Volume 2, No 1 2023

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IN PEDIATRIC NUTRITION

Infant Nutrition

Growing Up Milk for Toddlers

Cow's Milk Allergy

Functional Gastrointestinal Disorders

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Important Notice: Breastfeeding is best for infants and young children and Nutricia strongly recommends and supports breastfeeding. Nutricia supports the World Health Organization's global public health recommendation for exclusive breastfeeding for the first six months of life and continued for two years along with the introduction of safe and appropriate complementary foods after the first six months of life. For advice on breastfeeding and on decisions related to the health and nutrition of your baby, please consult your physician or other qualified healthcare providers. A well balanced diet, before, during and after delivery, will help sustain an adequate supply of breast-milk. Frequent feeding is the best way to establish and maintain a good milk supply. The introduction of partial bottle-feeding and/or other drinks and foods may have a negative effect on breastfeeding. It is very difficult to reverse a decision not to breast-feed.

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EDITOR'S NOTE

The world of Medicine has made great advances since its early days. In recent years we have had the privilege of witnessing developments in understanding the pathogenesis of many of the diseases burdening humankind. It is frustrating, though, to realize that most of this up-to-date knowledge does not reach its natural recipients, who are specialists working in daily practice. Thus, we believe that the need for an informative journal is obvious and self-explanatory.

For this reason, CCM fills the gap in continuing medical education to benefit every day clinical practice, by publishing this innovative series of Current Views. In every issue, readers will find a review article and several summary articles. *Current Views in Pediatric Nutrition* was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the CCM editorial team based on an ongoing review of the international literature, and articles are selected for review and citation on the basis of their relevance to clinical practice.

Current Views in Pediatric Nutrition provides specialists with an attractive means of continuing medical education that demonstrates the best of critical thinking and is a source of, and a catalyst for, new ideas and learning. The editors and medical advisors at CCM have made every effort to search the international literature to present the most current, interesting and cutting edge articles, in order to make *Current Views in Pediatric Nutrition* a respected and useful tool for physicians with one aim: to provide a good service to their patients. For this issue, we have retrieved information from several well respected peer reviewed journals:

Am J Clin Nutr
Ann Nutr Metab
Br J Nutr
Foods
Front Neuroendocrinol
Front Pediatr
Gut Microbes
J Allergy Clin Immunol Pract
J Pediatr (Rio J)
J Pediatr Gastroenterol Nutr
J Pediatr
Neonatology
Neuroimage
Nutrients
Nutrition
Pediatrics
PLoS One
Prev Med
Trends Microbiol

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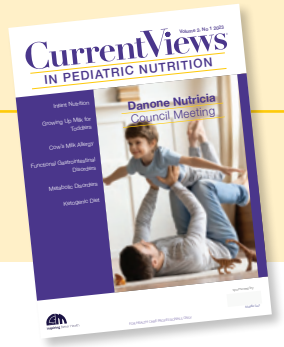

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A Note from the Regional Editors

Progress in Pediatric Nutrition has continued at a spectacular pace culminating in a rapid surge in the number of increasingly precise articles on the assessment of growth, the nutritional status assessment and feeding guidelines, biochemical evaluation of nutritional status, infant nutrition, enteral nutrition, parenteral nutrition, nutritional management in health as well as in disease for residents in Pediatrics, powered by research. The cumulative knowledge of the complexities of Pediatric Nutrition continues to be the foundation of new advances across the clinical care continuum.

Discoveries in the fields of metabolism, genomics and immunology have been particularly fruitful and have firmly established two new pillars of clinical care. These exciting fields of research also show immense promise for the future. Furthermore, Clinical Medical Societies have been updating their Guidelines for Pediatric Nutrition.

Current Views in Pediatric Nutrition was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the Regional Editors based on an ongoing review of the international literature, and articles are selected and then summarized for citation and review on the basis of their relevance to clinical practice.

Current Views in Pediatric Nutrition mainly caters to the needs of the professionals, researchers, clinical practitioners and medical practitioners in the field of Pediatrics. Our content covers topics that advance clinical practice, and tackle issues related to global Pediatrics. The Regional Editorial Board's aim is to include the most complete and reliable sources of information and discoveries ongoing in Pediatrics and Nutrition research and treatment. The Regional Editors work as a distinguished team of experts to ensure the highest standards of article selection. All relevant articles in the international literature are carefully considered and once selected, all materials are promptly processed and published.

The stringency of selecting and voting state-of-the-art articles was done by our respected Regional Editorial team members who are listed within the journal. Our fundamental purpose is to advance clinically-relevant knowledge of Pediatric Nutrition, and improve the outcome of prevention, diagnosis and treatment of pediatric disease.

In this first issue, due to the spectacular developments seen lately, original research articles, early reports and review articles covering key points, potential pitfalls, and management algorithms which allow for rapid-reference, and link with the latest evidence, related to the food fortification interventions, postbiotics in early life, the role of synbiotics in cow's milk allergy, iron supplementation, and ketogenic diet in epilepsy have been included.

We believe that the readers will find many topics of interest related to their everyday practice.

The Regional Editorial Board

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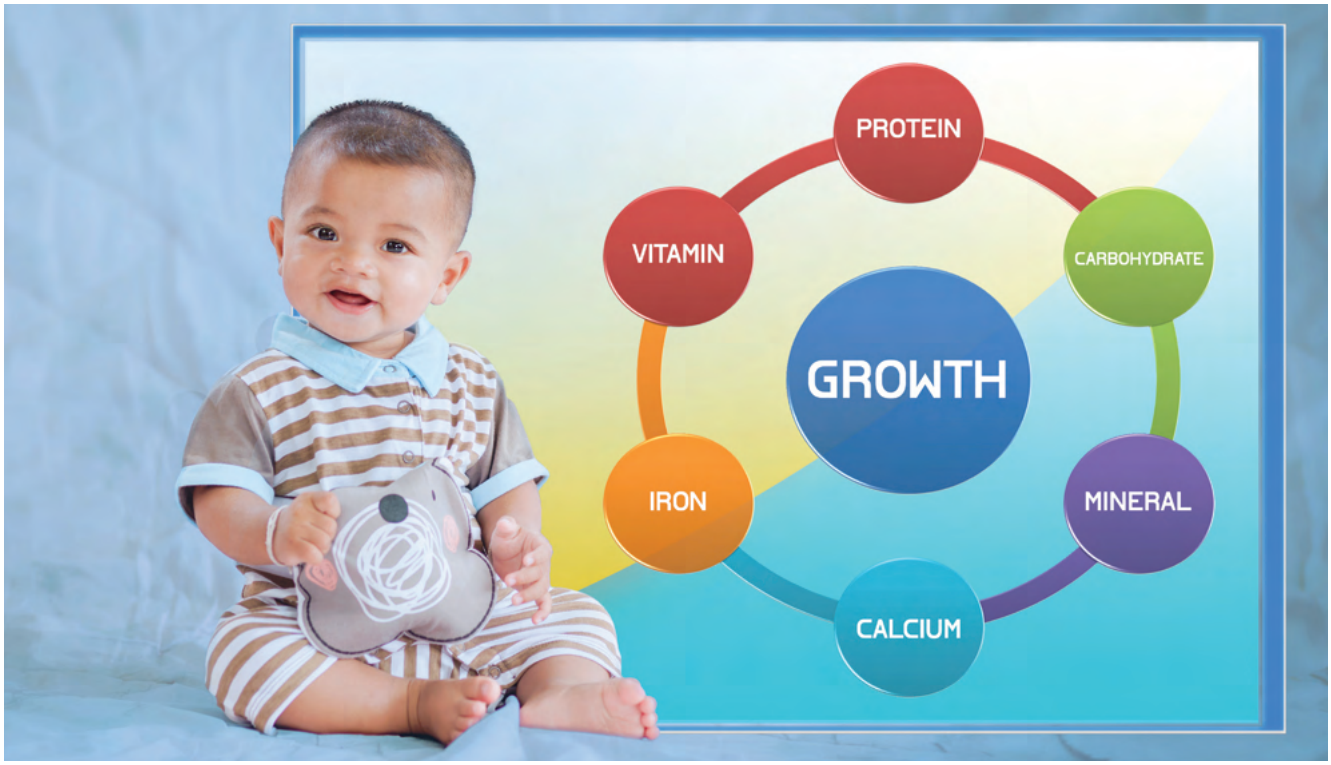


Nutrition for Infant Feeding[1]

Source: *Consales A, Morniroli D, Vizzari G, Mosca F, Giannì ML. Nutrition for Infant Feeding. Nutrients. 2022 Apr 27;14(9):1823. doi: 10.3390/nu14091823.*

It has long been demonstrated that nutrition in the first 1000 days of life can affect health outcomes later in life. Indeed, according to the Developmental Origins of Health and Disease (DOHaD) hypothesis, the roots of several disorders manifesting in childhood and adult life can be traced back to the prenatal and early infant phases. Infant feeding is now recognized as one of the main modifiable risk factors for long-term health outcomes.

This special issue focuses on the influence of nutrition, from lactation to complementary feeding, on infants' health, with the intention of updating knowledge on the impact of specific feeding strategies on anthropometric growth, body composition, neurofunctional development, metabolic processes and protection against infections through the first years of life.

Kouwenhoven et al conducted an interesting multi-center, double-blinded randomized clinical trial (RCT) investigating if and how a 20% reduction in protein intake could alter the metabolic and hormonal profile at the age of 4 months in term infants fed a low-protein formula with a unique customized blend of essential amino acids compared to infants fed a standard formula and breastfed infants.

Analyzing data from the National Health and Nutrition Examination Survey (NHANES), Young et al sought an answer to whether and how variation in macronutrient ingredients within the standard formula category may affect infant growth. Through

their results, the authors remind us that not all infant formulas are the same.

The paper by Shek et al describes an RCT study protocol evaluating the impact on infant growth and body composition of a concept infant formula containing lipid droplets closely mimicking those in human milk. Importantly, the study will apply an innovative breastfeeding-friendly cohort-like recruitment approach, randomizing study participants based on the parents' autonomous decision to start (or not) formula feeding during the study period.

In conclusion, the original articles and reviews included in this special issue are likely to substantially aid our understanding of the influence of early nutritional exposure on infants' health and promote the identification of effective feeding strategies to improve growth and developmental outcomes. The advances presented are of great interest from a clinical perspective and may hopefully act as the basis for future research on this fascinating topic.

Environmental Impact of Feeding with Infant Formula in Comparison with Breastfeeding[2]

Source: *Andresen EC, Hjelkrem AR, Bakken AK, Andersen LF. Environmental Impact of Feeding with Infant Formula in Comparison with Breastfeeding. Int J Environ Res Public Health. 2022 May 24;19(11):6397. doi: 10.3390/ijerph19116397.*

Young children have unique nutritional requirements, and breastfeeding is the best option to support healthy growth and development. Concerns have been raised around the increasing use of milk-based infant formulas in replacement of breastfeeding, in regards to health, social, economic and environmental factors. However, literature on the environmental impact of infant formula feeding and breastfeeding is scarce.

In line with international recommendations, Norwegian health authorities recommend exclusive breastfeeding for 4–6 months after birth, and thereafter a gradual introduction of appropriate complementary foods with continued breastfeeding for one year or beyond. Despite this, less than two out of five infants living in Norway are exclusively breastfed at four months of age, and only five percent up to six months of age. Additionally, 35% of infants in Norway consume infant formula during the first four months of life.

In this study, Andresen et al estimated the environmental impact of four months exclusive feeding with infant formula compared to four months exclusive breastfeeding in a Norwegian setting. The authors used life-cycle assessment (LCA) methodology, including the impact categories global warming potential, terrestrial acidification, marine and freshwater eutrophication, and land use.

The authors found that the environmental impact of four months exclusive feeding with infant formula was 35–72% higher than that of four months exclusive breastfeeding, depending on the impact category. For infant formula, cow milk was the main contributor to the total score for all impact categories.

It was observed that for the five environmental impact categories assessed, scores were 24–60% higher for 1 kg ready-to-feed infant formula compared to 1 kg breastmilk. In addition, it was found that four months feeding with infant formula compared to breastfeeding resulted in 38% higher global warming potential, 72% higher terrestrial acidification, 35% higher freshwater eutrophication, 59% higher marine eutrophication, and 53% higher land use.

The environmental impact of breastfeeding was dependent on the composition of the lactating mother's diet.

Breastfeeding has a lower environmental impact than feeding with infant formula. A limitation of the study is the use of secondary LCA data for raw ingredients and processes.

Assessing the Safety of Bioactive Ingredients in Infant Formula that Affect the Immune System[3]

Source: *Callahan EA, Chatila T, Deckelbaum RJ, Field CJ, Greer FR, Hernell O, Järvinen KM, Kleinman RE, Milner J, Neu J, Smolen KK, Wallingford JC. Assessing the safety of bioactive ingredients in infant formula that affect the immune system: recommendations from an expert panel. Am J Clin Nutr. 2022 Feb 9;115(2):570-587. doi: 10.1093/ajcn/nqab346.*

Bioactive ingredients for infant formula have been sought to reduce disparities in health outcomes between breastfed and formula-fed infants. Traditional food safety methodologies have limited ability to assess some bioactive ingredients. It is difficult to assess the effects of nutrition on the infant immune system because of coincident developmental adaptations to birth, establishment of the microbiome and introduction to solid foods, and perinatal environmental factors.

An expert panel was convened to review information on immune system development published since the 2004 Institute of Medicine report on evaluating the safety of new infant formula ingredients and to recommend measurements that demonstrate the safety of bioactive ingredients intended for that use. Panel members participated in a 2-day virtual symposium in November 2020 and in follow-up discussions throughout early 2021.

Key topics included identification of immune system endpoints from nutritional intervention studies, effects of human milk feeding and human milk substances on infant health outcomes, ontologic development of the infant immune system, and microbial influences on tolerance.

Considering that bioactive ingredients in infant formula refer to an ingredient that has a physiologic effect on the human body, the expert panel discussed several key considerations in the process of developing its recommendations.

Key considerations for developing recommended endpoints to assess the safety of bioactive ingredients in infant formula

- Considering the different types of data needed to establish safety and to demonstrate physiologic effects (efficacy).
- Determining the age of interest for measurements.
- Using data on human milk composition and health outcomes of breastfed infants.
- Addressing complexities associated with many bioactive ingredients of interest.
- Identifying suitable markers of developmental immune competence.
- Developing comprehensive and pragmatic recommendations.

The panel explored how “non-normal” conditions such as preterm birth, allergy, and genetic disorders could help define developmental immune markers for healthy term infants. With consideration of breastfed infants as a reference, ensuring proper control groups, and attention to numerous potential confounders, the panel recommended a set of standard clinical endpoints including growth, response to vaccination, infection, variables related to infections and antibiotic use and other adverse effects related to inflammation, allergy and atopic diseases.

The expert panel compiled a set of candidate markers to characterize stereotypical patterns of immune system development during infancy, but absence of reference ranges, variability in methods and populations, and unreliability of individual

markers to predict disease prevented the panel from including many markers as safety endpoints.

The panel discussed that if major differences in immune system outcomes are not observed by the age of 12 months, it is unlikely that such differences would be detected later in childhood. It concluded that 12 months is an appropriate and feasible follow-up period for interventions examining the immune system effects of bioactive ingredients in infant formula.

The panel's findings and recommendations are applicable for industry, regulatory, and academic settings, and will inform safety assessments for immunomodulatory ingredients in foods besides infant formula.

Comprehensiveness of Infant Formula and Bottle Feeding Resources[4]

Source: *Cheng H, Rossiter C, Size D, Denney-Wilson E. Comprehensiveness of infant formula and bottle feeding resources: A review of information from Australian healthcare organisations. Matern Child Nutr. 2022 Apr;18(2):e13309. doi: 10.1111/mcn.13309*

The use of infant formula is widespread internationally. In Australia, 55% of infants receive formula before 6 months of age, with higher rates among disadvantaged communities. The use of infant formula can contribute to childhood overweight and obesity, through formula composition and feeding behaviors, such as adding cereal to bottles and parental feeding style. While information abounds to promote and support breastfeeding, insufficient formula-feeding support from health services can lead to parents relying on formula packaging or other commercial information.

This study systematically searched and reviewed online resources for infant formula and bottle feeding from Australian governments, health services, hospitals, and not-for-profit parenting organizations. A comprehensive search strategy located 74 current resources, mostly for parents. Researchers evaluated the resources against best practice criteria derived from Australian government and UNICEF guidelines on six topics. They assessed how comprehensively the resources addressed each topic and whether the resources provided all the information necessary for parents to understand each topic.

Most formula-feeding resources from Australian healthcare organizations focus on preparing infant formula and using infant formula. However, comprehensiveness of information varies—on average, information on preparing infant formula was more comprehensive than that on using infant formula.

The mean 'comprehensiveness' rating for topics across all resources was 54.36%. However, some topics were addressed more fully than others. Information on 'discussing infant formula with health workers' and on 'preparing infant formula' was more frequently accurate and comprehensive. There was much less comprehensive information on 'using infant formula', including amounts of formula to feed, use of bottle teats, appropriate bottle-feeding practice and responsiveness to infant satiety cues.

The Australian government infant feeding guidelines should be revised to include more comprehensive best-practice formula-feeding recommendations; subsequently, this should be reflected in formula-feeding information from health organizations.

A Nation-wide Study on the Common Reasons for Infant Formula Supplementation among Healthy, Term, Breastfed Infants[5]

Source: *Bookhart LH, Anstey EH, Kramer MR, Perrine CG, Reis-Reilly H, Ramakrishnan U, Young MF. A nation-wide study on the common reasons for infant formula supplementation among healthy, term, breastfed infants in US hospitals. Matern Child Nutr. 2022 Apr;18(2):e13294. doi: 10.1111/mcn.13294.*

Infant formula supplementation of breastfed newborns often occurs during the intrapartum period, in which the mother-infant dyad remain in the hospital following birth. In-hospital infant formula supplementation of breastfed infants reduces breastfeeding duration, yet little is known about common reasons for infant formula supplementation.

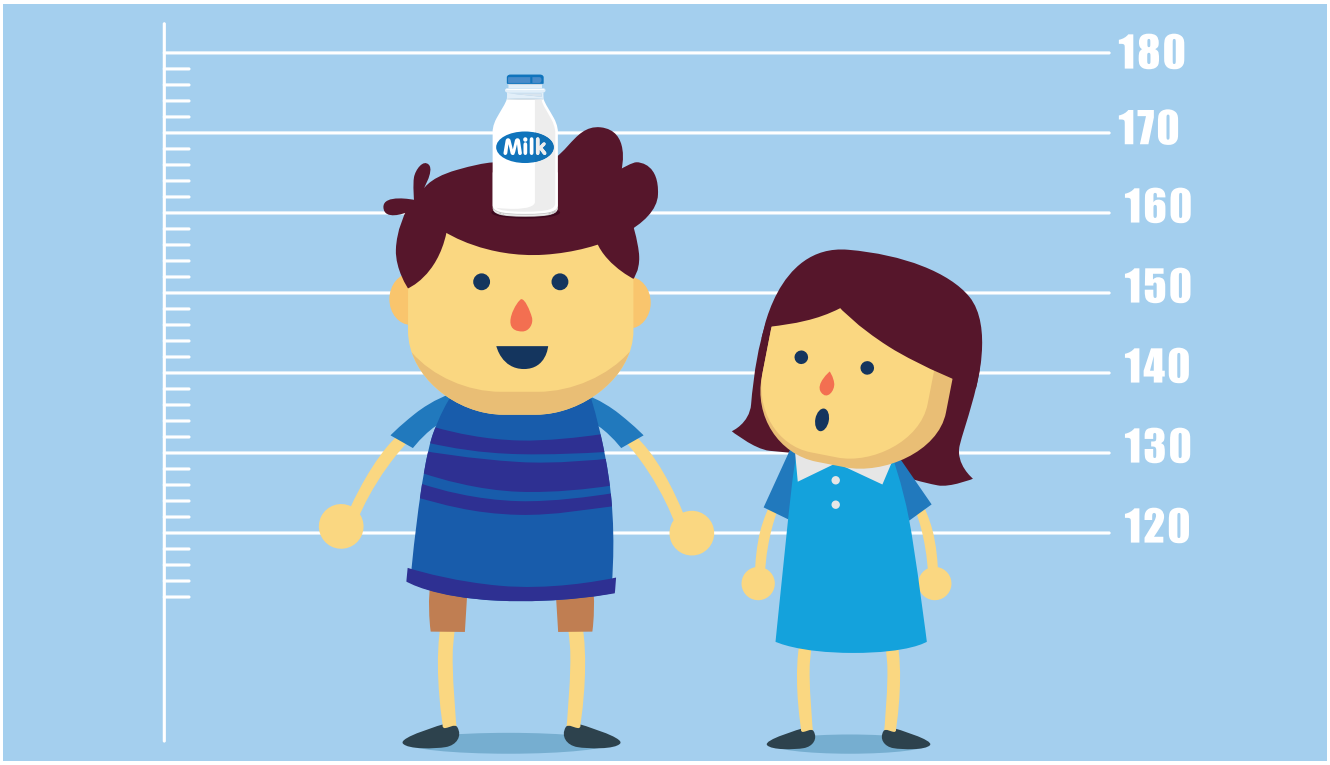
Bookhart et al examined the three most common reasons for in-hospital infant formula supplementation of healthy, term, breastfed infants in the US reported by hospital staff. Hospital data were obtained from the 2018 Maternity Practices in Infant Nutrition and Care survey (n=2045), which was completed by hospital staff. An open-ended question on the top three reasons for in-hospital infant formula supplementation was analyzed using thematic qualitative analysis and the frequencies for each reason were reported.

The top three most common reasons for in-hospital infant formula supplementation reported by hospital staff included medical indications (70.0%); maternal request/preference/feelings (55.9%); lactation management-related issues (51.3%); physical but non-medically indicated reasons (36.1%); social influences (18.8%); perceived cultural/societal/demographic factors (8.2%) and medical staff/institutional practices (4.7%).

Underlying many of the reported three most common reasons for infant formula supplementation is potentially lack of lactation management support that considers the social influences (and that is culturally relevant.

These findings suggest that a variety of factors should be considered to address unnecessary infant formula supplementation. Lactation management support delivered in a timely and culturally sensitive manner and targeted to mother-infant dyads with potential medical and physical indications may reduce unnecessary in-hospital infant formula supplementation.

Growing Up Milk for Toddlers



The Role of Young Child Formula in Ensuring a Balanced Diet in Young Children (1-3 Years Old)[6]

Source: *Chouraqui JP, Turck D, Tavoularis G, Ferry C, Dupont C. The Role of Young Child Formula in Ensuring a Balanced Diet in Young Children (1-3 Years Old). Nutrients. 2019 Sep 13;11(9):2213. doi: 10.3390/nu11092213.*

Early childhood (1–3 years of age) is a period of rapid growth and development, with a gain of approximately 25% in height and 50% in weight occurring during this period. While milk remains a major food, this is a transition period from weaning foods towards a family diet, rendering children vulnerable to nutrient inadequacy and unbalanced diet.

Young child formula (YCF) has been proposed as a means of improving nutrition in this age group. Chouraqui et al compared the food consumption and nutrient intake of 241 YCF consumers (YCF-C) to those of 206 non-consumers (YCF-NC), selected from among the children enrolled in the Nutri-Bébé survey, an observational cross-sectional survey, conducted from 3 January to 21 April 2013.

Food consumption and nutrient intake were analyzed from a three-day dietary record. The YCF-C < 2 years group had a protein (-8 g/d; $p < 0.0001$) and sodium (-18%; $p = 0.0003$) intake that was lower than that of YCF-NC, but still above the respective EFSA (European Food Safety Authority) Average Requirement (AR) or Adequate Intake (AI).

Consumption of YCF was higher than that of CM, but the difference was only significant from 2 to 3 years of age. The mean total intake of food (liquid and solid) in each age group was similar in both YCF-C and YCF-NC groups, whatever the age

Mean daily intake of YCF, FSB, CM and common foods in YCF-C

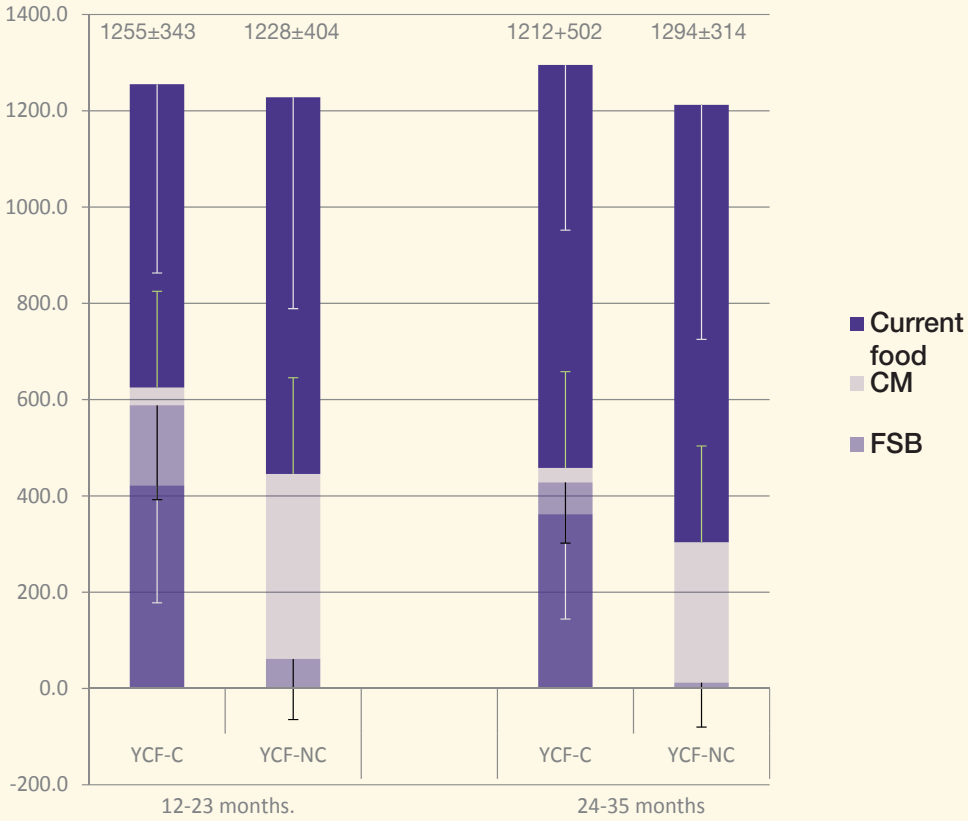


Figure 1. *Mean (± SD) daily intake (g) of YCF, foods intended specifically for babies (FSB), CM and common foods in YCF-C (n = 241) and YCF-NC (n = 206) according to age group.*

group (Figure 1). The share of "foods intended specifically for babies" (FSB) was higher in the YCF-C groups at all ages (respectively 166 ± 196 vs. 61 ± 126 g/d, and 66 ± 126 vs. 12 ± 92 g/d) ($p < 0.001$). Together, YCF and FSB accounted for 47% vs. 5% of the total daily food intake in the 12–23 months group and for 33% vs. 1% in the 24–35 months group.

At all ages, the YCF-C group had higher intakes of essential fatty acids ($p < 0.0001$), vitamins C ($p < 0.0001$), A, D, and E ($p < 0.0001$), all B vitamins ($p < 0.001$) except B12, iron (9 vs. 5 mg/d, $p < 0.0001$), reaching the Dietary Reference Values (DRVs, AR or AI), but similar docosahexaenoic acid (DHA) and arachidonic acid (ARA) intakes. Getting closer to the reference values proposed by EFSA required at least 360 mL/d of YCF.

The consumption of YCF may help infants and children at risk of nutrient deficiencies to meet their nutritional requirements. However, protein, sodium, and vitamin A intakes remained above the EFSA DRVs, and DHA, ARA, and vitamin D remained below.

Validation and Calibration of the Eating Assessment in Toddlers FFQ or Children, Used in the Growing Up Milk - Lite Randomised Controlled Trial[7]

Source: *Lovell AL, Davies PSW, Hill RJ, Milne T, Matsuyama M, Jiang Y, Chen RX, Heath AM, Grant CC, Wall CR. Validation and calibration of the Eating Assessment in Toddlers FFQ (EAT FFQ) for children, used in the Growing Up Milk - Lite (GUMLi) randomised controlled trial. Br J Nutr. 2021 Jan 28;125(2):183-193. doi: 10.1017/S0007114520002664.*

The Eating Assessment in Toddlers Food Frequency Questionaire (FFQ) (EAT FFQ) has been shown to have good reliability and comparative validity for ranking nutrient intakes in young children. With the addition of food items (n=4), Lovell et al aimed to re-assess the validity of the EAT FFQ and estimate calibration factors in a sub-sample of children (n=97) participating in the Growing Up Milk - Lite (GUMLi) randomized control trial (2015-2017).

The participants completed the ninety-nine-item GUMLi EAT FFQ and record-assisted 24-h recalls (24HR) on two occasions. Energy and nutrient intakes were assessed at months 9 and 12 post-randomization and calibration factors calculated to determine predicted estimates from the GUMLi EAT FFQ. The validity was assessed using Pearson correlation coefficients, weighted kappa (κ) and exact quartile categorization. The calibration was calculated using linear regression models on 24HR, adjusted for sex and treatment group.

Nutrient intakes were significantly correlated between the GUMLi EAT FFQ and 24HR at both time points. Energy-adjusted, de-attenuated Pearson correlations ranged from 0.3 (fibre) to 0.8 (Fe) at 9 months and from 0.3 (Ca) to 0.7 (Fe) at 12 months. Weighted κ for the quartiles ranged from 0.2 (Zn) to 0.6 (Fe) at 9 months and from 0.1 (total fat) to 0.5 (Fe) at 12 months. For secondary outcome nutrients of the GUMLi trial, exact agreement was 70% (Fe) and 74% (vitamin D) at month 9 and 52% for both Fe and vitamin D at month 12. The calibration factors predicted up to 56% of the variation in the 24HR at 9 months and 44% at 12 months.

In conclusion, the Growing Up Milk - Lite (GUMLi) Eating Assessment in Toddlers FFQ had a similar estimated level of validity compared with other FFQ measurements in children under 2 years of age. The Growing Up Milk - Lite Eating Assessment in Toddlers FFQ remained a useful tool to rank the nutrient intakes of young children living in Australia and New Zealand in the latter half of the second year of life, where dietary intakes may be more reflective of the family diet. The calibration factors from this study can be used to correct for attenuation and regression dilution bias of nutrient densities in future studies, particularly when relating relative risk estimates to disease outcomes.

Cow's Milk Allergy

Consensus Statement on the Epidemiology, Diagnosis, Prevention, and Management of Cow's Milk Protein Allergy in the Middle East: A Modified Delphi-based Study[8]

Source: *El-Hodhod MA, El-Shabrawi MHF, AlBadi A, Hussein A, Almehaidib A, Nasrallah B, AlBassam EM, El Feghali H, Isa HM, Al Saraf K, Sokhn M, Adeli M, Al-Sawi NMM, Hage P, Al-Hammadi S. Consensus statement on the epidemiology, diagnosis, prevention, and management of cow's milk protein allergy in the Middle East: a modified Delphi-based study. World J Pediatr. 2021 Dec;17(6):576-589. doi: 10.1007/s12519-021-00476-3.*

It has been reported that in the Middle East the practice of exclusive breastfeeding up to 6 months of life is poorly followed. The early introduction of cow's milk can significantly increase the risk of CMPA among infants from the Middle East. This study aimed to develop an expert consensus regarding the epidemiology, diagnosis, and management of CMPA in the Middle East.

A three-step modified Delphi method was utilized to develop the consensus. Fifteen specialized pediatricians participated in the development of this consensus. Each statement was considered a consensus if it achieved an agreement level of ≥ 80%.

The panel emphasized the importance of early diagnosis and exclusive or partial breastfeeding. The panel agreed that infants with a positive family history of atopy in first-degree relatives are at increased risk of CMPA.

The experts agreed that the double-blind placebo-controlled oral challenge test (OCT) should be performed for 2-4 weeks using an amino acid for-

mula (AAF) in formula-fed infants or children with suspected CMPA. Formula-fed infants with confirmed CMPA should be offered a therapeutic formula.

The panel stated that an extensively hydrolyzed formula (eHF) is indicated in the absence of red flag signs. At the same time, the AAF is offered for infants with red flag signs, such as severe anaphylactic reactions. The panel agreed that infants on an eHF with resolved symptoms within 2-4 weeks should continue the eHF with particular attention to the growth and nutritional status. On the other hand, an AAF should be considered for infants with persistent symptoms and should be continued if the symptoms resolve within 2-4 weeks, with particular attention to the growth and nutritional status. In cases with no symptomatic improvement after the introduction of an AAF, other measures should be followed. The panel developed a management algorithm, which achieved an agreement level of 90.9%.

The present Delphi-based study combined the best available evidence and clinical experience to optimize the diagnosis and management of CMPA presenting to the healthcare settings in the Middle East. The experts developed several statements and a clinical pathway algorithm to aid primary healthcare physicians and general pediatricians in diagnosis and management of CMPA presenting to primary and advanced healthcare settings in the Middle East. Multidisciplinary collaboration is needed to develop regional consensus regarding the diagnosis and treatment of CMPA in infants and children.

Nutritional Counseling for Cow's Milk Protein Allergy In Infants From Birth to 2 y of Ages[9]

Source: *Zamanillo-Campos R, Coto Alonso L, Fuentes Martín MJ, Nevot Escusa P, Tejón Fernández M. Nutritional counseling for cow's milk protein allergy in infants from birth to 2 y of ages: Scoping review. Nutrition. 2022 Jun;98:111633. doi: 10.1016/j.nut.2022.111633*

Cow's milk protein allergy (CMPA) is a clinical condition that requires appropriate nutritional counseling during breastfeeding and the introduction of complementary feeding. Using evidence-based dietetic advice is critical for correct growth and development during childhood. Zamanillo-Campos et al reviewed the most recent literature on nutritional counseling aiming at infants between 0 and 2 years of age diagnosed with CMPA.

Six databases were searched and updated on August 22, 2020. Retrieved articles were screened in duplicate and independently by all the authors, and these were selected according to the following inclusion criteria: clinical trials, reviews, meta-analyses, and clinical practice guidelines published since 2013 on any dietetic intervention aimed at infant populations between 0 and 2 years of age with CMPA. Critical appraisal through the AGREE instrument and CASP tools enabled the risk of bias assessment.

The authors obtained 2874 results, of which 40 were included for reviewing. The authors were able to answer all the research questions with the information retrieved, including aspects of the nutritional counseling aimed at mothers who breastfeed infants with CMPA, as well as infants during breastfeeding and the introduction of complementary feeding.

The authors also reviewed the specific nutritional requirements of infants with CMPA to assess nutritional supplementation and the evidence available on the use of probiotics, prebiotics, and symbiotics.

In this scoping review study, the lines of action for an appropriate nutritional approach in infants with CMPA, from birth and ≤2 years of age, were presented in a structured manner. Having the specific information about nutritional counseling will contribute to gaining more specialized knowledge as to the nutrition of the infant with CMPA for specialized professionals who work with these patients. Moreover, pediatric dietitians who advise families affected by this early allergy will have improved guidance to facilitate their professional decision making.

World Allergy Organization Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines Update[10]

Source: *Fiocchi A, Bognanni A, Brożek J, Ebisawa M, Schünemann H; WAO DRACMA guideline group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions. World Allergy Organ J. 2022 Feb 1;15(1):100609. doi: 10.1016/j.waojou.2021.100609.*

IgE-mediated cow's milk protein allergy (IgE-CMA) has been a primary topic of interest for the World Allergy Organization (WAO) since 2010, the year in which the first Grading of Recommendations Assessment, Development, and Evaluation (GRADE)-based guidelines on the management of this condition were published. Since the World Allergy Organization Diagnosis and Rationale against Cow's Milk Allergy (DRACMA) Guidelines were published 10 years ago, new evidence has accumulated about the diagnosis, therapy, and specific immunotherapy for cow's milk allergy (CMA). For this reason, WAO has felt the need to update the guidelines.

In this study, Fiocchi et al introduced the updated DRACMA guidelines aiming to illustrate the progress in diagnosis, therapy, and immunotherapy of IgE-CMA that could tailor the management of CMA. Since the first edition of DRACMA, other guidelines, consensuses, and position papers have been issued on CMA at the regional or national level. Some of them were national guidance items, implementing locally the DRACMA guidelines, others were de novo publications, developed using different methodologies.

In developing the meta-analyses and the guidelines, the authors adhered to the following definitions:

- **Cow's milk hypersensitivity** indicates nonallergic hypersensitivity (traditionally termed "cow's milk intolerance") and allergic milk hypersensitivity.
- **Cow's milk allergy** (CMA) indicates "a hypersensitivity reaction initiated by specific immunological mechanisms.
- **IgE-mediated CMA** (IgE-CMA) indicates a hypersensitivity reaction to cow's milk proteins initiated by specific Immunoglobulin E binding to Fcε receptors on effector cells as mast cells and basophils. This causes release of histamine and other preformed mediators, and rapid symptom onset.
- **Non IgE-mediated** CMA (non-IgE-CMA) indicates a hypersensitivity reaction to cow's milk proteins initiated by non-IgE mediated (mainly cell-mediated) mechanisms.
- **Anaphylaxis** is defined according to the amended WAO criteria for the diagnosis of anaphylaxis.

The new DRACMA guidelines aim to comprehensively address the guidance on diagnosis and therapy of both IgE non-IgE-mediated forms of cow's milk allergy in children and adults. They will be divided into 18 chapters, each of which will be dedicated to one aspect. The focus will be on the meta-analyses and recommendations that will be expressed for the 3 most relevant clinical aspects: (a) the diagnostic identification of the condition; (b) the choice of the replacement formula in case of CMA in infancy when the mother is not able to breastfeed, and (c) the use of specific immunotherapy for cow's milk protein allergy.

Functional Gastrointestinal Disorders

Pediatric Aspects of Nutrition Interventions for Disorders of Gut-Brain Interaction[11]

Source: *Nurko S, Benninga MA, Solari T, Chumpitazi BP. Pediatric Aspects of Nutrition Interventions for Disorders of Gut-Brain Interaction. Am J Gastroenterol. 2022 Jun 1;117(6):995-1009. doi: 10.14309/ajg.0000000000001779.*

Dietary factors may play an important role in the generation of symptoms in children with disorders of gut-brain interaction (DGBIs). Although dietary modification may provide successful treatment, there is a relative paucity of controlled trials that have shown the effectiveness of dietary interventions.

Infants with colic	Removing cow's milk from the infant's diet or from the maternal diet in those who are breastfed.
Infants with regurgitation	Adding thickeners to the formula or removing cow's milk protein from the infant's diet or the maternal diet in those who are breastfed.
Children with pain-predominant DGBIs	Using soluble fiber supplementation or a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet.
Children with functional constipation	There is no evidence that adding fiber is beneficial. The current European and North American pediatric gastroenterology society functional constipation guidelines recommend that a 2 - to 4 - week trial of cow's milk avoidance should be reserved for children who do not respond to conventional treatment.

This study is a narrative review that explores the existing literature on food and pediatric DGBIs. The interventions, shown in the table, have been shown to be beneficial.

Given that most dietary interventions include restriction of different foods in children, a thoughtful approach and close follow-up are needed.

Nonpharmacologic Treatment for Children with Functional Constipation[12]

Source: *Wegh CAM, Baaleman DF, Tabbers MM, Smidt H, Benninga MA. Nonpharmacologic Treatment for Children with Functional Constipation: A Systematic Review and Meta-analysis. J Pediatr. 2022 Jan;240:136-149.e5. doi: 10.1016/j.jpeds.2021.09.010.*

According to international guidelines, the first steps in the treatment of children with functional constipation include demystification, education, toilet training, and laxative treatment with polyethylene glycol (PEG). In addition, guidelines advise a normal fiber and fluid intake, and regular physical activity, but do not recommend the use of probiotics, prebiotics, or behavioral therapy owing to a lack of evidence.

In this study, Wegh et al evaluated the effectiveness and safety of nonpharmacologic interventions for the treatment of childhood functional constipation. The authors reviewed randomized controlled trials (RCTs) evaluating nonpharmacologic treatments in children with functional constipation which reported at least 1 outcome of the core outcome set for children with functional constipation.

The authors included 52 RCTs with 4668 children, aged between 2 weeks and 18 years, of whom 47% were females. Studied interventions included gut microbiome-directed interventions, other dietary interventions, oral supplements, pelvic floor-directed interventions, electrical stimulation, dry cupping, and massage therapy.

An overall high risk of bias was found across the majority of studies. Meta-analyses for treatment success and/or defecation frequency, including 20 RCTs, showed abdominal electrical stimulation (n = 3), Cassia Fistula emulsion (n = 2), and a cow's milk exclusion diet (n = 2 in a subpopulation with constipation as a possible manifestation of cow's milk allergy) may be effective. Evidence from RCTs not included in the meta-analyses, indicated that some prebiotic and fiber mixtures, Chinese herbal medicine (Xiao'er Biantong granules), and abdominal massage are promising therapies. In contrast, studies showed no benefit for the use of probiotics, synbiotics, an increase in water intake, dry cupping, or additional biofeedback or behavioral therapy. The researchers did not find RCTs on physical movement or acupuncture.

The authors found that some prebiotic and fiber mixtures may be effective treatments, whereas no evidence was found for the use of probiotics or synbiotics. This difference may be explained by the fact that fibers and prebiotics stimulate fecal bulking via their own mass and the ability of insoluble fibers to bind water directly.

More well-designed high quality RCTs concerning nonpharmacologic treatments for children with functional constipation are needed before changes in current guidelines are indicated.

Metabolic Disorders

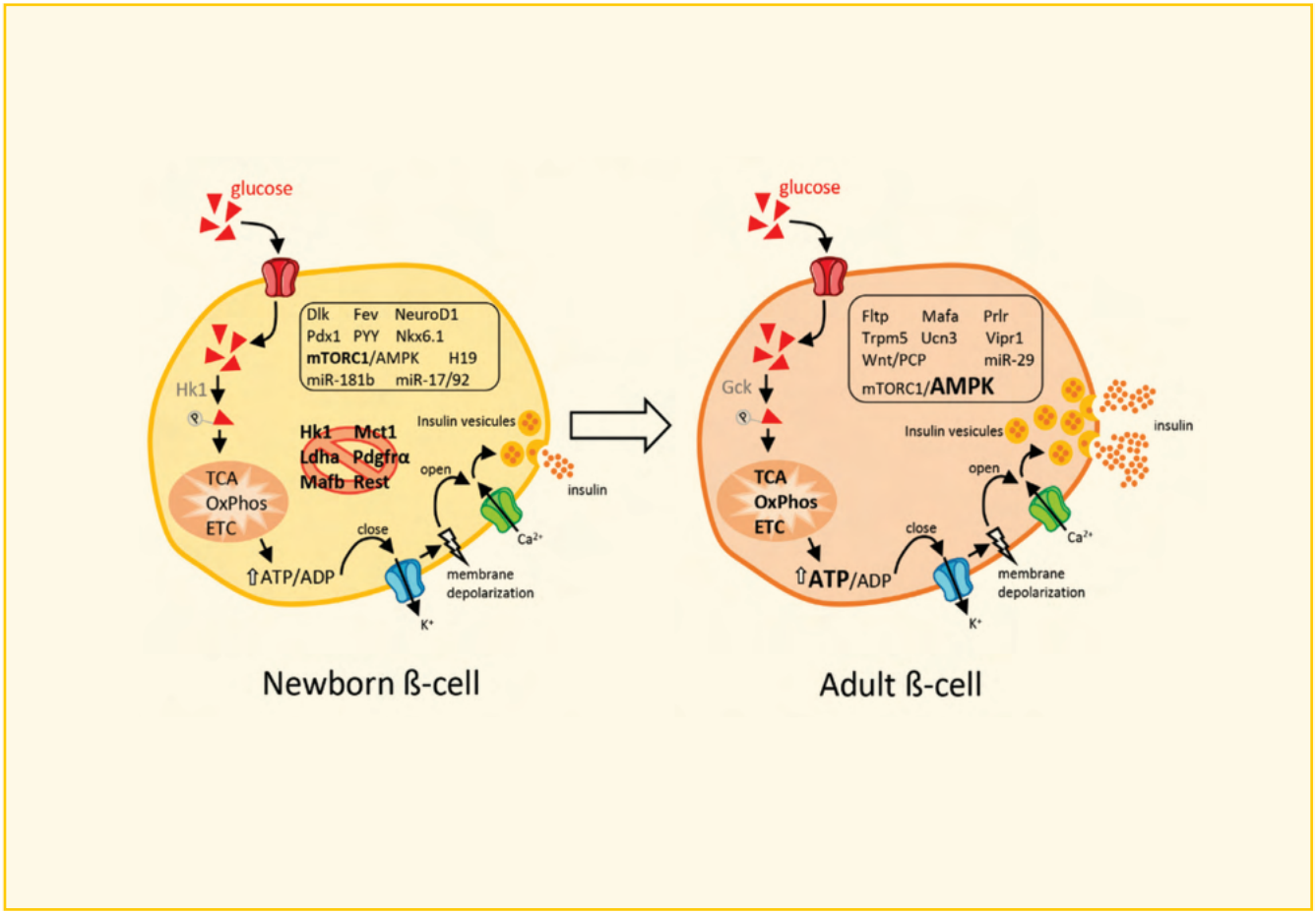
Mechanisms Underlying the Expansion and Functional Maturation of β-Cells in Newborns[13]

Source: *Jacovetti C, Regazzi R. Mechanisms Underlying the Expansion and Functional Maturation of β-Cells in Newborns: Impact of the Nutritional Environment. Int J Mol Sci. 2022 Feb 14;23(4):2096. doi: 10.3390/ijms23042096.*

The acquisition of a suitable and fully functional adult pancreatic β-cell mass is a fundamental prerequisite for the maintenance of carbohydrate homeostasis and for facing the pathophysiological challenges encountered by our organism throughout life. The postnatal period is a key window where the endocrine pancreas is expanding to reach an appropriate adult β-cell mass and in which insulin-secreting cells finalize their functional maturation. This process has a critical impact on the acquisition of an adequate functional β-cell mass and on the capacity to meet and adapt to insulin needs later in life.

Many cellular pathways playing a role in postnatal β-cell development have already been identified. However, single-cell transcriptomic and proteomic analyses continue to reveal new players contributing to the acquisition of β-cell identity.

In this review, Jacovetti et al provided an updated picture of the mechanisms governing postnatal β-cell mass expansion and the transition of insulin-secreting cells from an immature to a mature state. The authors highlighted the contribution of the environment to β-cell maturation and discussed the



adverse impact of an in utero and neonatal environment characterized by calorie and fat overload or by protein deficiency and undernutrition.

Inappropriate nutrition early in life constitutes a risk factor for developing diabetes in adulthood and can affect the β-cells of the offspring over two generations.

The transition from a lipid-dominant to a carbohydrate-rich diet in the postnatal period appears as a crucial determinant in the transcriptomic changes associated with the functional maturation of adult β-cells.

Diabetes, obesity, and over- or undernutrition during pregnancy may be responsible for many alterations in pancreatic development and significantly increase the susceptibility of the offspring to develop metabolic diseases in adulthood such as metabolic syndrome, obesity, cardiovascular disease, and type 2 diabetes (T2DM).

A better understanding of these events occurring in the neonatal period will help in the development of better strategies to produce functional β-cells and to design novel therapeutic approaches for the prevention and treatment of diabetes.

Transforming Obesity Prevention for CHILDren (TOPCHILD) Collaboration: Protocol for a Systematic Review with Individual Participant Data Meta-analysis[14]

Source: *Hunter KE, Johnson BJ, Askie L, Golley RK, Baur LA, Marschner IC, Taylor RW, Wolfenden L, Wood CT, Mihrshahi S, Hayes AJ, Rissel C, Robledo KP, O'Connor DA, Espinoza D, Staub LP, Chadwick P, Taki S, Barba A, Libesman S, Aberoumand M, Smith WA, Sue-See M, Hesketh KD, Thomson JL, Bryant M, Paul IM, Verbestel V, Stough CO, Wen LM, Larsen JK, O'Reilly SL, Wasser HM, Savage JS, Ong KK, Salvy SJ, Messito MJ, Gross RS, Karssen LT, Rasmussen FE, Campbell K, Linares AM, Øverby NC, Palacios C, Joshipura KJ, González Acero C, Lakshman R, Thompson AL, Maffeis C, Oken E, Ghaderi A, Campos Rivera M, Pérez-Expósito AB, Banna JC, de la Haye K, Goran M, Røed M, Anzman-Frasca S, Taylor BJ, Seidler AL; Transforming Obesity Prevention for CHILDren (TOPCHILD) Collaboration. Transforming Obesity Prevention for CHILDren (TOPCHILD) Collaboration: protocol for a systematic review with individual participant data meta-analysis of behavioural interventions for the prevention of early childhood obesity. BMJ Open. 2022 Jan 20;12(1):e048166. doi: 10.1136/bmjopen-2020-048166.*

Behavioral interventions in early life appear to show some effect in reducing childhood overweight and obesity. However, uncertainty remains regarding their overall effectiveness, and whether effectiveness differs among key subgroups. These evidence gaps have prompted an increase in very early childhood obesity prevention trials worldwide. Combining the individual participant data (IPD) from these trials will enhance statistical power to determine overall effectiveness and enable examination of individual and trial-level subgroups.

In this study, Hunter et al present a protocol for a systematic review with IPD meta-analysis aiming to evaluate the effectiveness of obesity prevention interventions commencing antenatally or in the first year after birth, and to explore whether there are differential effects among key subgroups.

To this end, systematic searches of Medline, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycInfo and trial registries for all ongoing and completed randomized controlled trials evaluating behavioral interventions for the prevention of early childhood obesity have been completed up to March 2021 and will be updated annually to include additional trials.

Eligible trialists will be asked to share their IPD; if unavailable, aggregate data will be used where possible. An IPD meta-analysis and a nested prospective meta-analysis will be performed using methodologies recommended by the Cochrane Collaboration.

The primary outcome will be body mass index z-score at age 24±6 months using WHO Growth Standards, and effect differences will be explored among prespecified individual and trial-level subgroups. The secondary outcomes include other child weight-related measures, infant feeding, dietary intake, physical activity, sedentary behaviors, sleep, parenting measures and adverse events.

This will be the largest individual participant data (IPD) meta-analysis evaluating behavioral interventions for the prevention of early childhood obesity to date, and will provide the most reliable and precise estimates of early intervention effects to inform future decision-making. IPD meta-analysis methodology will enable unprecedented exploration of important individual and trial-level characteristics that may be associated with childhood obesity or that may be effect modifiers.

Fructose Intake, Hypertension and Cardiometabolic Risk Factors in Children and Adolescents: from Pathophysiology to Clinical Aspects[15]

Source: *Giussani M, Lieti G, Orlando A, Parati G, Genovesi S. Fructose Intake, Hypertension and Cardiometabolic Risk Factors in Children and Adolescents: From Pathophysiology to Clinical Aspects. A Narrative Review. Front Med (Lausanne). 2022 Apr 12;9:792949. doi: 10.3389/fmed.2022.792949.*

Arterial hypertension, dyslipidemia, alterations in glucose metabolism and fatty liver, either alone or in association with each other, are frequently observed in obese children and may seriously jeopardize their health. For obesity to develop, an excessive intake of energy-bearing macronutrients is required; however, ample evidence suggests that fructose may promote the development of obesity and/or metabolic alterations, independently of its energy intake.

Fructose consumption is particularly high among children, because they do not have the perception, and more importantly, neither do their parents, that high fructose intake is potentially dangerous. In fact, while this sugar is erroneously viewed favorably as a natural nutrient, its excessive intake can actually cause adverse cardio-metabolic alterations. Fructose induces the release of pro-inflammatory cytokines, and reduces the production of anti-atherosclerotic cytokines, such as adiponectin. By interacting with hunger and satiety control systems, particularly by inducing leptin resistance, fructose leads to increased caloric intake.

Fructose, directly or through its metabolites, promotes the development of obesity, arterial hypertension, dyslipidemia, glucose intolerance and fatty liver. The uncontrolled entry of fructose into the hepatocyte is a crucial point for the establishment of metabolic alterations that accompany an excessive and time-concentrated intake of this nutrient (Figure 2).

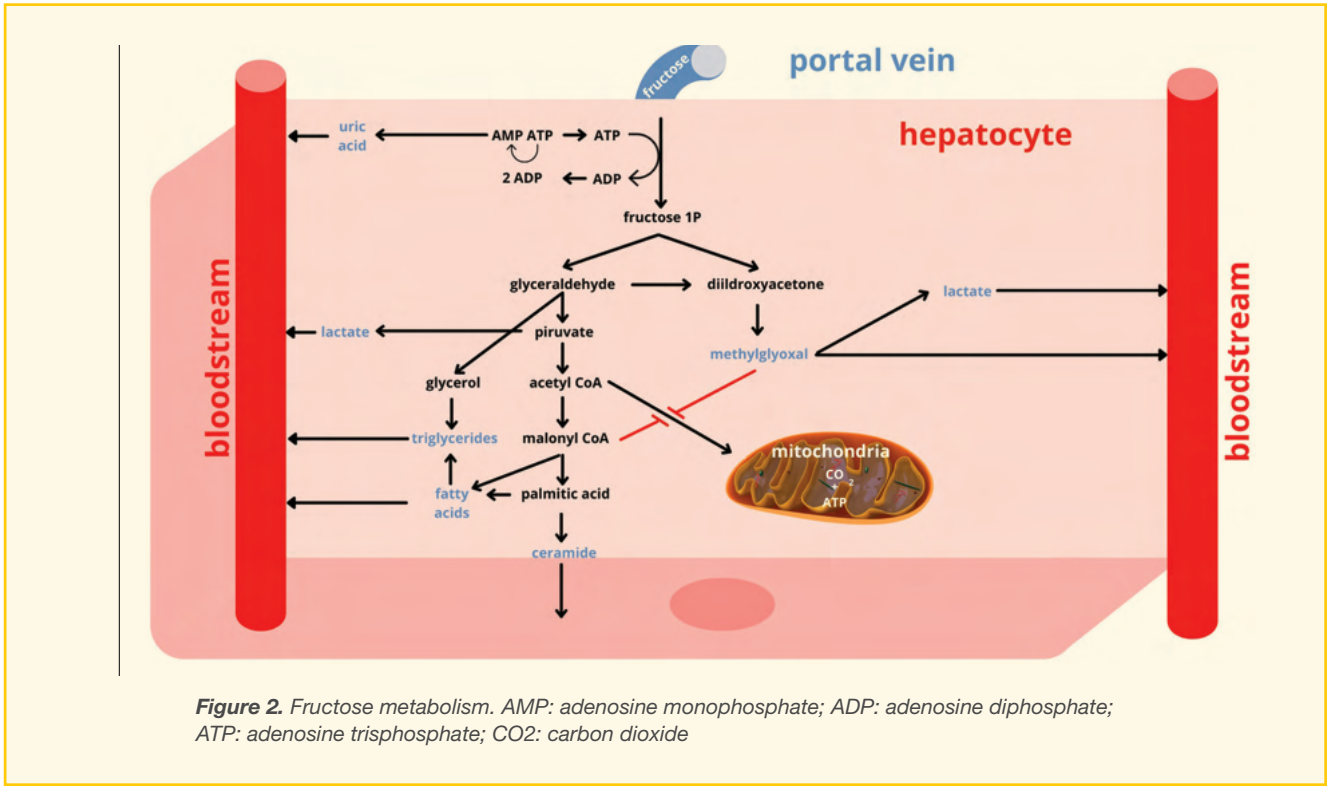


Figure 2. *Fructose metabolism. AMP: adenosine monophosphate; ADP: adenosine diphosphate; ATP: adenosine trisphosphate; CO2: carbon dioxide*

This review aimed to highlight the mechanisms by which the early and excessive consumption of fructose may contribute to the development of a variety of cardiometabolic risk factors in children, thus representing a potential danger to their health. It also described the main clinical trials performed in children and adolescents that have evaluated the clinical effects of excessive intake of fructose-containing drinks and food, with particular attention to the effects on blood pressure. Finally, the authors discussed the effectiveness of measures that can be taken to reduce the intake of this sugar.

Despite the fact that in recent years the attention of parents to the eating habits of their children has increased, there still may be not enough concern about the intake of free sugars and fructose, as these nutrients may be erroneously perceived as "natural" and "necessary" and are therefore proposed even to the youngest children. Free sugars, however, are not at all indispensable in a correct diet.

Fructose has specific metabolic pathways and, directly or through its metabolites, may promote the development of arterial hypertension and metabolic syndrome. Given the large increase in the consumption of foods and beverages with added fructose in recent decades by children and adolescents, it is reasonable to think that increased fructose intake currently represents a real problem for the health of the younger generations.

Accuracy of Different Cutoffs of the Waist-to-Height Ratio as a Screening Tool for Cardiometabolic Risk in Children and Adolescents[16]

Source: *Ezzatvar Y, Izquierdo M, Ramírez-Vélez R, Del Pozo Cruz B, García-Hermoso A. Accuracy of different cutoffs of the waist-to-height ratio as a screening tool for cardiometabolic risk in children and adolescents: A systematic review and meta-analysis of diagnostic test accuracy studies. Obes Rev. 2022 Feb;23(2):e13375. doi: 10.1111/obr.13375.*

This systematic review with meta-analysis sought to estimate the accuracy of different waist-to-height ratio (WHtR) cutoff ranges as risk indicators for cardiometabolic health in different populations of children and adolescents. Systematic searches were undertaken to identify studies in apparently healthy participants aged 3-18 years that conducted receiver operating characteristic curve analysis and reported area under the receiver operating characteristic curves for WHtR with any cardiometabolic biomarker.

Forty-one cross-sectional studies were included in the meta-analysis, including 138,561 young individuals (50% girls). Higher area under summary receiver operating characteristic (AUSROC) values were observed in cutoffs between 0.46 and 0.50 (AUSROC = 0.83, 95%CI 0.80-0.86) and ≥0.51 (AUSROC = 0.87, 95%CI 0.84-0.90) ($p < 0.001$ in comparison with cutoffs 0.41 to 0.45), with similar results in both sexes.

The authors found that the AUSROC value increased in the East and Southeast Asian regions using a WHtR cutoff of ≥0.46 (AUSROC = 0.90, 95%CI 0.87 to 0.92). A cutoff of ≥0.54 was optimal for the Latin American region (AUSROC = 0.96, 95%CI 0.94-0.97).

Although WHtR is a simple measure of adiposity in children and adolescents, the use of the universal cutoff value of 0.50 to identify cardiometabolic risk remains controversial. To date, previous meta-analyses have consistently shown the clinical utility of this cutoff for identifying cardiometabolic risk and metabolic syndrome in the young population.

This meta-analysis identified optimal cutoff values of WHtR for use in children and adolescents from different regions. Despite the widely accepted WHtR cutoff of 0.50, this study indicated that a single cutoff value of WHtR may be inappropriate.

Mealtime Media Use and Cardiometabolic Risk in Children[17]

Source: *Jamnik J, Keown-Stoneman C, Eny KM, Maguire JL, Birken CS; TARGet Kids! Collaboration. Mealtime media use and cardiometabolic risk in children. Public Health Nutr. 2022 Mar;25(3):670-679. doi: 10.1017/S1368980020003821.*

Possible mechanisms to explain the link between mealtime media use and excess body weight include eating despite the lack of hunger, reduced satiety signals while watching media and exposure to advertisements promoting energy-dense foods and poor dietary habits.

Jamnik et al aimed to examine the association between mealtime media use and non-HDL-cholesterol as well as other markers of cardiometabolic risk (CMR) in children. To this end, a repeated measures study using a multivariable linear regression with generalized estimating equations was conducted in children ≥1 year of age participating in the TARGet Kids (The Applied Research Group for Kids) cohort. Analyses were stratified a priori by age groups (1-4 and 5-13 years). In total, 2117 children aged 1-13 years were included in the analysis.

After adjusting for covariates, there was no evidence that total mealtime media use was associated with non-HDL-cholesterol in 1-4 year olds (p = 0.10) or 5-13 year olds (p = 0.29). Each additional meal with media per week was associated with decreased HDL-cholesterol in 5-13 year olds (-0.006 mmol/l; 95%CI -0.009, -0.002; p = 0.003) and log-TAG in 1-4 year olds (β = -0.004; 95%CI -0.008, -0.00009; p = 0·04).

Media use during breakfast was associated with decreased HDL-cholesterol in 5-13 year olds (-0.012 mmol/l; 95%CI -0.02, -0.004; p = 0.002), while media during lunch was associated with decreased log-TAG (-0.01 mmol/l; 95%CI -0.03, -0.002; p = 0.03) in children aged 1-4 years. Total mealtime media use was not associated with total cholesterol, glucose or insulin in either age group.

While there was no evidence that mealtime media use was associated with non-HDL-cholesterol, it may be associated with unfavorable lipid profiles through effects on HDL-cholesterol independent of body weight in children ≥5 years. This suggests that promoting media-free meals in school-aged children may have beneficial effects on minimizing CMR.

Ketogenic Diet

Clinical Implementation of Ketogenic Diet in Children with Drug-resistant Epilepsy[18]

Source: *Tong X, Deng Y, Liu L, Tang X, Yu T, Gan J, Cai Q, Luo R, Xiao N. Clinical implementation of ketogenic diet in children with drug-resistant epilepsy: Advantages, disadvantages, and difficulties. Seizure. 2022 Jul;99:75-81. doi: 10.1016/j.seizure.2022.04.015.*

Ketogenic diet (KD) is a well-established non-pharmacologic treatment for drug-resistant epilepsy. However, although KD has a long history of clinical use, there are still many difficulties with its real-world practice. This study retrospectively described the situation of KD practice in two children's hospitals in Southwest China.

Tong et al reviewed and analyzed clinical data collected at the baseline, and during follow ups at 1, 3, 6, 12, 18, and 24 months, focusing on the patient retention, the efficacy, the side effects of KD, and the reasons for discontinuation.

The authors found that there was increasing availability of KD for children with epilepsy in Southwest China and its effectiveness in controlling seizures was reconfirmed. Nonetheless, less than half of the patients adhered to KD for one year and about 1/5 of the patients for two years. Unsatisfactory seizure control was the most common reason for discontinuation, followed by patient/caregiver preference, acute infection, and loss to follow up. Adverse ef-

fects were mostly tolerable and not the main reason for discontinuation. Meanwhile, KD showed negative impacts on linear growth, and our cohort seemed to have more infections and deaths.

The findings of this study confirmed the effect of KD on seizure suppression, which is consistent with earlier studies. Notably, the retention rate and seizure control of our patients at each follow-up were comparable to existing literature. Taking the time points of six and 12 months as examples, the retention rates at these time points were 68.2% and 42.7%, respectively, whereas and the response rates were 80.4% and 97%, respectively.

Despite increasing availability and good efficacy, long-term adherence to KD was difficult. Compliance issues appeared to be prominent. Enhancing food taste and patient support can help improve the retention rate.

Higher Levels of Bifidobacteria and Tumor Necrosis Factor in Children with Drug-resistant Epilepsy are Associated with Anti-seizure Response to the Ketogenic Diet[19]

Source: *Dahlin M, Singleton SS, David JA, Basuchoudhary A, Wickström R, Mazumder R, Prast-Nielsen S. Higher levels of Bifidobacteria and tumor necrosis factor in children with drug-resistant epilepsy are associated with anti-seizure response to the ketogenic diet. EBioMedicine. 2022 Jun;80:104061. doi: 10.1016/j.ebiom.2022.104061.*

Recently, studies have suggested a role for the gut microbiota in epilepsy. Gut microbial changes during ketogenic diet (KD) treatment of drug-resistant epilepsy have been described. Inflammation is associated with certain types of epilepsy and specific inflammation markers decrease during KD. The gut microbiota plays an important role in the regulation of the immune system and inflammation.

In this observational study, 28 children with drug-resistant epilepsy treated with the ketogenic diet were followed. Fecal and serum samples were collected at baseline and three months after dietary intervention.

Dahlin et al identified both gut microbial and inflammatory changes during treatment. KD had a general anti-inflammatory effect. Novel bioinformatics and machine learning approaches identified signatures of specific Bifidobacteria and TNF (tumor necrosis factor) associated with responders before starting KD. During KD, taxonomic and inflammatory profiles between responders and non-responders were more similar than at baseline.

By using a machine learning approach, the authors demonstrated that there was a discriminating microbial signature in fecal samples comparing patients before starting KD to after three months on KD.

The authors' results suggest that children with drug-resistant epilepsy are more likely to benefit from KD treatment when specific Bifidobacteria and TNF are elevated. They authors presented a novel signature of interaction of the gut microbiota and the immune system associated with anti-epileptic response to KD treatment. This signature could be used as a prognostic biomarker to identify potential responders to KD before starting treatment. These findings may also contribute to the development of new anti-seizure therapies by targeting specific components of the gut microbiota.

References

1. Consales A, Morniroli D, Vizzari G, Mosca F, Giannì ML. Nutrition for Infant Feeding. Nutrients. 2022 Apr 27;14(9):1823. doi: 10.3390/nu14091823.

2. Andresen EC, Hjelkrem AR, Bakken AK, Andersen LF. Environmental Impact of Feeding with Infant Formula in Comparison with Breastfeeding. Int J Environ Res Public Health. 2022 May 24;19(11):6397. doi: 10.3390/ijerph19116397.

3. Callahan EA, Chatila T, Deckelbaum RJ, Field CJ, Greer FR, Hernell O, Järvinen KM, Kleinman RE, Milner J, Neu J, Smolen KK, Wallingford JC. Assessing the safety of bioactive ingredients in infant formula that affect the immune system: recommendations from an expert panel. Am J Clin Nutr. 2022 Feb 9;115(2):570-587. doi: 10.1093/ajcn/nqab346.

4. Cheng H, Rossiter C, Size D, Denney-Wilson E. Comprehensiveness of infant formula and bottle feeding resources: A review of information from Australian healthcare organisations. Matern Child Nutr. 2022 Apr;18(2):e13309. doi: 10.1111/mcn.13309

5. Bookhart LH, Anstey EH, Kramer MR, Perrine CG, Reis-Reilly H, Ramakrishnan U, Young MF. A nation-wide study on the common reasons for infant formula supplementation among healthy, term, breastfed infants in US hospitals. Matern Child Nutr. 2022 Apr;18(2):e13294. doi: 10.1111/mcn.13294.

6. Chouraqui JP, Turck D, Tavoularis G, Ferry C, Dupont C. The Role of Young Child Formula in Ensuring a Balanced Diet in Young Children (1-3 Years Old). Nutrients. 2019 Sep 13;11(9):2213. doi: 10.3390/nu11092213.

7. Lovell AL, Davies PSW, Hill RJ, Milne T, Matsuyama M, Jiang Y, Chen RX, Heath AM, Grant CC, Wall CR. Validation and calibration of the Eating Assessment in Toddlers FFQ (EAT FFQ) for children, used in the Growing Up Milk - Lite (GUMLi) randomised controlled trial. Br J Nutr. 2021 Jan 28;125(2):183-193. doi: 10.1017/S0007114520002664.

8. El-Hodhod MA, El-Shabrawi MHF, AlBadi A, Hussein A, Almehaidib A, Nasrallah B, AlBassam EM, El Feghali H, Isa HM, Al Saraf K, Sokhn M, Adeli M, Al-Sawi NMM, Hage P, Al-Hammadi S. Consensus statement on the epidemiology, diagnosis, prevention, and management of cow's milk protein allergy in the Middle East: a modified Delphi-based study. World J Pediatr. 2021 Dec;17(6):576-589. doi: 10.1007/s12519-021-00476-3. Epub 2021 Nov 24. PMID: 34817828; PMCID: PMC8639571.

9. Zamanillo-Campos R, Coto Alonso L, Fuentes Martín MJ, Nevot Escusa P, Tejón Fernández M. Nutritional counseling for cow's milk protein allergy in infants from birth to 2 y of ages: Scoping review. Nutrition. 2022 Jun;98:111633. doi: 10.1016/j.nut.2022.111633

10. Fiocchi A, Bognanni A, Brožek J, Ebisawa M, Schünemann H; WAO DRACMA guideline group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions. World Allergy Organ J. 2022 Feb 1;15(1):100609. doi: 10.1016/j.waojou.2021.100609.

11. Nurko S, Benninga MA, Solari T, Chumpitazi BP. Pediatric Aspects of Nutrition Interventions for Disorders of Gut-Brain Interaction. Am J Gastroenterol. 2022 Jun 1;117(6):995-1009. doi: 10.14309/ajg.0000000000001779.

12. Wegh CAM, Baaleman DF, Tabbers MM, Smidt H, Benninga MA. Nonpharmacologic Treatment for Children with Functional Constipation: A Systematic Review and Meta-analysis. J Pediatr. 2022 Jan;240:136-149.e5. doi: 10.1016/j.jpeds.2021.09.010.

13. Jacovetti C, Regazzi R. Mechanisms Underlying the Expansion and Functional Maturation of β-Cells in Newborns: Impact of the Nutritional Environment. Int J Mol Sci. 2022 Feb 14;23(4):2096. doi: 10.3390/ijms23042096.

14. Hunter KE, Johnson BJ, Askie L, Golley RK, Baur LA, Marschner IC, Taylor RW, Wolfenden L, Wood CT, Mihrshahi S, Hayes AJ, Rissel C, Robledo KP, O'Connor DA, Espinoza D, Staub LP, Chadwick P, Taki S, Barba A, Libesman S, Aberoumand M, Smith WA, Sue-See M, Hesketh KD, Thomson JL, Bryant M, Paul IM, Verbestel V, Stough CO, Wen LM, Larsen JK, O'Reilly SL, Wasser HM, Savage JS, Ong KK, Salvy SJ, Messito MJ, Gross RS, Karssen LT, Rasmussen FE, Campbell K, Linares AM, Øverby NC, Palacios C, Joshipura KJ, González Acero C, Lakshman R, Thompson AL, Maffeis C, Oken E, Ghaderi A, Campos Rivera M, Pérez-Expósito AB, Banna JC, de la Haye K, Goran M, Røed M, Anzman-Frasca S, Taylor BJ, Seidler AL; Transforming Obesity Prevention for CHILDren (TOPCHILD) Collaboration. Transforming Obesity Prevention for CHILDren (TOPCHILD) Collaboration: protocol for a systematic review with individual participant data meta-analysis of behavioural interventions for the prevention of early childhood obesity. BMJ Open. 2022 Jan 20;12(1):e048166. doi: 10.1136/bmjopen-2020-048166.

15. Giussani M, Lieti G, Orlando A, Parati G, Genovesi S. Fructose Intake, Hypertension and Cardiometabolic Risk Factors in Children and Adolescents: From Pathophysiology to Clinical Aspects. A Narrative Review. Front Med (Lausanne). 2022 Apr 12;9:792949. doi: 10.3389/fmed.2022.792949.

16. Ezzatvar Y, Izquierdo M, Ramírez-Vélez R, Del Pozo Cruz B, García-Hermoso A. Accuracy of different cutoffs of the waist-to-height ratio as a screening tool for cardiometabolic risk in children and adolescents: A systematic review and meta-analysis of diagnostic test accuracy studies. Obes Rev. 2022 Feb;23(2):e13375. doi: 10.1111/obr.13375.

17. Jamnik J, Keown-Stoneman C, Eny KM, Maguire JL, Birken CS; TARGet Kids! Collaboration. Mealtime media use and cardiometabolic risk in children. Public Health Nutr. 2022 Mar;25(3):670-679. doi: 10.1017/S1368980020003821.

18. Tong X, Deng Y, Liu L, Tang X, Yu T, Gan J, Cai Q, Luo R, Xiao N. Clinical implementation of ketogenic diet in children with drug-resistant epilepsy: Advantages, disadvantages, and difficulties. Seizure. 2022 Jul;99:75-81. doi: 10.1016/j.seizure.2022.04.015.

19. Dahlin M, Singleton SS, David JA, Basuchoudhary A, Wickström R, Mazumder R, Prast-Nielsen S. Higher levels of Bifidobacteria and tumor necrosis factor in children with drug-resistant epilepsy are associated with anti-seizure response to the ketogenic diet. EBioMedicine. 2022 Jun;80:104061. doi: 10.1016/j.ebiom.2022.104061.

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