countries, with lack of data for the rest of the world. The authors of this study examined the associations between maternal dietary patterns to possible birthweight outcomes. This prospective study was performed in Shanghai in 2017 as part of the Iodine Status in Pregnancy and Offspring Health Cohort (ISPOHC) study. The study included 4,184 singleton pregnant women who were enrolled in each trimester. Women completed food frequency questionnaire upon enrollment and offspring's information was gathered after delivery. The study identified three major dietary patterns – plant-based, animal-based, and processed food and beverage dietary patterns. The study revealed that a higher plant-based dietary pattern score was significantly associated with increased risk for macrosomia, even after multivariate adjustment. No associations were observed between the three dietary patterns and small-for-gestational-age or large-for-gestational-age babies. In multivariable-adjusted logistic regression models, increased potato consumption was associated with a higher risk for macrosomia. Sensitivity analysis demonstrated that the results remained significant among women with term

infants. But when stratifying for women with spontaneous labor or after excluding potatoes, most of the associations were attenuated. Previous studies demonstrated inconclusive results between plant-based food intake and macrosomia, even among Asians. But, several other studies found that potato consumption, a high-carbohydrate food, is associated with risk factors for macrosomia and gestational diabetes. The study has several limitations. It is an observational study by nature; self-reported questionnaires may be susceptible to recall bias; and potential diet changes during pregnancy were not evaluated. To conclude, plant-based diet pattern, probably due to high carbohydrate content, was associated with a higher risk of macrosomia.

Animal Studies

Maternal adiponectin decreases placenta nutrient transport in mice

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Comments: Low serum adiponectin is associated with insulin resistance, gestational diabetes, and obesity. Furthermore, a significant drop in serum adiponectin during pregnancy is linked to large-for-gestational-age babies. The authors of this study tried to evaluate the effect of maternal and fetal adiponectin on placental function, fetal growth, and metabolism. In this trial, 16 wild-type (wt) and 14 adiponectin-overexpressing (APNtg) mice were fed in either normal chow or a high-fat/high-sucrose (HF/HS) diet for 8 weeks prior to and during pregnancy. APNtg females were mated with WT males, and WT females were mated with APNtg males. The dams were euthanized on gestation day 18, and fetuses and placentas were removed for evaluation. APNtg dams had 40%–50% higher serum adiponectin compared to wt dams, with higher levels in those fed with HF/HS diet. There was no difference in the total glucose and lipid uptake in adipose tissue between genotypes, though APNtg dams had increased clearance of glucose, reduced hepatic triglyceride accumulation, and increased subcutaneous fat gain, possibly explaining an enhanced ability to store excess nutrients. The placental uptake of glucose, lipid, and amino acid tracer was reduced in APNtg, suggesting that adiponectin decreases placental transfer of nutrients. Fetuses to APNtg dams had downregulated liver lipid and amino acid metabolic pathways, perhaps due to an energy deficit. Since adiponectin cannot pass the placental barrier,

its effect is on the placenta and not directly on the fetus. Past studies also demonstrated that adiponectin decreases placental glucose uptake via decreased insulin signaling, but this study also demonstrated a reduced fatty acid uptake due to adiponectin. It is important to remember that among humans, fat deposition increases exponentially near term while mice are born largely without white adipose tissue. To conclude, increased levels of maternal adiponectin in obese dams lead to lower placenta nutrient transport, fetal growth restriction, and altered fetal liver function.

Comparative impact of alternate-day fasting and time-restricted feeding on placental function and fetal development in maternal obesity

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Comments: Intermittent fasting (IF) has become recognized as a promising strategy for weight management and possibly impacts reproduction. This study evaluates the impact of different types of IF diets, alternate-day fasting (ADF), and time-restricted feeding (TRF) on reproductive performance. In this RCT, 100 mice were divided into two groups: a control group and the HA group, which was fed high-fat diet (HFD). After 30 days, the HA mice were subdivided: HA continued HFD, ADF on HFD, and TRF on HFD. The mice were mated and euthanized on gestational day 18 and the fetuses were evaluated. The HA group exhibited greater insulin resistance and elevated lipid levels, while the ADF and TRF had improved glucose tolerance and improvements in lipid profiles. The ADF mice had lower litter weight, higher rate of fetal growth restriction (FGR), and lower fetal plasma glucose concentrations; while TRF resulted in improved fetal free fatty acid concentrations. The placental weight was higher in HA mice but with lower efficiency, and with decreased size in the ADF and TRF groups. The HA group exhibited a significant increase in the expression of endoplasmic reticulum (ER) stress-related mRNA and proteins, while TRF treatment had decreased ER stress-related genes. Previous research has shown that ADF improves lipid profiles. It was also demonstrated that reduced activity of nutrient transport in the placenta may contribute to FGR. The study has several limitations to be acknowledged. The duration of the HFD was not enough to induce obesity, there are many kinds of IF patterns, and there was no long-term follow-up on postnatal health outcomes. To conclude, TRF enhances fetal weight by mitigating maternal metabolic disorders probably by optimizing placental function. Conversely, an ADF regimen leads to a reduced expression of placental nutrient transporters, intensifying placental stress and inflammatory response, which leads to FGR.

Overall Commentary

A mother's diet affects her child long before the child's birth. Nutritional choices made during pregnancy do not just influence the immediate health of the fetus but lay the groundwork for physical, neurological, and metabolic outcomes that can last a lifetime. Therefore, the medical and scientific community should remember the importance of looking beyond isolated variables and embracing a more nuanced, individualized approach to maternal care – one that considers the full context of both patient's life and biology.

Conflict of Interest Statement

The authors report no conflict of interest.

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129 **Nutrition and Growth:** Yearbook 2026

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Advancing our understanding of how nutrition shapes human growth across the lifespan is essential for improving health outcomes. The Nutrition and Growth Yearbook 2026 delivers a rigorous synthesis of peer-reviewed studies published between July 2024 and June 2025, offering critical insights into the impact of diet on developmental milestones, pubertal growth, and skeletal and muscular health. Renowned experts provide concise summaries and expert commentary on the most significant findings, highlighting emerging trends, controversies, and future directions in nutrition and growth science.
This volume bridges foundational research and clinical application, equipping professionals with evidence-based strategies to optimize care. Designed as a practical resource, the Yearbook supports translating evidence into actionable strategies and fosters continued exploration in nutrition and growth science across all stages of life.

128 **Nutrition and Growth: Yearbook 2025**

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