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Shaping the Future with Nutrition

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Foreword

This year marks an historical milestone: the 100th Nestlé Nutrition Institute (NNI) Workshop. As we celebrate it, we've been reflecting on Nestlé's rich history, immense dedication, and tireless efforts in supporting and nurturing the nutrition science community through continuous education. This century stands as a testament to our unwavering commitment to advancing the field of nutrition and embracing continuous learning.

Starting with the publication of the first *Annales Nestlé* in 1942, we have been growing in credibility as a source of scientific nutrition-focused information. Along with the growth of the publication, more major milestones were achieved with the first Nestlé Nutrition Workshop, held in France in 1980. The title of that first workshop was "Maternal Nutrition in Pregnancy: Eating for Two?", reminding us that maternal nutrition – also one of the topics covered within the 100th workshop – was already an important theme back then.

These workshops continued to be held, traveling to various regions across the world and providing better access to nutrition science knowledge in different countries, and also providing the launch pad for the iconic publication series, the NNI "Blue Books".

In 2004, the Nestlé Nutrition Institute was created, which then became a not-for-profit association based in Switzerland in 2010. NNI has a long-lasting commitment to unbiased, reliable nutritional science and education. Further milestones were reached as the organization embraced digital technology, launching a website in 2006 and an app in 2022. NNI stays true to its commitment to empowering healthcare providers and supporting the nutrition science community with more accessible digital innovations.

Fast forward to the 100th NNI Workshop, the overall agenda was focused on shaping the future with nutrition, covering topics from preconception through the first month of life up to school age.

In the first section of the workshop, our speakers looked at current understanding of the fundamentals of maternal and child nutrition. They explored how an individual's health and well-being are shaped by many factors, from maternal preconception nutrition to mode of birth, infant nutrition with the importance of breastfeeding and human milk research, complementary feeding practices, environmental factors, and more.

The second section examined food dietary habits for optimal development. Speakers highlighted a strong evidence base for the nutritional approach that supports good health, but how in practice there are many challenges to achieving this.

During the third session, speakers discussed research into how the food system has evolved to accommodate the challenges that the global nutrition landscape is going through. This involves the shift to a more plant-based diet to account for sustainability in the diet, as well as new technological advancements to help address current and future issues that may persist.

We hope that this summary of the talks provides some food for thought on the strides we have made in nutrition for the different life stages, and the new strategies and solutions, especially in food technology, we can use to overcome the challenges of feeding the future.

Sara Colombo Mottaz
Global Head of the Nestlé Nutrition Institute

Achievements, Challenges, and Future Direction in Early Life Nutrition

Ian A. Macdonald, Eline M. van der Beek, Aristea Binia

Micronutrient deficiencies occur in most countries across the world, with classical undernutrition, low-nutrient-content diets, and even overnutrition with diets rich in energy but poor in micronutrients all contributing to poor nutritional status. This review starts with an overview of nutrient requirements and the associated dietary recommendations, which contribute to health across the lifespan. These recommendations aim to prevent deficiency diseases in all age groups, to achieve optimal growth and development in childhood and adolescence, and to maintain health during adulthood. However, these recommendations do not include all potential components of the diet, do not adequately cover the variations in requirements between individuals and ethnic groups, and focus mainly on undernutrition without much attention to the increasing problem of overnutrition. The recommendations are focused on individual nutrients and based on the assumption that all other nutrients in the diet are being consumed in adequate amounts. Clearly for many countries this is not the case, as a wide range of nutrient inadequacies are present in the groups experiencing major undernutrition [1].

Variations in nutritional requirements linked to different physiological states need further attention in the future. For example, the specific needs of women in the post-partum period should be addressed, especially in relation to further pregnancies occurring relatively quickly. The high prevalence of teenage pregnancies in many countries leads to major problems due to inadequate nutrient supply for the developing mother and child [2]. Focusing attention on adequate nutrition during pregnancy is beneficial for both mother and baby, reducing the risk for the baby of chronic disease in adulthood as well as reducing the depletion of the mother's nutrient stores/reserves during pregnancy and lactation (Fig. 1). There is now clear evidence that dietary intervention during pregnancy and lactation is of benefit to mother and baby [3], but the magnitude of the benefit depends on the background diet, and so any interventions need to have a clear focus (Fig. 2). The composition of the background diet not only varies

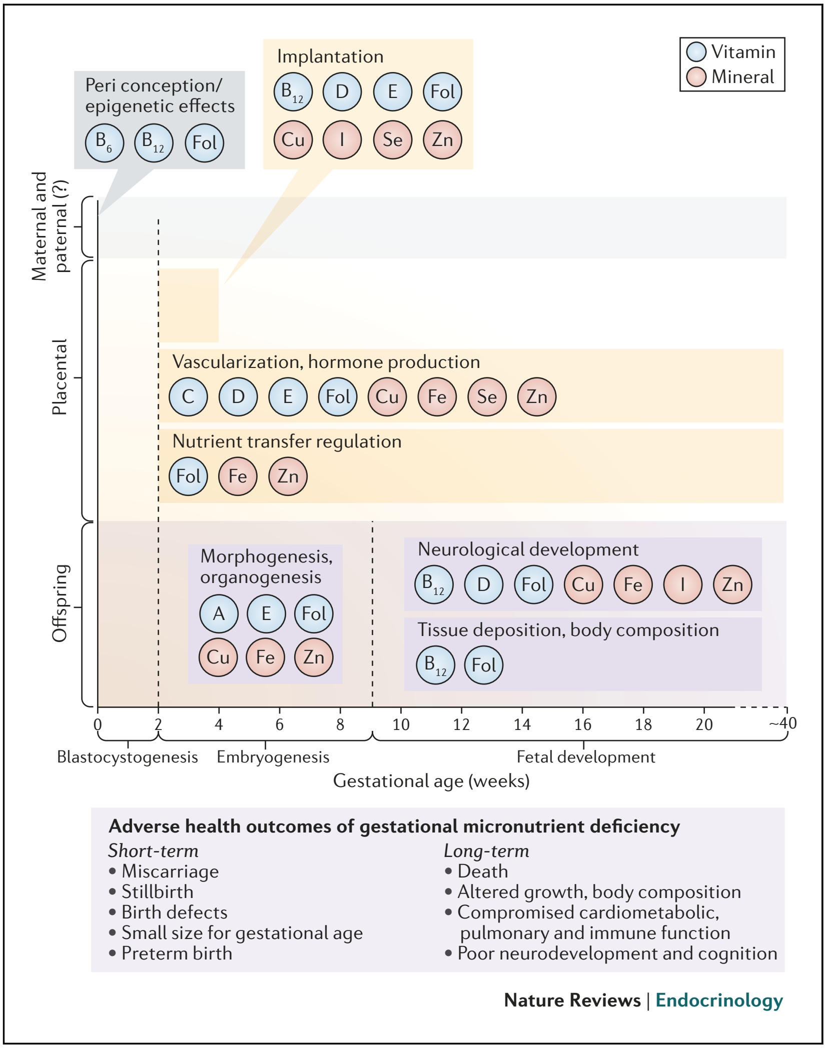

Fig. 1. The function and timing of micronutrients that affect outcomes in offspring. Insights on micronutrient function are primarily derived from reviews of data from in vitro studies, experimental animal models, observational data in human studies, and a limited number of trials that have explored metabolic mechanisms and outcomes. The relevant time of action and the function of micronutrients is depicted, but the accumulation of fetal micronutrient stores, generally dependent on the status of the mother, is not. Availability of fetal micronutrient stores to support growth and developmental processes into infancy and beyond is, therefore, an implied pathway. Fol, folate. Reproduced with permission from Gernand et al. [6].

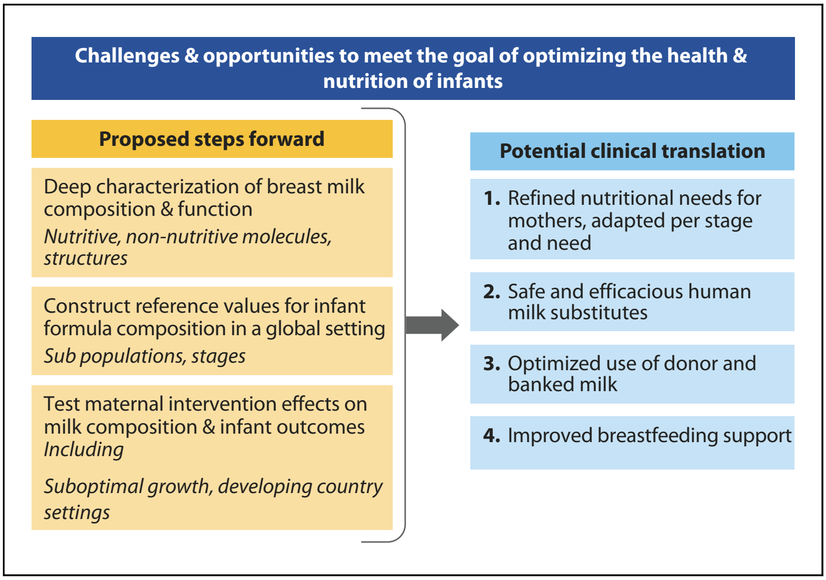

Fig. 2. Challenges and opportunities for early life nutrition.

between countries but has also changed over the last few decades. This has clear implications for dietary recommendations, which may need to be modified accordingly.

Inappropriate fat and sugar intakes in infancy, childhood, and adolescence can also increase the risk of non-communicable diseases in later life. The capacity of the infant microbiome to utilize HMO has been associated with certain beneficial effects such as immune competence and bone development. A novel distinct *Bifidobacterium longum* clade was found during weaning in a population of exclusively breast-fed infants from Bangladesh [4]. The novel clade is equipped with enzymes that can utilize both milk and food substrates and produces metabolites implicated in infant health outcomes.

Obesity is the major concern for child and adolescent nutrition in many countries. For example, in England the prevalence of obesity in children aged 5–6 years is just under 10%, and in 11–12 years it is 20%. The prevalence is much higher in areas of socio-economic deprivation than in less deprived areas. The solution to this is complex and requires the involvement of multiple stakeholders.

Young children have a relatively larger brain than adults, and that brain requires an adequate supply of glucose over the 24-h period. A recent study used magnetic resonance imaging and spectroscopy to measure liver glycogen in young children before and after a night's sleep and throughout the morning after breakfast or just water [5]. Future work should establish the functional importance of adequate glycogen stores and the amounts of carbohydrate needed at breakfast.

References

1 Prentice AM. The triple burden of malnutrition in the era of globalization. In: Rogacion JM, ed. *Interactions of Nutrition: Retracing Yesterday, Redefining Tomorrow. 97th Nestle Nutrition Institute Workshop, June 2022. Nestle Nutrition Institute Workshop Series*. Basel: Karger; 2023. Vol. 97; pp. 51–61. https://doi.org/10.1159/000529005.

2 Hanson MA, Bardsley A, De-Regil LM, Moore SE, Oken E, Poston L, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". *Int J Gynaecol Obstet*. 2015;*131*(suppl 4):S213–53. https://doi.org/10.1016/S0020-7292(15)30034-5.

3 Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev*. 2018;*11*: CD003402. https://doi.org/10.1002/14651858.CD003402.pub3.

4 Vatanen T, Ang QY, Siegwald L, Sarker SA, Le Roy CI, Duboux S, et al. A distinct clade of *Bifidobacterium longum* in the gut of Bangladeshi children thrives during weaning. *Cell*. 2022;*185*(23):P4280–4297.e12. https://doi.org/10.1016/j.cell.2022.10.011.

5 Horstman AMH, Bawden SJ, Spicer A, Darwish N, Goyer A, Egli L, et al. Liver glycogen stores via ^{13}C magnetic resonance spectroscopy in healthy children: randomized, controlled study. *Am J Clin Nutr*. 2023;*117*(4):709–16. https://doi.org/10.1016/j.ajcnut.2023.01.014.

6 Gernand AD, Schulze KJ, Stewart CP, West KP Jr, Christian P. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. *Nat Rev Endocrinol*. 2016;*12*(5):274–89. https://doi.org/10.1038/nrendo.2016.37.

An Offspring's Health Starts Before Conception and Results of the NiPPeR Randomized Trial

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There is wide consensus that early life events can shape future health and wellbeing. It is hypothesized that the earlier the exposure to a particular environmental factor, the greater the impact on future outcome; small changes in early life can lead to the emergence of significant consequences later, with epigenetic mechanisms thought to play a key role. A new life begins at conception when sperm fertilizes the oocyte. This initial environment within which this new life is formed is determined by both maternal and paternal lifestyle prior to pregnancy in addition to genetic makeup (Fig. 1). These could influence pregnancy events and have consequences on the offspring health, including the risk of developing non-communicable diseases and mental health issues.

Appreciation of the extent of this most early influence of preconception parental lifestyle and health on future offspring conditions is increasing as many studies of pregnancy interventions have demonstrated more limited effects than expected. After all, epigenetic plasticity peaks around the time of conception. It has led to the postulation that preconception interventions could be more effective in optimizing offspring health trajectories. There is a need now to build good and specific evidence on the benefit of preconception interventions, the optimal timing of their administration, and the population that would derive clear benefit.

Maternal nutritional supplementation is one such pre-pregnancy intervention but evidence supporting its use is scarce to date. To address this, the NiPPeR (Nutritional Intervention Preconception and During Pregnancy to Maintain Healthy Glucose Metabolism and Offspring Health) double-blind randomized controlled trial recruited 1729 UK, Singapore, and New Zealand women planning a pregnancy in 2015–2017. We investigated the effects of a nutritional formulation containing myo-inositol, probiotics, and multiple micronutrients (intervention), compared with a standard micronutrient supplement (control), taken preconception and throughout pregnancy. The primary outcome of gestational glycemia at 28 weeks' gestation showed no difference [1].

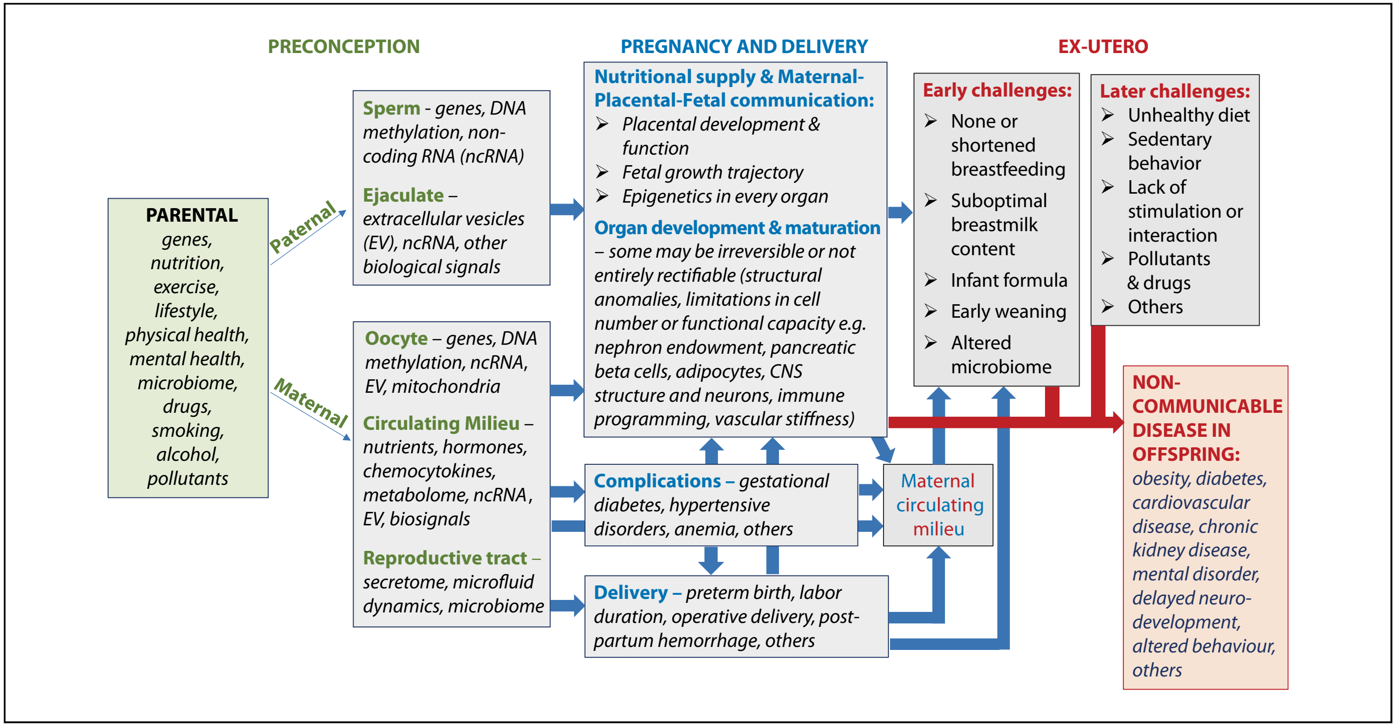

Fig. 1. Influential factors impacting risk of non-communicable diseases in offspring extend from the preconception phase in both parents, during pregnancy and delivery, and to events and challenges after delivery.

However, differences in several pre-specified secondary outcomes were notable. The intervention reduced the incidence of preterm delivery, particularly those associated with preterm pre-labor rupture of membranes, operative delivery for delayed second stage, and major postpartum hemorrhage. It may also shorten time to conception in overweight women compared to that of normal weight women. Importantly, the intervention associated with a reduction in the incidence of rapid infant weight gain and high body mass index at 2 years among offspring [2]. Further follow-up of these children is ongoing to assess the persistence of such effects and to evaluate other child outcomes.

Such evidence indicates that the potential for preconception interventions, which may perhaps only result in small changes in maternal health status, could potentially have tremendous impact in shaping the long-term health of an individual and building resilience against non-communicable chronic diseases.

References

1 Godfrey KM, Barton SJ, El-Heis S, Kenealy T, Nield H, Baker PN, et al. *Myo*-inositol, probiotics, and micronutrient supplementation from preconception for glycemia in pregnancy: NiPPeR international multicenter double-blind randomized controlled trial. *Diabetes Care*. 2021;*44*(5):1091–9. https://doi.org/10.2337/dc20-2515.

2 Lyons-Reid J, Derraik JGB, Kenealy T, Albert BB, Ramos Nieves JM, Monnard CR, et al. Impact of preconception and antenatal supplementation with myo-inositol, probiotics, and micronutrients on offspring BMI and weight gain over the first 2 years. *BMC Med*. 2024;*22*(1):39. https://doi.org/10.1186/s12916-024-03246-w.

Gut Microbiome Assembly Begins at Birth and Needs to Be Nurtured

Jens Walter

Humans maintain symbiotic relationships with complex microbial communities in their intestinal tracts that are paramount to their host's health and development. Given their importance, it is essential for the host to reliably acquire key members of the gut microbiota and assemble communities that provide benefits during important windows of host development. Epidemiological studies over the last 2 decades have convincingly shown that clinical and nutritional factors that disrupt early-life microbiome assembly predispose humans to infections and chronic non-communicable diseases (NCDs). These connections emphasize the importance of understanding host-microbiome symbiosis on a mechanistic level and the clinical and lifestyle factors that shape and disrupt interactions during time-windows that are most important for host-microbe crosstalk.

It is important to consider evolutionary and ecological principles to understand the timing and dynamics of early-life microbiome assembly and the factors that shape and disrupt the process. Recent research has re-established strong support for the 'sterile womb hypothesis' and emphasized the importance of vertical transmission of intestinal microbes that originate from the mother [1]. Of key importance are microbial species that have co-evolved with humans and are adapted to utilize human milk oligosaccharides (HMOs) present in breast milk, such as *Bifidobacterium* species. These bacteria become highly abundant in healthy, breast-fed infants born vaginally over the first few months of life, and they perform important functions for both the development of the microbial community and the host. Our understanding of the dynamics of early colonization has grown, and microbiome assembly is now viewed as a process of ecological succession that comprises different stages of community maturation [2], a process that has a major impact on the developing host.

There is an increasing appreciation for a "windows of opportunity" for both microbiome assembly and the microbiome's impact on the host's immune system. Experiments with gnotobiotic mice that allowed strict control of the timing of microbial colonization demonstrated the importance of "priority effects" in microbiome assembly. Arrival timing of bacterial strains influenced their own ecological success during colonization as well as their impact on the development of the broader microbial community [3]. A follow-up study in mice further showed that the early postnatal period is more important for microbial signals to influence immune development than the prenatal period [4]. There is an increasing body of literature that supports the concept of a "window of opportunity" early in the postnatal period, during which the acquisition of microbial symbionts makes important contributions to both microbiome assembly and immune system development, with long-lasting consequences. This provides a mechanistic explanation for the epidemiological links between clinical and nutritional practices that disrupt gut microbiome assembly early in life, such as caesarean sections (c-sections), perinatal antibiotic use, and formula feeding, and the increasing incidence of NCDs in industrialized societies.

The connections discussed above provide a strong rationale for therapeutic and nutritional strategies to modulate and restore microbiome assembly early in life. Breastfeeding remains essential (as no infant formula is yet able to resemble its effects), but it is insufficient to redress microbiome perturbations caused by caesarean sections and antibiotics. Different strategies to restore early life microbiome assembly have been proposed and range from vaginal seeding and fecal microbiota transplantation (FMT) to more defined microbial-based approaches (e.g., probiotics and synbiotics) (see Table 1). Such approaches, if designed on an evolutionary and ecological basis, show great promise to redress microbiome aberrations and restore key features of early-life microbiomes [5]. However, research is needed to determine which procedure is efficacious in reducing the risk of chronic disease while still being safe, and the regulatory environment has been challenging to establish early-life microbiome-targeted approaches for disease prevention.

Table 1. Microbial-based strategies to modulate and restore microbiomes early in life and the evolutionary and ecological principles that determine outcomes

Strategy	Characteristics of the microbes/microbial communities used	Effects on early-life microbiome assembly	Evolutionary and ecological principles	Health effects, safety considerations, and limitations
Vaginal seeding	Undefined microbial communities present in the mother's vagina	Partially restores the fecal microbiota of c-section infants, but effects are specific to certain bacterial groups (e.g., lactobacilli) and only detectable very early in life	Microbes that inhabit the vagina of humans do lack adaptation to form stable populations in the infant's gut. Gut microbes seem to be largely absent and do not become transmitted. Vaginal microbes can colonize early on in high numbers and might impact microbiome assembly through priority effects, but evidence for this is currently lacking in humans	Unclear if early exposure to vaginal microbes and microbial communities impacts host development and health in humans. Safety concerns have been raised as communities are undefined and might contain pathogens, but risk should not be higher than that of a natural vaginal birth and can potentially be mitigated through pathogen testing
Fecal microbiota transplant (FMT)	Undefined microbial communities prepared from fecal samples, preferentially the mother	Efficiently restores the fecal microbiota in c-section-born infants compared to that seen in infants born through vaginal birth	Restores vertical transmission of the fecal microbiome equivalent to levels observed during a healthy vaginal birth. Introduces well-adapted microbes and communities	Clinical data on the health effects and prevention of NCDs of early-life FMT treatment are lacking. Safety concerns have been raised as communities are undefined and might contain pathogens, but risk

Table 1 (continued)

Strategy	Characteristics of the microbes/microbial communities used	Effects on early-life microbiome assembly	Evolutionary and ecological principles	Health effects, safety considerations, and limitations
			that can initiate and support gut microbiome assembly	should not be higher than that of a natural vaginal birth and can potentially be mitigated through pathogen testing
Probiotic strains and consortia	Defined microbes or microbial consortia	If infant- and HMO-adapted microbes are used, strategies can restore important compositional (e.g., domination of bifidobacteria, reduction of opportunistic pathogens) and functional (low pH, high levels of organic acids, bioactive metabolites) features of the early-life microbiome in breast-fed infants	Dependent on strain selection, probiotics can aid in the acquisition of key members of the infant gut microbiome that stably colonize and contribute to microbiome assembly and maturation. By doing this, probiotics can redress some of the adverse effects of c-sections and antibiotic use on microbiome assembly	Clinical benefits of probiotics for necrotizing enterocolitis (NEC) are well established, but their use in preterm infants is controversial and there is disagreement among organization if probiotics should be recommended. Effects of probiotics on other pathologies have been extensively studied, but findings are less consistent. There is a lack of well-designed clinical trials that tested whether probiotics that contain autochthonous strains can prevent NCDs. Good safety

Table 1 (continued)

Strategy	Characteristics of the microbes/microbial communities used	Effects on early-life microbiome assembly	Evolutionary and ecological principles	Health effects, safety considerations, and limitations
				record of bifidobacteria and lactobacilli in infants born at term, and composition of products can be defined and controlled. However, small and standardized set of strains might miss important species and functions present in whole microbiomes
Synbiotics	Combination of probiotic strains or consortia with compounds that serve as growth substrates for the microbes (e.g., prebiotics or HMOs)	Same effects as probiotics, but persistence and functionality of strains can be enhanced, especially in formula-fed infants	Both traditional prebiotic and HMOs provide resources and thus a niche opportunity to gut microbes that support their ecological performance. HMOs have likely evolved to support key members of the microbiota, such as bifidobacteria	Synbiotics might be able to enhance the health effects of probiotics, but evidence from well-designed clinical studies is lacking. HMOs are diverse and it will be impossible and expensive to reflect their natural diversity in products. Although clearly bifidogenic, traditional prebiotics differ chemically from HMOs and might therefore not exert the same functions. Good safety record

References

1 Kennedy KM, de Goffau MC, Perez-Munoz ME, Arrieta MC, Backhed F, Bork P, et al. Questioning the fetal microbiome illustrates pitfalls of low-biomass microbial studies. *Nature*. 2023;*613*(7945):639–49. https://doi.org/10.1038/s41586-022-05546-8.

2 Tannock GW. Building robust assemblages of bacteria in the human gut in early life. *Appl Environ Microbiol*. 2021;*87*(22):e0144921. https://doi.org/10.1128/AEM.01449-21.

3 Martinez I, Maldonado-Gomez MX, Gomes-Neto JC, Kittana H, Ding H, Schmaltz R, et al. Experimental evaluation of the importance of colonization history in early-life gut microbiota assembly. *Elife*. 2018;*7*:e36521. https://doi.org/10.7554/eLife.36521.

4 Archer D, Perez-Munoz ME, Tollenaar S, Veniamin S, Cheng CC, Richard C, et al. The importance of the timing of microbial signals for perinatal immune system development. *Microbiome Res Rep*. 2023;*2*(2):11. https://doi.org/10.20517/mrr.2023.03.

5 Korpela K, de Vos WM. Infant gut microbiota restoration: state of the art. *Gut Microb*. 2022;*14*(1):2118811. https://doi.org/10.1080/19490976.2022.2118811.

Understanding the Ovarian Clock – Essential Knowledge for Paediatricians

Zhongwei Huang

A woman is born with her life-time supply of eggs, and these are surrounded by a group of cells, the follicular cells, which formed the ovarian follicles. The ovarian follicles will determine a woman's entire reproductive lifespan and healthspan. The ovarian follicles are at their peak numbers in utero and start to decline in numbers upon birth and a non-linear decline throughout a girl's growing up, reaching adolescence and adulthood (see Fig. 1). This decline also represents the inevitable loss of fertility, culminating in the menopause in women, where the ovaries have too few ovarian follicles left to result in monthly menstrual bleeding. The role of these ovarian follicles is vital for a woman's fertility due to the eggs which they protect. Importantly, the hormones secreted by the ovarian follicles, e.g., estradiol, maintain a woman's healthspan by ensuring optimal cardiovascular, musculoskeletal, and neurocognitive health [1]. Conditions which accelerate the loss of these ovarian follicles or reduce the already short lifespan of the ovaries will result in systemic issues detrimental to women's health. These conditions may perpetuate from birth and develop over childhood to puberty. When girls present to paediatricians at expected pubertal age with the absence of menarche or irregular cycles, it may be the harbinger of reproductive health issues for the rest of her life affecting her future fertility and general health. Conditions affecting the menstrual cycles warrant a deep understanding of the hypothalamus-pituitary-ovarian axis and their individual functions in addition to interactions with in utero, lifestyle, and environmental factors. Despite the essential role ovaries play in a girl's lifespan and healthspan, the biological processes that determine the ovarian clock remain understudied. This phenomenon of the ovary being one of the first organs to undergo ageing and functional decline [2] needs further research to ensure that novel diagnostics and therapeutics are discovered for optimal women's reproductive health.

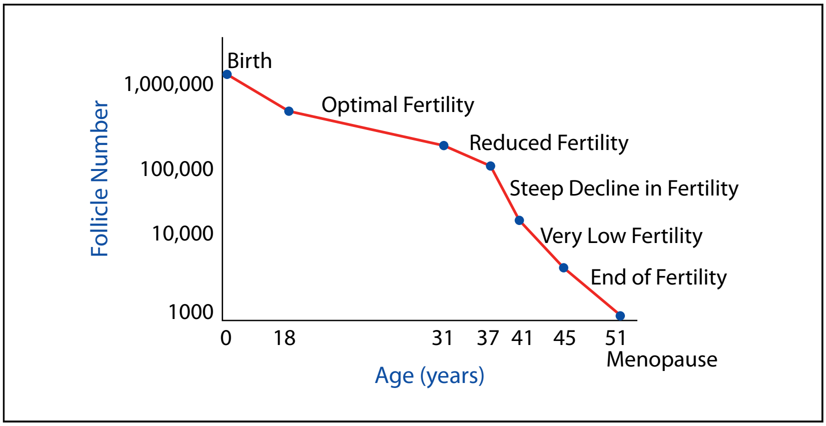

Fig. 1. A girl's ovarian lifespan is dependent on the number of ovarian follicles she is born with, and it is a downwards trajectory until the clinical menopause as the girl goes into adolescence and adulthood.

References

1 Dong L, Teh DBL, Kennedy BK, Huang Z. Unraveling female reproductive senescence to enhance healthy longevity. *Cell Res*. 2023;*33*(1):11–29. https://doi.org/10.1038/s41422-022-00718-7.

2 Khan SS, Singer BD, Vaughan DE. Molecular and physiological manifestations and measurement of aging in humans. *Aging Cell*. 2017;*16*(4):624–33. https://doi.org/10.1111/acel.12601.

Human Milk Research, More to Learn?

Norbert Sprenger, Cathriona R. Monnard

Milk production is a unique characteristic of mammals that all share a common ancestry. This, together with evolutionary adaptation, needs to be considered when investigating the biology of milk and lactation. Human milk is a dynamic secretion of nutritive and bioactive components that support infant development during the first 6 months of life and beyond. Hence, human milk is the recommended sole nutrition source for infants during the first 6 months of age, while continued breastfeeding is recommended after introduction of weaning and family food. Analytics allowed for a detailed description of components and their variability within and among mothers fueling interest of pediatricians and biologists to investigate the role of milk and its individual components for infant development. The variation in its composition throughout lactation and in response to maternal factors such as genetics and environment provide the basis to look for associations to infant health and development outcomes, with HMO concentrations being a prime example.

Today, mainly individual HMOs or structural groups of HMOs were associated with infant outcome measures, ranging from anthropometry to immunity (infections and allergies) and brain development (social and cognitive skills). Such associations help to formulate working hypotheses, but generally lack causality. In part, mechanistic insights gained from translational research with clinical samples (stool microbiota and markers) or supporting measures (brain structure and myelination), as well as basic research models, can explain and further substantiate such findings [1, 2]. Yet, associations seen in different clinical observational studies with breast-fed infants often lack consistency. Gaining an understanding of the reasons behind these disparate findings is key going forward, because lack of consistency and limited effect sizes hamper our understanding of the true physiological relevance of existing findings.

Furthermore, studying human milk components like HMOs and their expected benefits using a systems biology approach can reveal further important insights [3]. Likely, there is more to learn by trying to understand HMO interaction networks and how these relate to clinical outcomes. Largely, HMOs may exert their action through the developing

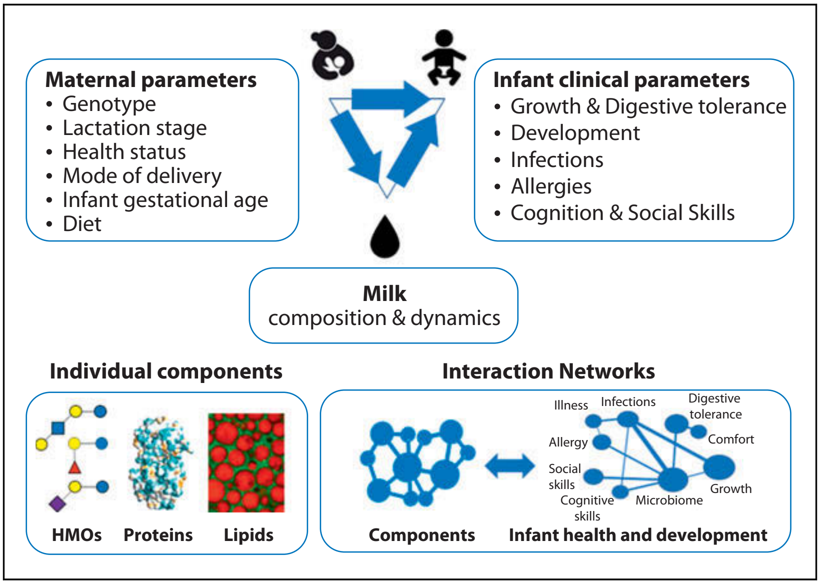

Fig. 1. Maternal parameters that may affect milk composition and dynamics, and infant health and development outcome measures.

gut microbiome. Hence, as illustrated in Figure 1, novel insight can be gained through the interaction analysis of HMOs and specific gut microbiota like infant-type *Bifidobacterium* species and *Bacteroides* species that have the right biochemical pathways to utilize specific HMOs and to produce health-related biochemicals [4]. Eventually, shifting analysis further toward a systems biology approach, including modeling of interaction networks not only among one compound group, like the HMOs, but extending to other milk components, will allow us to expand our understanding of human milk. Future advancements in the field of human milk biology require a more integrative approach to explore the interactions between human milk components and how such interactions drive the functionality and physiological benefits of human milk.

References

1 Sprenger N, Tytgat HLP, Binia A, Austin S, Singhal A. Biology of human milk oligosaccharides: from basic science to clinical evidence. *J Hum Nutr Diet*. 2022;*35*(2):280–99. https://doi.org/10.1111/jhn.12990.

2 Rajhans P, Mainardi F, Austin S, Sprenger N, Deoni S, Hauser J, et al. The role of human milk oligosaccharides in myelination, socio-emotional and language development: observational data from breast-fed infants in the United States of America. *Nutrients*. 2023;*15*(21):4624. https://doi.org/10.3390/nu15214624.

3 Christian P, Smith ER, Lee SE, Vargas AJ, Bremer AA, Raiten DJ. The need to study human milk as a biological system. *Am J Clin Nutr*. 2021;*113*(5):1063–72. https://doi.org/10.1093/ajcn/nqab075.

4 Cho S, Samuel TM, Li T, Howell BR, Baluyot K, Hazlett HC, et al. Interactions between *Bifidobacterium* and *Bacteroides* and human milk oligosaccharides and their associations with infant cognition. *Front Nutr*. 2023;*10*:1216327. https://doi.org/10.3389/fnut.2023.1216327.

Nutrition for the Sick Preterm: Can We Make It More Precise?

Josef Neu

Introduction

The history of neonatal intensive care is fraught with struggles as to how to best nourish preterm infants for the best possible outcomes. During the early era of modern neonatal intensive care, the 1970s, up to the last decade it was common practice to withhold parenteral and enteral nutrition in preterm infants for fear of causing metabolic imbalances and inducing intestinal injury. These infants have very low energy and protein stores and are thus highly susceptible to undernutrition and catabolism. In the early era of neonatal intensive care (about 5–6 decades ago), many nutritional approaches were based largely on the physician's intuition, previous experience, and patient signs and symptoms. Not all physicians had similar previous experiences, and there were numerous different approaches to care. This resulted in heterogeneity of diagnostic, preventative, and therapeutic measures.

More recently, evidence-based approaches such as retrospective data reviews, cohort studies, and prospective randomized clinical trials have begun to form the foundation for nutritional guidelines used in most NICUs. These are derived from population statistics and lead to recommendations aimed toward the average of the population and thereby meet the needs of many of these infants, but because of the extreme heterogeneity of the preterm population, marginalize others. In addition, helpful scoring programs have been developed to identify malnutrition in populations of preterm infants using defined indicators [1, 2] but, like growth curves, do very little to provide proactive guidance.

There is currently a trend toward precision-based approaches using algorithms and predictive analytics based on artificial intelligence (AI) and machine learning (ML) that provide for *a priori* based preventative approaches.

Problems with Current Guideline-Based Approaches

As previously mentioned, guideline-based nutritional approaches that rely on evidence-based studies have provided major advances over previous intuition-based approaches for nourishing these infants. However, preterm infants are highly heterogeneous, and the suitability of guideline-based approaches is being questioned [3, 4]. One guideline does not fit all preterm nutritional needs.

This begs for a different nutritional approach in these infants compared to those born appropriate for gestational age. A proactive, precision-based approach directed toward personal needs for preterm infants that transcends a one-size-fits-all guideline-based approach is urgently needed.

A promising approach includes machine learning (ML) and multiomics. Machine learning provides the opportunity for high-resolution classification of infants at greatest risk and predictive analytics for pre-emptive precision-based approaches initiated very early after birth. Multiomic integrations provide mechanistic characterization and provide the opportunity for discovery of biomarkers that can be applied for precisely guiding nutritional interventions in individual infants.

Conclusion

The rapidly emerging fields of artificial intelligence and multiomics are highly applicable to various problems we see in perinatology and neonatal intensive care. Predictive analytics using supervised and unsupervised machine learning techniques, as well as closely related neural network technologies, will help in the categorization of infants with specialized needs and who may be on a path toward either early- or late-onset pathologies. With such recognition, we should be able to intervene early to prevent these problems from occurring.

Similarly, we are beginning to make significant strides in precision nutrition. Previous studies show interesting associations between giving or withholding certain nutrients and clinical outcomes. However, the mechanisms and causal nature of these associations are not well understood. These are amenable to analysis by newly developing technologies such as multiomics and artificial intelligence. These will be applied in the future to better understand mechanisms and to provide personalized nutrition for both mothers and their infants.

References

1 Goldberg DL, Becker PJ, Brigham K, Carlson S, Fleck L, Gollins L, et al. Identifying malnutrition in preterm and neonatal populations: recommended indicators. *J Acad Nutr Diet*. 2018;*118*(9):1571–82. https://doi.org/10.1016/j.jand.2017.10.006.

2 Izquierdo Renau M, Aldecoa-Bilbao V, Balcells Esponera C, Del Rey Hurtado de Mendoza B, Iriondo Sanz M, Iglesias-Platas I. Applying methods for postnatal growth assessment in the clinical setting: evaluation in a longitudinal cohort of very preterm infants. *Nutrients*. 2019;*11*(11):2772. https://doi.org/10.3390/nu11112772.

3 Young A, Beattie RM, Johnson MJ. Optimising growth in very preterm infants: reviewing the evidence. *Arch Dis Child Fetal Neonatal Ed*. 2023;*108*(1):2–9. https://doi.org/10.1136/archdischild-2021-322892.

4 Webbe J, Uthaya S, Modi N. Nutrition for the micro preemie: beyond milk. *Semin Fetal Neonatal Med*. 2022;*27*(3):101344. https://doi.org/10.1016/j.siny.2022.101344.

Better Early: Critical Windows in Brain and Cognitive Development

Bernadette C. Benitez

Current scientific and clinical evidence shows how the ecosystem of nature and nurture variables impact intricately on early brain development and subsequently, on a child's learning ability, his overall health, his adaptability and resilience, and his future capacity to become a productive adult [1].

The first 3 years of life, starting from conception, are when dynamic neurodevelopmental processes like neuronal formation, myelination, and synaptic connections unfold. This period is thus marked by sensitive windows of opportunities where neuroplasticity – a feature of the young brain that lends it its adaptability – is most vulnerable [2]. Adequate nutrition, especially breastfeeding, in the first 1,000 days as a main driver of these processes cannot be overemphasized. The advent of newer modalities of research utilizing magnetic resonance imaging continues to reinforce the significant influence of early nutrition on brain development, particularly myelination, which is predictive of cognition.

These critical epochs are also when nutrient deficiencies are more likely to negatively impact development, especially when necessary and timely identification and intervention are not put in place. Stunting, a manifestation of chronic malnutrition, especially in the first 2 years is associated with lower cognitive scores and subsequent academic achievement, which can be possibly mitigated both by appropriate nutritional support and high-quality home environment [3].

The recent pandemic, and the disruptive systemic ripples that it brought along, has shown its impact not only on children's nutrition but also on their behavior and development. Findings in the 2020 Rapid Nutrition Assessment Survey (RNAS) by the Philippines' Food and Nutrition Research Institute (FNRI) [4] showed that households with 0- to 5-year-old children were 1.3 times more likely to experience moderate to severe food insecurity. Another study showed that compared to 10-year historical data, 2021 and 2022 cognitive measures among 0- to 3-year-old children born before and during the pandemic are significantly lower than any other year in the past decade. These findings were associated with lesser social and language interactions between the children and their parents and/or caregivers [5].

In light of these, there is a renewed call for pediatricians and other healthcare practitioners in clinics and communities to more ardently screen, monitor for, and provide proper advice for concerns in growth and development during the first 3 years of life to help mitigate the impact of current global events on children's potential to adapt, learn, and be productive adults in the future.

References

1 Lake A, Chan M. Putting science into practice for early child development. *Lancet*. 2015;*385*(9980):1816–7. https://doi.org/10.1016/S0140-6736(14)61680-9.

2 Shonkoff JP, Phillips DA. The developing brain. In: *From Neurons to Neighborhoods: The Science of Early Childhood Development*. United States: National Academies Press; 2000 [cited August 15, 2023]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK225562/.

3 Nguyen, PH, DiGirolamo, AM, Gonzalez-Casanova I, Young M, Kim N, Nguyen S, et al. Influences of early child nutritional status and home learning environment on child development in Vietnam. *Matern Child Nutr*. 2018;*14*(1):e12468. https://doi.org/10.1111/mcn.12468.

4 Angeles-Agdeppa I, Javier CA, Duante CA, Maniego MLV. Impacts of COVID-19 pandemic on household food security and access to social protection programs in the Philippines: findings from a telephone rapid nutrition assessment survey. *Food Nutr Bull*. 2022;*43*(2):213–31. https://doi.org/10.1177/03795721221078363.

5 Deoni SCL, Beauchemin J, Volpe A, D'Sa V, The Resonance Consortium. Impact of the COVID-19 pandemic on early child cognitive development: initial findings in a longitudinal observational study of child health. MedRxiv(pre-print). 202. https://doi.org/10.1101/2021.08.10.21261846.

The Art of Chewing: Optimizing Early-Life Sensory Exposure to Develop Healthy Eating Behaviour

Marlou P. Lasschuijt, Ciarán G. Forde

Eating behaviour and food preferences develop early in life and shape long-term dietary patterns [1]. Current dietary advice for infants and toddlers focusses on the nutritional value of foods with little to no guidelines on age-appropriate food textures, while food texture plays an important role in the development of healthy dietary behaviour, shown in Figure 1.

During the weaning period, newborns rely on sucking, swallowing, and rooting reflexes when drinking breastmilk or infant formula. Within the first months of life, newborns' oral anatomy develops rapidly concurrently with oral-facial muscle development and coordination to be able to process semi-solids, soft solids, and eventually hard solids. For an infant to be able to orally process more complex food textures than liquids, it has to be able to sit in an upright position and balance the head in order to prevent choking hazards. Starting around 6 months, the volume of the oral cavity of infants increases, as fat from the cheeks decreases, teeth erupt, and the palate increases in width and height. When of toddler age, children will learn to have better control over their tongue and will be able to move the tongue laterally and circular to move food particles in between molars. Consuming hard-textured foods is a complex process that requires coordination of 26 muscle pairs and involves 5 cranial nerves. Oral processing of complex textures is a skill that has to be acquired and is learned through experience and interaction with food. These early-life experiences with food shape oral processing behaviour as a strong personal trait, which ultimately shapes food preferences and dietary patterns. Once toddlers have developed their oral processing behaviour, it becomes a trait which is stable throughout life [1, 2]. Children who develop a fast eating rate are at a higher risk of developing overweight and obesity compared to children with a relatively slow eating rate [2]. The extent to which feeding strategies at a young age can alter oral processing behaviour is unknown. Comparing bottle-to breast-fed infants, there is evidence that breast-feeding shapes oral anatomy such that it is protective against malocclusions, posterior crossbite, and teeth crowding. However, there is little

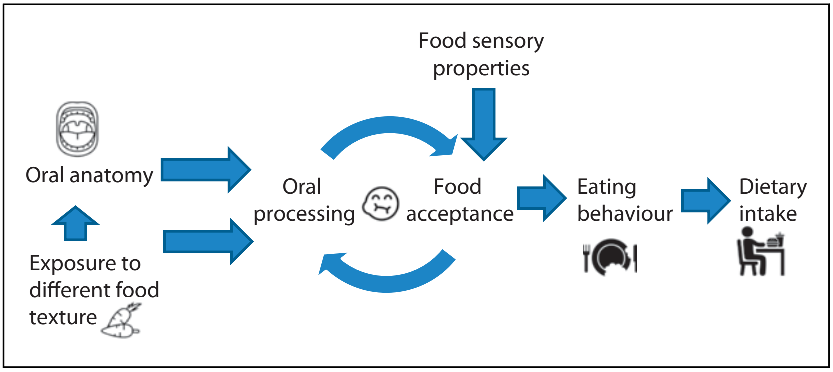

Fig. 1. The process of developing dietary behaviour in early life.

evidence that it translates to oral processing behaviour later in life. The start of complementary feeding may be the optimal window to shape healthy eating behaviour. Generally, parental feeding strategies of gradually introducing more complex texture are based on their child's age and number of teeth [3]. However, research has shown that there is no association between the ability to oral process complex textures and number of teeth [4]. A better prediction of whether or not a child can oral process a specific food is the developmental stage and muscle and tongue coordination ability [4].

An evident demonstration of the effects of early-life feeding strategies on eating behaviour derives from research in clinical populations. Children or infants whose first experience with food has been enteral nutrition are prone to develop appetite dysregulation and hypersensitivity for food sensory properties and may develop food avoidance behaviours [5]. Similarly, infants with Down syndrome are often tube-fed to prevent malnutrition and to minimize choking hazards. However, especially in this group breastfeeding is beneficial in shaping oral anatomy and in the development of oral processing behaviour, as often they are predisposed to oral processing dysfunction. Evidence from these clinical groups shows the importance of early-life food experiences, yet contrary to food taste, there is little understanding of food texture introduction in early life. Therefore, there is a need for science-based guidelines on texture-appropriate feeding for healthy and clinical child populations to help shape healthy dietary behaviour.

References

1 Tournier C, Forde CG. Food oral processing and eating behavior from infancy to childhood: evidence on the role of food texture in the development of healthy eating behavior. *Crit Rev Food Sci Nutr*. 2023:1–14. https://doi.org/10.1080/10408398.2023.2214227.

2 Fogel A, Goh AT, Fries LR, Sadananthan SA, Velan SS, Michael N, et al. A description of an 'obesogenic' eating style that promotes higher energy intake and is associated with greater adiposity in 4.5 year-old children: results from the GUSTO cohort. *Physiol Behav*. 2017;*176*:107–16. https://doi.org/10.1016/j.physbeh.2017.02.013.

3 Demonteil L, Ksiazek E, Marduel A, Dusoulier M, Weenen H, Tournier C, et al. Patterns and predictors of food texture introduction in French children aged 4–36 months. *Br J Nutr*. 2018;*120*(9):1065–77. https://doi.org/10.1017/S0007114518002386.

4 Tournier C, Demonteil L, Canon F, Marduel A, Feron G, Nicklaus S. A new masticatory performance assessment method for infants: a feasibility study. *J Texture Stud*. 2019;*50*(3):237–47. https://doi.org/10.1111/jtxs.12388.

5 Wilken M, Bartmann P, Dovey TM, Bagci S. Characteristics of feeding tube dependency with respect to food aversive behaviour and growth. *Appetite*. 2018;*123*:1–6. https://doi.org/10.1016/j.appet.2017.11.107.

Strategies to Develop Balanced Dietary Habits: Solving the Dilemma

Eslam Tawfik ElBaroudy

Inadequate dietary variation due to selective eating behaviours or malnutrition is a global cause of micronutrient deficiencies, especially iron, zinc, vitamins A and D, iodine, and folic acid [1].

According to a caregivers questionnaire, the prevalence of picky eating is reported as 19% at the age of 4 months and can increase up to 50% at the age of 24 months [2]. Other studies have suggested that whilst incidence declines over time, the cumulative impact of eating difficulties increases, as usually it is a chronic cumulative problem with 40% of picky eating episodes having a duration of between 2 and 10 years (Fig. 1).

The consequences of picky eating or poor food availability include limited food intake and variation (food quantity and quality are impacted), which can lead to macronutrient and micronutrient deficiencies and physical, behavioural, emotional, cognitive, and developmental issues [3].

Dietary supplementation provides an individually targeted approach to address micronutrient inadequacies and deficiencies, but worldwide data suggest low compliance.

In India, only 8.8% of infants were receiving appropriate routine vitamin D supplementation in terms of dose, frequency, and duration [4]. In Egypt, compliance with a vitamin A supplementation program was poor, with only 44% and 49% of children aged 9–11 and 18–27 months receiving this supplement, respectively. In the United States, use of oral vitamin D supplements in infants aged 1–10.5 months was low, ranging from 1% to 13%; and in France, only 41.5%–66.6% of the vitamin D prescriptions in children between 0 and 5 years complied with the recommendations [5, 6].

This would leave a question mark about the widely used strategy worldwide to compensate for the nutritional deficiencies and suggests that a collaborative approach is required to develop, implement, and monitor individual-level strategies to improve diet quality for children around the world.

Home fortification strategy is an innovation aimed at improving diet quality of nutritionally vulnerable groups, such as young children [7]. Choosing a food-first approach utilises everyday foods and drinks and centres around making them as nutritious as possible by adding additional

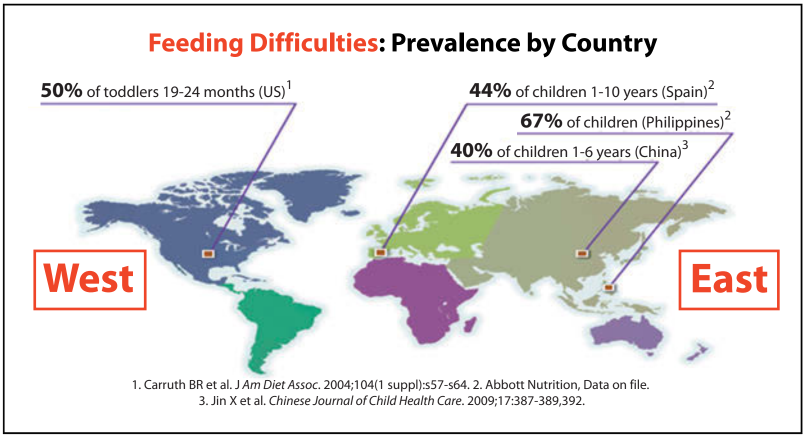

Fig. 1. Feeding difficulties: Prevalence by country.

food items or ingredients. However, this relies somewhat on the dietary knowledge of the caregiver, socioeconomic constraints, and dietary preferences of the child. In addition, some families may have limited access to healthcare professionals, such as dietitians, to support them with implementing these changes.

An alternative home fortification strategy utilises ready-made oral nutritional supplements, which can be added directly to the foods during preparation to help increase the nutritional value [8]. This approach can help to overcome some of the potential challenges associated with food fortification, such as palatability/acceptability, compliance, and cost. Oral nutritional supplements provide a source of protein, carbohydrates, fats, and vitamins and minerals. They are also simple and easy to use with a long shelf life that can make them a cost-effective option.

In addition to individual supplementation, foods can be fortified at a wider population level. This effectively prevents micronutrient deficiencies in high-income countries for more than a century.

Commercial food fortification is defined as the mandatory or voluntary addition of essential micronutrients to the widely consumed staple foods and condiments during production [9]. Whilst this is used more widely in Western countries, commercial food fortification in the Middle East is sporadic and ineffective (Fig. 2).

There is a risk of malnutrition and micronutrient deficiencies in children who are picky eaters and with poor access to nutritionally adequate food [10]. Food fortification, done at an individual or population level, can help to ensure that nutritional requirements are met and reduce adverse consequences of imbalanced dietary intake.

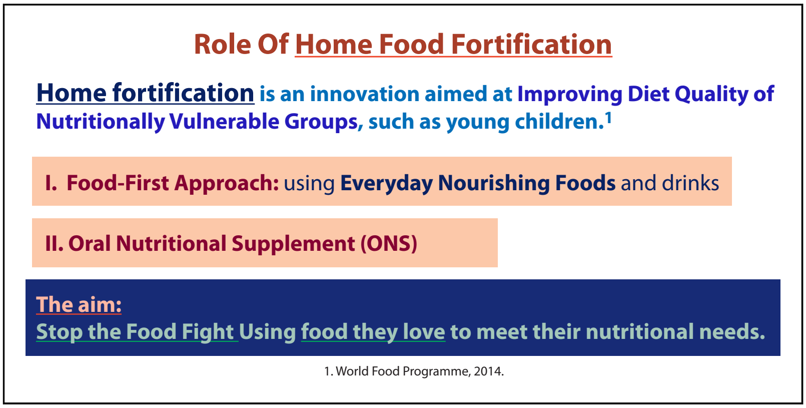

Fig. 2. Role of home food fortification.

References

1 Kedesdy JH, Budd KS. *Childhood Feeding Disorders: Biobehavioral Assessment and Intervention*. Baltimore, MD: Paul H. Brookes Publishing Company; 1998.

2 Carruth BR, Ziegler PJ, Gordon A, Barr SI. Prevalence of picky eaters among infants and toddlers and their caregivers' decisions about offering a new food. *J Am Diet Assoc*. 2004;*104*(1 suppl 1):s57–64. https://doi.org/10.1016/j.jada.2003.10.024.

3 Taylor CM, Emmett PM. Picky eating in children: causes and consequences. *Proc Nutr Soc*. 2019;*78*(2):161–9. https://doi.org/10.1017/S0029665118002586.

4 Meena P, Saran AN, Shah D, Gupta P. Compliance to prescription of routine vitamin D supplementation in infants. *Indian Pediatr*. 2020;*57*(11):1067–9. https://doi.org/10.1007/s13312-020-2037-x.

5 Perrine CG, Sharma AJ, Jefferds MED, Serdula MK, Scanlon KS. Adherence to vitamin D recommendations among US infants. *Pediatrics*. 2010;*125*(4):627–32. https://doi.org/10.1542/peds.2009-2571.

6 Mallet E, Gaudelus J, Reinert P, Stagnara J, Bénichou J, Castanet M, et al. [Prophylactic prescription of vitamin D in France: national multicenter epidemiological study of 3240 children under 6 years of age]. *Arch Pediatr*. 2012;*19*(12):1293–302. https://doi.org/10.1016/j.arcped.2012.09.011.

7 Taylor CM, Wernimont SM, Northstone K, Emmett PM. Picky/fussy eating in children: review of definitions, assessment, prevalence and dietary intakes. *Appetite*. 2015;*95*:349–59. https://doi.org/10.1016/j.appet.2015.07.026.

8 De-Regil LM, Suchdev PS, Vist GE, Walleser S, Peña-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. *Cochrane Database Syst Rev*. 2011;(9):CD008959. https://doi.org/10.1002/14651858.CD008959.pub2.

9 Olson R, Gavin-Smith B, Ferraboschi C, Kraemer K. Food fortification: the advantages, disadvantages and lessons from *sight and life* programs. *Nutrients*. 2021;*13*(4):1118. https://doi.org/10.3390/nu13041118.

10 Taylor CM, Northstone K, Wernimont SM, Emmett PM. Macro- and micronutrient intakes in picky eaters: a cause for concern? *Am J Clin Nutr*. 2016;*104*(6):1647–56. https://doi.org/10.3945/ajcn.116.137356.

Micronutrient Hunger or Hidden Hunger Among Infants and Young Children on Healthy Diets

George Jacob Elizabeth, Gibby Koshy

"Hidden hunger" is a term used to explain the condition of multiple micronutrient deficiencies in the absence of an energy-deficit diet [1]. Over 2 billion people, or one-third of the global population, are affected by hidden hunger, especially in low- and middle-income nations where dietary choices are constrained by poverty, the food pattern remains constant with very less variations, and low-cost staples typically form the diet [1]. Micronutrient deficiencies are frequently undetected, particularly in young children and newborns. Nonetheless, it can be identified if there is a high suspicion index.

The Global Hunger Index (GHI) is a tool designed to monitor and quantify hunger globally by nation and region. Each nation's GHI score is computed based on four indicators – undernourishment, child stunting, child wasting, and child mortality [2]. The biggest threat to global public health is posed by deficiencies in four micronutrients – iron, iodine, zinc, and vitamin A. These deficiencies are becoming more common and have detrimental consequences on development and health. Infant and Young Child Feeding (IYCF) is essential for boosting children's survival rates and fostering development and healthy growth.

Strategies for addressing micronutrient malnutrition include supplementation, fortification, and diversification of diet.

Micronutrient supplementation: Supplementation, or the delivery of large amounts of micronutrients in a highly absorbable form, usually results in the fastest improvement in the micronutrient status of individuals or targeted populations. The United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) is a novel multiple-micronutrient supplementation strategy that includes 15 nutrients as shown in Table 1 [3] and is recommended by the United Nations (UN) for prenatal mothers. However, it is yet to be implemented globally. India has universal and targeted supplementation programs for micronutrients such as iron, folic acid, iodine, zinc, and vitamins A, D, K, and B12.

Table 1. Multiple micronutrient supplement (MMF) formulation [3]

Component	Chemical entity	Amount
Vitamin A	Retinyl acetate	800 μg RAE
Vitamin C	Ascorbic acid	70 mg
Vitamin D	Cholecalciferol	5 μg (200 IU)
Vitamin E	Alpha tocopheryl succinate	10 mg α-TE
Vitamin B1	Thiamine mononitrate	1.4 mg
Vitamin B2	Riboflavin	1.4 mg
Vitamin B3	Niacinamide	18 mg NE
Vitamin B6	Pyridoxine HCl	1.9 mg
Folic acid	Folic acid	680 μg DFE (400 μg)
Vitamin B12	Cyanocobalamin	2.6 μg
Iron	Ferrous fumarate	30 mg
Iodine	Potassium iodide	150 μg
Zinc	Zinc oxide	15 mg
Selenium	Sodium selenite	65 μg
Copper	Cupric oxide	2 mg

α-TE, alpha tocopherol; DFE, dietary folate equivalents; HCl, hydrochloride; NE, niacin equivalents; RAE, retinol activity equivalents; IU, international units.

Commercial food fortification: The technique of fortifying food involves adding vital micronutrients to food products at a reasonable cost [4]. Iodization of salt; the addition of B complex vitamins, zinc, and iron to wheat flour; and the addition of vitamin A to sugar and cooking oil are examples of food fortification.

Biofortification: Biofortification is a sophisticated approach to crop production that uses cutting-edge biotechnology techniques to boost the nutritional value of crops, particularly of important micronutrients like minerals and vitamins [4]. Examples of biofortified crops include iron beans, zinc wheat and rice, and vitamin A cassava and maize.

Dietary diversification: One of the most effective methods of preventing nutritional hunger is by increasing dietary diversity. Dietary diversity can address micronutrient deficiencies by incorporating a variety of foods from different food groups over time, and it is associated with better nutritional outcomes in children. In most instances, parents and caretakers consider the diet of infants and young children as "healthy," as they often lack information on the 17 key IYCF indicators, particularly minimum dietary diversity (MDD), minimum meal frequency (MMF), and minimum acceptable diet (MAD) [2, 5].

All the aforementioned interventions have advantages, but their effectiveness depends on the particular setting and available resources. Enhancing young children's diets during the supplemental feeding phase necessitates a multisectoral approach at both national and international levels. This manuscript highlights an overview of these issues along with practical solutions.

References

1 Lowe NM. The global challenge of hidden hunger: perspectives from the field. *Proc Nutr Soc*. 2021;*80*(3):283–9. https://doi.org/10.1017/S0029665121000902.

2 Global Hunger Index (GHI). Food systems transformation and local governance [Cited January 30, 2024]. Available from: https://www.globalhungerindex.org.

3 The Multiple Micronutrient Supplement Technical Advisory Group MMS-TAG, The Micronutrient Forum MNF. Expert consensus on an open-access United Nations International Multiple Micronutrient Antenatal Preparation-multiple micronutrient supplement product specification. *Ann N Y Acad Sci*. 2020;*1470*(1):3–13. https://doi.org/10.1111/nyas.14322.

4 Thakur S, Singh A, Insa B, Sharma S. Food fortification in India as malnutrition concern: a global approach. *Sustainable Food Technol*. 2023;*1*(5):681–95. https://doi.org/10.1039/d3fb00079f.

5 Elizabeth KE. Infant and young child feeding—a panacea for current & future health with macro and micronutrient sufficiency. *Ind J Pract Pediatr*. 2023;*25*(1):43–8. Available from: https://www.ijpp.in/admin/uploadimage/Vol.25_No.1.pdf.

Two Sides of the Same Coin: Strategies to Address Over- and Undernutrition

Andrew M. Prentice

Worldwide progress against most forms of undernutrition has been impressive in recent decades notwithstanding the fact that there remain too many stunted and underweight children, and mothers and young children suffering from a range of micronutrient deficiencies (so-called "hidden hunger"). This admirable progress has been driven by national governments spurred on by the Millennium Development Goals (MDGs) and subsequent Sustainable Development Goals (SDGs), with guidance from numerous non-governmental alliances.

Some of the progress has been achieved through the short-term exigencies of supplementation programmes, UNICEF's support of childhood vitamin A supplementation being a prime example. Other progress has been achieved through fortification; with iodine fortification of salt, vigorously and successfully promoted by the IDD among others, making goitre and foetal abnormalities rare in the modern world.

Much of the progress has also been achieved through economic advancement and the ability of peoples to access foods with a higher nutrient density, many of them produced in large scale by local or multinational corporations. Such companies are often damned by nutrition purists, sometimes with justification but often not. Manufactured foods have been a major driver of improved nutritional status globally, but can also contribute to ill health if eaten in excess; hence the "two sides of the same coin" in the title of this presentation.

Nutrient density is a key determinant of nutritional health. Many traditional diets, and particularly traditional weaning foods for infants and toddlers in low-income settings, have very low nutrient density (energy, protein, and micronutrients) and hence have been associated with poor growth. Carefully balanced alternatives have been manufactured and have driven the improvements in growth in most advanced nations, but remain unaffordable for most of the world. Unfortunately, this gap has been filled by ultra-processed "junk" foods which have high energy levels of refined energy (sugars and fats, and sodium) but lack fibre and quality micronutrients. Energy density is a major driver of weight gain and adipocity [1].

Families with a poor understanding of the principles of nutrition allow their children to consume excess amounts of such foods with inevitable consequences: weight gain, obesity, and associated metabolic diseases. Of note recent research suggests that, as yet unknown, aspects of "ultra" processing of foods contribute to poor heart health and diabetes (e.g., [2]).

The EAT-Lancet recommendations for diets in the Anthropocene make cogent suggestions as to how families should modify their food plate to optimise their own as well as the planet's health [3]. Unfortunately, their application would require levels of nutritional education well beyond most people. A return to more traditional, unrefined, and locally grown foods is an admirable goal but, unless accompanied by a sophisticated understanding of the principles of good nutrition – especially good child nutrition – may lead to a resurgence in nutrient deficiencies. Thus, food manufacturers will continue to play a vital role in feeding the planet. As the dangers of excess energy density and low nutrient content of "junk" foods become ever more obvious, and the concerns of ultra-processing start to be understood, responsible manufacturers will find fertile markets within populations whose nutritional awareness is gradually becoming more sophisticated.

References

1 Prentice AM, Jebb SA. Fast foods, energydensityand obesity: a possible mechanistic link. *Obes Rev*. 2003;*4*:187–94. https://doi.org/10.1046/j.1467-789x.2003.00117.x.

2 Wang L, Pan XF, Munro HM, Shrubsole MJ, Yu D. Consumption of ultra-processed foods and all-cause and cause-specific mortality in the Southern Community Cohort Study. *Clin Nutr*. 2023;*42*(10):1866–74. https://doi.org/10.1016/j.clnu.2023.08.012.

3 Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet*. 2019;*393*(10170):447–92. https://doi.org/10.1016/S0140-6736(18)31788-4.

What Does Healthy Microbiome Development Look Like? State of the Art and Beyond

Giles Major, Shaillay Kumar Dogra, Norbert Sprenger

The three concepts expressed in the title – "health," "microbiome," and development" – are critical to how we shape the future with nutrition. Health describes how individuals survive, feel, function, and develop; the microbiome describes the ecosystem of micro-organisms in a specific environment, here the human gut; and development trajectory describes the rate of change from the past to the future. In early life nutrition, we predicate our actions on the principle that what we do now brings future benefits. This review will describe the current state of our knowledge on how early life microbiome development can influence health, how nutrition might play a role, and on-going work to bring new insight in the years to come.

The gut microbiome enhances the principal functions of the gut: nutrient harvest; defense; and regulation of metabolism and behavior. The abnormal physiology of germ-free and gnotobiotic mice illustrates this, as have multiple microbiome-transfer animal studies. The developing field of fecal microbiota transplant has demonstrated the importance of the gut microbiome in response to infectious pathogens [1]. Applications for other conditions have struggled to show an effect because of the stability and resilience of the mature adult microbiome.

This stability contrasts with the infant microbiome, which remains responsive to external influence for several years after birth. Mode of delivery, exposure to medication (particularly antibiotics) or pets, and living environment all influence the commensal bacteria acquired in early life. Dietary intake also contributes significantly with measurable differences between breast-fed and formula-fed infants. The microbiome develops in a stochastic manner, meaning that the current state of the ecosystem determines its next stage of development. It is therefore important to understand how diet modifies the microbiome in early life, and how this might have an impact on future health [2].

The microbiome can be characterized in various ways such as the abundance of specific beneficial or pathological species, the number of species present (richness), their variety and evenness (diversity), or the range of genetic functions present across the ecosystem (metagenomics).

Microbiome maturity is a "functional" parameter that may integrate elements of all the above but needs further characterization as a developmental concept. There is, however, evidence of its relevance: co-habiting twins discordant for malnutrition status were shown to have differences in their microbiome's ability to digest maize, and thus recover energy from the predominant diet [3]. Recent reports have proposed a link between early acquisition of a more adult microbiome and later increased risk of immune-mediated disorders such as atopy. Both situations suggest that there is a preferred rate of development of the microbiome: a healthy trajectory of maturation that is disrupted by medical events such as caesarean section or early-life antibiotic use [4].

Various methods have been proposed to measure microbiome development and maturity, including microbiome-for-age Z scores [5] and progressive clusters of organisms [4]. Longitudinal cohorts can train algorithms that identify the age/stage of the microbiome development toward a mature and resilient state using machine learning methods. Infants with exposures that should optimize microbiome development, such as vaginal delivery and breastfeeding, can be considered to indicate a normal maturation process.

Various cohorts around the world are attempting to collect the necessary data to identify associations between nutrition, microbiome maturation, and relevant markers of health such as growth or infectious events. Very few achieve the necessary sample size, frequency of sampling, and granularity of data across all relevant variables to draw robust inferences about the influence of diet on the trajectory of microbiome maturation. The BAMBOO cohort currently under follow-up in China, a collaboration between Nestlé Research and key academic partners, should address these questions in the next years.

References

1 van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med*. 2013;*368*(5):407–15. https://doi.org/10.1056/NEJMoa1205037.

2 Dogra SK, Kwong Chung C, Wang D, Sakwinska O, Colombo Mottaz S, Sprenger N. Nurturing the early life gut microbiome and immune maturation for long term health. *Microorganisms*. 2021;*9*(10):2110. https://doi.org/10.3390/microorganisms9102110.

3 Smith MI, Yatsunenko T, Manary MJ, Trehan I, Mkakosya R, Cheng J, et al. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science*. 2013;*339*(6119):548–54. https://doi.org/10.1126/science.1229000.

4 Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature*. 2018;*562*(7728):583–8. https://doi.org/10.1038/s41586-018-0617-x.

5 Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, Alam MA, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature*. 2014;*510*(7505):417–21. https://doi.org/10.1038/nature13421.

Integrating Next-Generation Evidence-Based Medicine Into Clinical Studies on Gut Microbiota Modulation

Hania Szajewska

The human gut microbiota comprises a diverse community of microorganisms, including bacteria, archaea, eukaryotes, and viruses, all of which reside within the gastrointestinal tract. Its role in human health is increasingly being recognized, attracting considerable attention from both the scientific community and the media. In addition to the influence of diet, a range of strategies has emerged to optimize health through gut microbiota modulation, including the use of biotics such as probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplants [1].

Evidence-based medicine (EBM) is an approach to medical practice that integrates the best available evidence with clinical expertise and patient values to make informed decisions about patient care. In line with this approach, there has been a surge in randomized controlled trials (RCTs) exploring gut microbiome modifications. These trials have contributed to systematic reviews and shaped clinical practice guidelines [2]. However, the expected health benefits from these interventions are not always clear or consistent. Some of the challenges with current clinical studies on gut microbiota modulation strategies are presented in Table 1.

EBM is a continuously evolving field. While there is no widely accepted definition of "next-generation EBM", it generally refers to new approaches addressing the limitations of traditional EBM methods by incorporating a wider range of evidence and evaluation criteria into medical practice [3]. The need for changes in EBM had been recognized even before the COVID-19 pandemic. However, the pandemic, possibly one of the most significant challenges to EBM, underscored and magnified the urgency of these changes [4, 5]. Table 2 presents examples of these next-generation EBM methods and their potential applications in biotics.

The next-generation EBM holds great promise, including in the field of gut microbiota modulation [2]. However, there are many unknowns. For example, the incorporation of big data, including real-world data and data from electronic health records, wearables, and social media, raises

Table 1. Key challenges in clinical gut microbiota modulation pediatric research

Challenge	Examples in biotics
Intervention specificity	Different probiotic strains may have varying effects on infant colic, making it difficult to generalize findings
Study heterogeneity	Some studies on probiotics for neonatal necrotizing enterocolitis use high dosages for short durations, while others use low dosages over extended periods, leading to inconsistent results
Population differences	A synbiotic effective in European infants with gastroenteritis may not work as well in Asian infants due to differences in diet and gut microbiota composition
Short study duration	Studies showing positive effects of probiotics in reducing pediatric antibiotic-associated diarrhea after 2 weeks may not reflect long-term benefits or risks of continuous use
Power, sample size, and endpoints	Estimating appropriate sample size and power in studies involving biotics for pediatric gut health is challenging, especially for time-to-event endpoints such as time-to-relapse in conditions such as pediatric inflammatory bowel disease. Incorrect assumptions about event rates can affect the timing and interpretation of analyses
Placebo effect	Parents might report improvements in their child's gut health due to their belief in the treatment's efficacy, making it hard to attribute benefits solely to the active biotic
Variable product quality	Different brands of probiotics may contain varying active ingredients or doses, complicating comparisons in studies on pediatric constipation
Storage and viability	Probiotics that require refrigeration may lose their effectiveness if not properly stored, impacting study results
Lack of standardization	Trials assessing probiotics for pediatric irritable bowel syndrome may use different outcome measures, making comparisons difficult
Publication bias	Studies showing that synbiotics significantly reduce pediatric infectious diarrhea are more likely to be published than those with negative or inconclusive findings
Lack of mechanistic insights	A study may find that a postbiotic reduces neonatal sepsis, but not explain the underlying

(Continued)

Table 1 (continued)

Challenge	Examples in biotics
	mechanism, making replication or application difficult
Interaction effects	The efficacy of a probiotic in preventing pediatric allergic diseases may be influenced by the child's diet or existing gut microbiota, complicating result interpretation
Safety concerns	Probiotics that benefit healthy children may cause adverse effects in immunocompromised children, raising safety concerns

Table 2. Methods in next-generation EBM with examples in the field of biotics

Method	Description	Potential use in the field of biotics
Real-World Data/ Real-World Evidence (RWD/RWE)	RWD: Data collected from sources such as electronic health records, billing data, registries, and patient-generated data that inform health status RWE: Clinical evidence from RWD analysis about a medical product's use, benefits, or risks, sourced from various study designs or analyses	Observational studies analyzing the health effects of long-term consumption of biotics using data from electronic health records
Digitalization of Clinical Trials	Use of digital tools to enhance the efficiency and patient-centeredness of clinical trials	Clinical trials using wearable devices to monitor bowel movement and bloating in patients taking biotics or fecal microbiota transplants
Core Outcome Sets (COS)	Agreed-upon sets of outcomes that should be measured and reported in all clinical trials for a specific condition	Adoption of COS for measuring outcomes in trials assessing the effects of biotics on irritable bowel syndrome

(Continued)

Table 2 (continued)

Method	Description	Potential use in the field of biotics
Patient-Centered Outcomes	Focus on outcomes that matter most to patients	Studies evaluating patient's gastrointestinal comfort or quality of life after intake of biotics
Adaptive Trial Designs	Clinical trials that allow modifications to the procedures based on interim results	Adaptive trials testing different doses of biotics in patients with inflammatory bowel disease
Master Protocols	Master protocols are single plans for multiple sub-studies, such as Basket, Umbrella, and Platform Trials, that save resources and improve coordination compared to separate trials	Platform trials testing multiple probiotics against a common control group in patients with irritable bowel syndrome
Pragmatic Trials	Clinical trials designed to test the effectiveness of interventions in real-world clinical practice settings	Pragmatic trials assessing the real-world effectiveness of biotics in patients with functional dyspepsia
Artificial Intelligence and Machine Learning	Use of advanced computational techniques to analyze complex data sets and predict outcomes	Machine learning models predicting the efficacy of specific biotics in altering gut microbiota composition
Social Media and Online Community Research	Utilization of social media platforms and online communities to increase awareness of clinical trials and engage underrepresented populations	Promoting biotics clinical trials for pediatric gastrointestinal issues on social media such as X (formerly Twitter) and Facebook to reach rural parents. Engaging adolescents in online communities for gut health studies

questions about data quality, privacy, and the appropriate statistical methods for analyzing these large, heterogeneous datasets. The potential of artificial intelligence (AI) to revolutionize EBM is significant, but there are uncertainties about the transparency, interpretability, and reliability of AI-driven analyses and recommendations. While patient involvement in decision-making is a core principle of EBM, the practicalities of how best to involve patients (or their care providers in the case of infants and young children), consider their preferences, and integrate their insights into the evidence base are still being explored.

In conclusion, integrating next-generation EBM methods into gut microbiota studies offers a promising avenue for improved understanding and patient-centered interventions. While these new approaches address traditional EBM limitations and offer valuable insights, they also raise questions about data quality, privacy, and patient involvement. As the field of EBM evolves, it is crucial to address these issues and ensure that evidence-based approaches remain robust, transparent, and patient-centric, ultimately contributing to optimized gut health for all.

References

1 Schmidt TSB, Raes J, Bork P. The human gut microbiome: from association to modulation. *Cell*. 2018;*172*(6):1198–215. https://doi.org/10.1016/j.cell.2018.02.044.

2 Szajewska H, Berni Canani R, Domellöf M, Guarino A, Hojsak I, Indrio F, et al. Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN special interest group on gut microbiota and modifications. *J Pediatr Gastroenterol Nutr*. 2023;*76*(2):232–47. https://doi.org/10.1097/MPG.0000000000003633.

3 Subbiah V. The next generation of evidence-based medicine. *Nat Med*. 2023;*29*(1):49–58. https://doi.org/10.1038/s41591-022-02160-z.

4 Evidence-based medicine: how COVID can drive positive change. *Nature*. 2021;*593*(7858):168. https://doi.org/10.1038/d41586-021-01255-w.

5 Greenhalgh T, Fisman D, Cane DJ, Oliver M, Macintyre CR. Adapt or die: how the pandemic made the shift from EBM to EBM+ more urgent. *BMJ Evid Based Med*. 2022;*27*(5):253–60. https://doi.org/10.1136/bmjebm-2022-111952.

Nutrition Challenges and Opportunities When Shifting to Plant-Based Diets

Paula Hallam

There has been a large increase in the number of people shifting towards more "plant-rich" dietary patterns over the past decade due to an interest in protecting the health of the planet as well as improving human health. A move towards plant-based diets is particularly prevalent in young people, and if these young people go on to have families, it follows that they would likely raise them eating the same dietary pattern.

There is no single universally agreed definition for plant-based diets. However, the British Nutrition Foundation defines plant-based diets as "*eating patterns that have a greater emphasis on plants, such as fruits, vegetables, wholegrains, legumes, nuts, seeds and oils*".

Childhood obesity is a big problem in the UK with 10% of children aged 4–5 years classified as obese in 2021/22 and a further 12% overweight, according to data from the National Child Measurement Programme. Studies have shown that vegetarian diets are associated with a lower prevalence of obesity in adults and children [1], so a move towards a vegetarian diet in childhood may help prevent obesity later in life.

The VeChi study of 1- to 3-year-olds found that on average vegetarian and vegan children grew equally as well as omnivorous children [2]. However, 3.6% of the vegan children were considered underweight, compared to 0.6% of the omnivorous group and 0% of the vegetarian group. All of the children who were considered underweight were either exclusively breast-fed for extended periods of time without solid foods being introduced or had insufficient total energy intakes. This highlights the importance of providing sufficient calories to all children to support their growth and development. Conversely, there was a higher percentage of children in the omnivorous diet group (23.2%) who were classified as overweight or obese than in the vegetarian or vegan groups (18.1% and 18% respectively) [2] (see Fig. 1).

It is important to ensure children following plant-based diets have adequate amounts of key nutrients, such as iron, calcium, iodine, vitamin B12, and omega-3 fats. In the VeChi studies [3, 4], calcium and iodine intakes of vegetarian and vegan children were lower than those in

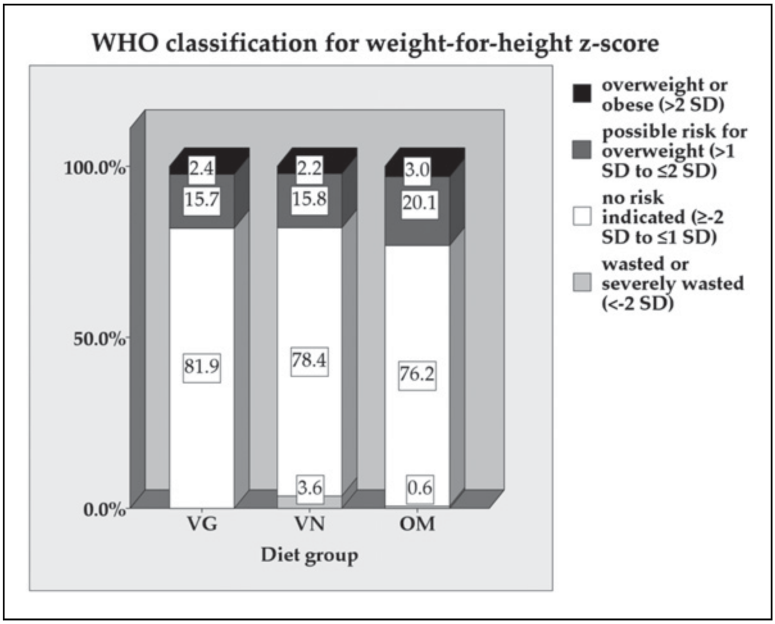

Fig. 1. Weight-for-height *z*-score according to the WHO Growth Standards of VG, VN, and OM children in the VeChi Diet Study by diet group (127 VG, 139 VN, and 164 OM). OM, omnivorous; VG, vegetarian; VN, vegan. From Weder et al [2].

omnivorous children, with vegan children having the lowest intakes. Offering children (over 1 year of age) 1–2 cups of calcium-fortified dairy alternative drink each day is one way to ensure an adequate calcium intake. Iodine is sometimes added to dairy alternative drinks, but a supplement is likely to be necessary to ensure a consistently adequate intake in most plant-based diets, especially if dairy products, eggs, and fish are all completely excluded from the diet.

In the VeChi studies [3, 4] the vegan children had the lowest vitamin B12 intakes without supplements, but when these were taken into account, the vegan children had the highest vitamin B12 intakes. I recommend that all vegan children (and adults) are given a vitamin B12 supplement, as plants are not a reliable source. One of the omega-3 fats, DHA, is another nutrient that should be considered for supplementation, as the only fully plant-based source of DHA is micro-algae.

Iron is a critical nutrient for infants, as iron stores they were born with start to deplete from around 6 months of age for most healthy, full-term infants [5]. Iron intakes in vegetarian children have been consistently reported to be higher than in omnivorous children; however, iron stores (indicated by low ferritin levels) tend to be lower in vegetarian compared to omnivorous children, due to lower bioavailability of non-haem iron found predominantly in plant foods [5]. Iron-rich foods should be offered to infants early when introducing solids and paired with iron enhancers such as vitamin C and beta-carotene.

References

1 Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr*. 2010;*91*(5):1525S–9S. https://doi.org/10.3945/ajcn.2010.28701F.

2 Weder S, Hoffmann M, Becker K, Alexy U, Keller M. Energy, macronutrient intake, and anthropometrics of vegetarian, vegan, and omnivorous children (1–3 years) in Germany (VeChi diet study). *Nutrients*. 2019;*11*(4):832. https://doi.org/10.3390/nu11040832.

3 Weder S, Keller M, Fischer M, Becker K, Alexy U. Intake of micronutrients and fatty acids of vegetarian, vegan and omnivorous children (1-3 years) in Germany (VeChi Diet Study). *Eur J Nutr*. 2022;*61*(3):1507–20. https://doi.org/10.1007/s00394-021-02753-3.

4 Alexy U, Fischer M, Weder S, Längler A, Michalsen A, Sputtek A, et al. Nutrient intake and status of German children and adolescents consuming vegetarian, vegan or omnivore diets: results of the VeChi youth study. *Nutrients*. 2021;*13*(5):1707. https://doi.org/10.3390/nu13051707.

5 Pawlak R, Bell K. Iron status of vegetarian children: a review of literature. *Ann Nutr Metab*. 2017;*70*(2):88–99. https://doi.org/10.1159/000466706.

Healthy Diets at the Intersection of Human and Planetary Health

Jose M. Saavedra

Our diets are the greatest determinant of our health. What we eat is sustained and shaped by the food we produce, and reciprocally, our food choices influence food production systems. Though unequally, food systems have increased production sufficiently to feed the growing world population. Science and technology, including progress in food systems, have led to decreased undernutrition worldwide, with large differences between high-income and low-income countries. At the same time, this has led to a dietary transition, with increases in energy and protein intakes, and a dramatic rise in non-communicable diseases. Cardiovascular disease, diabetes, chronic respiratory disease, and cancer are now responsible for 65% of all disability, or healthy life years lost to disease. High blood pressure, high fasting plasma glucose, high body mass index, and high LDL cholesterol – all diet-related – are in the top eight risk factors for disability, and they are the fastest-increasing risks for early death. Suboptimal diets are responsible for more deaths than any other risks globally, including tobacco smoking. The leading dietary risk factors for mortality are diets high in sodium, low in whole grains, low in fruit, low in nuts and seeds, and low in vegetables, together with global and regional excesses in red meat, sugar, sweetened beverages, and trans fats [1, 2].

Today, our food systems are being threatened by global warming and other environmental changes. Increased frequency of extreme weather events (heat waves, droughts, storms, and floods), and increases in sea level have long-lasting effects on our environment. And they also disrupt water systems, crop yields, and productivity, and can affect food quality through decreased crop diversity and nutrient density, posing major challenges to food production and security. Conversely, our food systems are a major contributor to climate change and the degradation of the environment. Food systems generate one-quarter of greenhouse gasses, use up to half of the world's habitable land, and are the largest contributor to water pollution. However, not all foods contribute similarly to this environmental impact. Of the foods we consume, animal products contribute 10–50 times more than plant products, with red meat being the highest contributor. On average, producing animal protein (meat and dairy) requires 11 times more fossil fuel energy than grain-based protein [3, 4].

Fortunately, there are synergies in improving human and planet health. The foods that are associated with lower health risks (fruits, vegetables, legumes, whole grain cereals, and nuts), are also associated with lower environmental impacts. On the other hand, aside from the overall excess intake of calories, foods associated with the greatest increases in morbidity and mortality, particularly meat, are associated with the greatest negative impact on the environment. On the "demand side" of the equation, shifting our current diets from high amounts of animal-based foods to increasingly healthier plant-based diets will decrease risks of global mortality and disability, especially from chronic disease (including obesity, type 2 diabetes, cardiovascular disease, and possibly neoplastic disease); while at the same time, decreasing the impact on the environment. On the 'supply side,' food systems will need to ensure access to safe, nutritious, and sustainable foods (e.g., improving agricultural yields, reducing food waste, greenhouse gas emissions, and polluting effects of foods), increasing plant-based foods, and decreasing animal-based food production. This will support and help shape healthier diets [4, 5].

These changes will require effort from all sectors of society, so everyone can play a role, in particular those engaged in the healthcare and nutrition sectors. There is an increasing level of awareness of the relationship between food, health, and the environment, particularly in our younger generations, which can be leveraged to implement these changes. Our diet is at the intersection of our health and our planet's health, and thus, a major instrument to improve both.

References

1 World Health Organization (WHO). Global health estimates September 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed November 10, 2023.

2 GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;*396*(10258):1223–49. https://doi.org/10.1016/S0140-6736(20)30752-2.

3 Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;*378*(9793):804–14. https://doi.org/10.1016/S0140-6736(11)60813-1.

4 Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet*. 2019;*393*(10170):447–92. https://doi.org/10.1016/S0140-6736(18)31788-4.

5 Clark MA, Springmann M, Hill J, Tilman D. Multiple health and environmental impacts of foods. *Proc Natl Acad Sci U S A*. 2019;*116*(46):23357–62. https://doi.org/10.1073/pnas.1906908116

New Food Technologies – Addressing Challenges at Food Systems Level

Julia K. Keppler, David L. Kaplan, Marine R.-C. Kraus

By 2050, the global population is expected to hit 10 billion people. The ever-growing human population will substantially increase the demand for food and require consideration of alternative approaches toward food sustainability, nutrition, and security [1]. The transition to a sustainable food system requires the reduction in consumption of meat and fish products and plant-based alternatives as a promising option. However, there is still opportunity to get closer to meat or fish proteins regarding the nutritional quality, technological limitations (texture challenges), and sensory properties of plant proteins such as soy or pea. Hence the food industry is constantly evolving, and new technologies are emerging to meet the changing demands of consumers.

Cellular agriculture, also known as cell culture-based food production, offers a potential alternative to conventional farming methods [2]. This innovative approach could minimize the environmental impact associated with traditional agriculture while ensuring high nutritional quality, ingredient safety, and food security. It is an interdisciplinary field that merges principles from engineering, biology, and chemistry to engineer and modify cells for diverse purposes. This field employs cutting-edge techniques such as genetic engineering, biomaterials, and microfabrication to design and modify cells and tissues.

The development of such meat alternatives combines a cell-based, tissue engineering approach (cells, scaffolding, feed ingredients, bioreactors), along with the integration of plant-based materials and alternative proteins as components for the process. Sustainable, cost-effective, and scalable cultivated-meat and alternative proteins may provide new and nutritious food alternatives, while decreasing negative environmental impacts [3]. Towards this goal, key cells, biomaterials, and systems engineering provide factors to optimize in terms of the quality of protein-rich foods generated with these alternative approaches. However, many influencing factors must be considered for successful systems integration for cellular agriculture processes and biomanufacturing needs.

Furthermore, the field of cellular agriculture is expanding beyond the production of animal-based products like meat, poultry, and seafood to also include dairy alternatives such as milk.

Recent development of primary cultures of mammary gland epithelial cells has paved the way for the creation of an ex vivo lactation system for cell-based milk production. This technology, combined with the ability to modify genetic and media culture factors, enables the modeling of mammary gland organogenesis and lactation processes in a dish. As a result, it becomes feasible to envision the production of functional and personalized milk-like products or bioactive components through cell-based approaches, also offering an alternative to traditional dairy farming.

Another way of producing, for instance, milk proteins in vitro is using genetically modified non-animal host cells cultivated in a fermenter [4]. These cells, which can be fungi, bacteria, or yeasts, are engineered to secrete the desired milk protein, with the host organism being excluded from the final product. This technology is called precision fermentation.

Although these animal-free milk proteins offer valuable food proteins without relying on animals, their physical functionality will have to be assessed as they may differ from animal-derived milk proteins due to minor amino acid sequence changes. The potential of such in vitro produced milk proteins depends on the specific application, and if used as bioactive nutrients, their bioactivity must be established. Using them as functional ingredients in animal-free dairy products like cheese, however, poses additional challenges in recreating protein structures and incorporating non-animal fat sources and nutrients. Careful evaluation is needed to fully harness the potential of cellular agriculture and precision fermentation for sustainable dairy alternatives.

Although this approach is a real opportunity to find answers to sustainable food production, the challenges of the development of these novel food technologies (i.e., culture media composition, scale-up, bioreactor costs, biomass valorization, and energy consumption) which impact food quality, consumer preferences, and economics of scale, pose significant barriers to the commercialization of cellular agriculture for meat and milk production [5].

References

1 World population prospects: the 2012 revision—highlights and advance tables. 2013.

2 Rischer H, Szilvay GR, Oksman-Caldentey KM. Cellular agriculture—industrial biotechnology for food and materials. Curr Opin Biotechnol. 2020;61:128–34. https://doi.org/10.1016/j.copbio.2019.12.003.

3 Stephens N, Di Silvio L, Dunsford I, Ellis M, Glencross A, Sexton A. Bringing cultured meat to market: technical, socio-political, and regulatory challenges in cellular

agriculture. Trends Food Sci Technol. 2018;78:155–66. https://doi.org/10.1016/j.tifs.2018.04.010.
4 Wikandari R, Manikharda, Baldermann S, Ningrum A, Taherzadeh, MJ. Application of cell culture technology and genetic engineering for production of future foods and crop improvement to strengthen food security. Bioengineered. 2021;12(2):11305–30. https://doi.org/10.1080/21655979.2021.2003665.
5 Tuomisto HL. Challenges of assessing the environmental sustainability of cellular agriculture. Nat Food. 2022;3(10):801–3. https://doi.org/10.1038/s43016-022-00616-6.

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