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The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions

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Karger

Nestlé Nutrition Institute

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Preface

This book presents the proceedings of the 99th Nestle Nutrition Institute Workshop, held in February 2023 in Riyadh, Saudi Arabia. The workshop brought together experts in the field of pediatric nutrition to discuss the latest trends and future directions.

Although the impact of early nutrition on short- and long-term health is widely accepted, the mechanisms of early nutrition programming are not yet fully understood. However, human milk stands out as a model for any comparison, highlighting the importance of breastfeeding, which should be effectively protected, promoted, and supported.

Significant research is focused on the pathways through which nutrition can influence development and health. One of the primary mechanisms of early nutrition programming is epigenetic modification. Nutrition during critical periods of development can induce epigenetic modifications, which can alter gene expression and affect long-term health outcomes.

COVID-19 and nutrition have a bidirectional relationship where COVID-19 and related lockdown restrictions, by various pathways, increase the prevalence of both, under- and overnutrition, which can negatively affect disease severity. Optimal nutrition interventions can help reduce COVID-19 severity and support recovery. Public health strategies promoting healthy eating habits and adequate nutrient intake can reduce infection risk and improve health outcomes.

In many settings, the prevalence of food allergies has been increasing in recent years, and researchers are exploring ways to reduce the burden of food allergies. While guidelines on food allergy prevention may differ in their specific recommendations for the age of introduction and target populations, overall, the paradigm has shifted from allergen avoidance to early introduction to potentially allergenic foods based on evidence showing that this approach can lower the risk of developing allergies to these foods. However, the discussion on the most effective strategies continues.

While the gut microbiota was once called "the forgotten organ," it is no longer forgotten. It is increasingly recognized as a potential key player in the pathogenesis of various chronic diseases. Diet is a key factor that has a substantial impact on the composition and function of the gut microbiota. A better understanding of how the early-life gut microbiota impacts our immunity could potentially lead to strategies modifying the risk of diseases later in life.

The title of this Workshop also embraces the "future directions," and therefore, the presenters also looked into the prospects ahead. Personalized pediatric nutrition is a rapidly growing field that aims to provide tailored nutrition interventions to optimize health outcomes for individual children. While there have been significant advances in this area in recent years, there are still more questions than answers. Digital health, which encompasses the use of technology and digital tools to improve health outcomes, has the potential to transform healthcare delivery and improve patient outcomes. However, there are both benefits (e.g., improved access to care) and challenges (e.g., privacy and security concerns) associated with digital health.

The workshop took place at a time when artificial intelligence (AI) and ChatGPT were addressed with increased frequency. It is becoming evident that AI, including machine learning and deep learning algorithms, can analyze large datasets and identify complex patterns that may not be apparent using traditional statistical methods. For example, AI can be applied to multiomics data to identify new biomarkers and develop predictive models (e.g., for prematurity risk). The rapid growth of AI is creating new and exciting opportunities for advancing the field of pediatric nutrition. We need to stay tuned!

We hope that this book will be a valuable resource for researchers and clinicians interested in pediatric nutrition. As the co-chairs of the workshop, we would like to extend our gratitude to all the speakers who contributed to the workshop and the Nestle Nutrition Institute teams in Saudi Arabia and Switzerland for their exceptional support, which made the workshop possible.

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Foreword

The past years have brought about big changes in the nutritional landscape of pediatric nutrition and health. Transitions in global health have greatly affected children, but with this comes significant advances in research to prevent illnesses and maximize overall health and wellness. These range from novel studies that have unlocked new information on human milk, metabolic programming, microbiome, allergy prevention, and immunomodulation, to practical applications that have allowed a shift in eating habits for better immunity and sustainability. The pandemic years ushered in challenges in infection control and prevention of diseases, and highlighted areas of immune health, supplementation, and child nutrition. This shifted the focus once again to what children eat and how to best protect the health of the child.

The 99th Nestle Nutrition Institute Workshop, The Changing Landscape of Pediatric Nutrition: The Latest Trends and Future Directions, held in Riyadh, KSA, explored some of the latest updates in child nutrition, dietary trends, the impact of early nutrition on long-term health, and breastmilk research. Also discussed were allergy prevention, diet and microbiome, immunomodulation, and new research on human milk oligosaccharides and multiomics in prematurity. To further address the changing scenario of clinical practice, the workshop also featured discussions on digital health and how engagement with patients in this new environment can be more effective. The learnings from the lectures and discussions in this workshop are truly beneficial for our healthcare professionals and support their efforts to improve the health of the children now and in the future.

We gratefully acknowledge the two Chairpersons Hania Szajewska and Sanja Kolaček, who assembled this outstanding scientific program. We would also like to thank all speakers and experts in the audience who have contributed to the content of the workshop and scientific discussions.

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Infant Feeding and Later Health: Exploring Mechanisms to Improve Preventive Approaches

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Abstract

Accumulated scientific evidence demonstrates that environmental cues, including nutrition during sensitive time periods of developmental plasticity, induce long-lasting programming effects on later health, performance, and disease risks. A particularly sensitive period comprises the "First 1,000 Days of Life" including pregnancy and the first two postnatal years. Powerful effects of early life nutrition and growth on later health, physical and mental performance, and risk of noncommunicable diseases (e.g., obesity, diabetes, cardiovascular disorders, allergy, asthma, and some cancers) have been demonstrated. Proposed mechanisms include modification of growth, body composition, epigenome, metabolome, hormones, and microbiome. In this chapter, we provide examples without discussing the microbiome as it is addressed in another contribution. Understanding underlying mechanisms of early nutrition programming is of paramount importance to establish better strategies for effective health promotion. This could facilitate more targeted interventions in susceptible subgroups, aiming at greater efficacy, efficiency, and cost-benefit ratios. Close trans-disciplinary collaboration between clinicians, scientists, and bioinformatics specialists is needed to link clinical characterization with biomarkers and large dataset evaluation utilizing artificial intelligence. The results may provide major benefits for scientific understanding, opportunities for future research, promotion of public health, nutrition recommendations, and development of improved food products.

Introduction

A convincing body of scientific work demonstrates that environmental cues acting during sensitive periods of developmental plasticity induce long-lasting programming effects on later health, performance, and disease risks [1]. The term "First 1,000 Days of Life" refers to a particularly sensitive time, comprising both the 290 days of pregnancy and the first two postnatal years (2 × 365 days). During this period, environmental factors, specifically maternal and infant nutrition, have marked and long-lasting effects on health. Initial indications of early programming of later health stem from retrospective epidemiological studies. Further evidence was provided by experimental animal studies, prospective epidemiology, and some controlled human intervention trials with long-term follow-up [2]. The available data demonstrate powerful effects of early life nutrition and growth on later health, physical and mental performance, and the risk of noncommunicable diseases (NCDs) such as obesity, diabetes, cardiovascular disorders, allergy and asthma, some forms of cancer, and others. Exploration of underlying mechanisms is crucial to fully utilizing the preventive potential of programming effects. This should lead to developing more targeted and more effective intervention strategies. A variety of potential mechanisms has already been proposed, including effects on growth, body structure and composition, epigenome, metabolome, hormones, and microbiome (Fig. 1). In this work, we provide a few examples, though we do not discuss the microbiome as this is specifically addressed in other chapters of this publication.

Growth Trajectories

Growth and development are the key characteristics of childhood. Rapid weight gain during the first 2 years of life has been consistently associated with an increased risk of obesity and associated disorders in later childhood, adolescence, and adulthood [3, 4]. Weight gain velocity during the first 6 months of life in healthy infants is also closely correlated to infant body fat mass, as assessed by the deuterium dilution method, but not to lean body mass [5]. Populations of breastfed infants tend to have a lower weight gain from birth to 1 year than those that are bottle-fed [6, 7]. A systematic review and meta-analysis of 15 studies examining body composition in healthy infants showed that breastfed infants had a lower body fat mass at age 1 year than formula-fed infants [6]. In a large cross sectional study with more than 9,000 children in Germany, we found less overweight and obesity in children at early school age if they were previously breastfed, compared to those that had been bottle-fed [8]. In this study, we also

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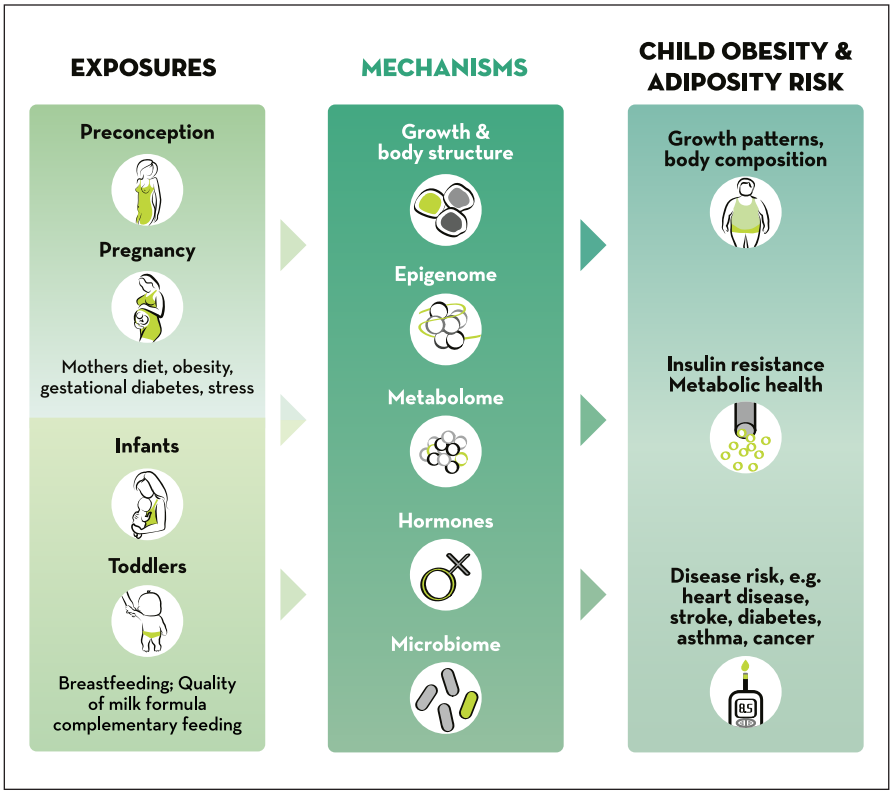

Fig. 1. Proposed mechanisms of early metabolic programming of later health and disease risk, linking nutritional exposures before and during pregnancy, and during early childhood, with later health outcomes. Adapted with permission from Child and Family Health Academy at Stiftung Kindergesundheit – Child Health Foundation (www.kindergesundheit.de).

found an inverse dose-response relationship between breastfeeding duration and the adjusted odds ratios (OR) for obesity. These findings were subsequently replicated in numerous but not all other cohort studies.

To further investigate the impact of early growth patterns, we analyzed longitudinal growth trajectories of more than 6,700 children from Europe and Australia. Only 50% of these children had a body mass index (BMI) evolution along reference values, with a BMI *z*-score remaining near 0 over time [3]. Almost another half of the children studied (48.5%) had an increase of the BMI *z*-score from about standard deviation score (SDS) 0 at birth to about SDS +1 at 2 years, with a subsequent slight decrease of the BMI *z*-score that remained elevated at about SDS +0.5 at early school age. This "early rapid growth trajectory" was associated with later increased overweight and obesity, as well as an increased BMI, fat mass, and fat mass index in adulthood at the age of 20 years [3]. In this

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study, early growth was also related to infant feeding: the odds of having the risky "early rapid growth trajectory" were doubled (OR 1.96, 95% CI: 1.51, 2.55) in children that had not been breastfed, or breastfed for less than 3 months, compared to those who were breastfed for longer. This is consistent with results of meta-analyses of numerous observational studies, showing breastfeeding associated with a consistent albeit moderate risk reduction for later obesity [9]. Interestingly, a longer duration of breastfeeding is associated with greater risk reduction, whereas exclusive and nonexclusive breastfeeding had a similar protective effect, suggesting that the total dosage of breastfeeding rather than breastfeeding exclusivity matters [9]. However, residual confounding is likely, since most of the available studies are from high-income countries. In high-income countries, higher socioeconomic status is associated with both greater likelihood of breastfeeding and longer breastfeeding duration, as well as with health-promoting behaviors, better overall health, and lower obesity risk. Nonetheless, the available data indicate that the mode of infant feeding and related patterns of weight gain may modulate subsequent obesity risk. Differences in substrate supply are a likely causal factor. However, we need a better understanding on how exactly infant feeding modulates growth and body composition, which substrates are major growth modulators, and which infants or population subgroups are most susceptible to infant feeding effects on later obesity and related NCDs.

Epigenetics

An intriguing question is how the body can remember early life cues over subsequent decades. Epigenetic modifications may be the missing link between nutritional and metabolic exposures and subsequent alterations in gene expression that induce persistent later effects. Epigenetics is the study of heritable changes in gene expression not caused by changes in the DNA sequence, but by biochemical modifications of DNA. Epigenetic mechanisms control modifications in chromatin, regulate its accessibility to transcription factors (TFs), and thus contribute to determining the expression of different genes. Mechanisms of epigenetic modification include the addition of methyl groups to DNA cytosine bases, the addition of methyl and acetyl groups to proteins (histones) around which DNA is folded, and interfering miRNA.

Addition of a methyl group to the 5′ carbon of a cytosine base in the context of CpG is the most frequent and stable form of epigenetic modification. Genes tend to be expressed when TFs bind to DNA and activate the gene. DNA methylation (DNAm) prevents TF binding while it favors the binding of transcription inhibiting proteins. Thus, enhanced DNAm is mostly associated with switching

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genes "off." The degree of activation of a given gene generally depends upon its degree of methylation.

Differentially methylated regions may result from environmental triggers acting in sensitive or critical early periods of life, which can lead to alternative pathways of cell and organ development. The role of epigenetics is supported by both numerous animal studies, as well as human observational studies that demonstrated, for example, associations of DNAm with body size, body fatness or adiposity, and disease markers or disease endpoints [10–12]. Large interindividual variation has been described. For example, diet effects on DNAm can markedly vary with genotype variation and infant sex [13]. Moreover, uncertainties remain as to the fluidity or persistence of DNAm with increasing age. Thus, exploring epigenetic markers over time may be an important path for exploring future strategies of individual disease prevention, and perhaps even treatment. Also, more studies are needed to characterize the exploration of functions and pathways that are altered by diet imprinted genes, and to substantiate causal epigenetic effects on clinical endpoints, for example, by corroboration in randomized controlled trials (RCTs).

Metabolic Regulation

Early nutrition affects metabolite concentrations in the child's body fluids and tissues, which modulate growth, tissue function, and health outcomes. Progress in analytical methodology now enables high throughput and precise analysis of infant metabolomic profiles from minimal sample volumes, for example, by using high-performance liquid chromatography and triple quad mass spectrometry, which is extremely powerful [14, 15]. Application of these sophisticated tools bears the very promising potential to detect relevant, but still unidentified regulatory metabolic mechanisms involved in the modulation of growth and body composition. For example, among 726 infants in the European Childhood Obesity Project Trial (CHOP trial), we found weight gain from birth to age 6 months, which predicts later health and obesity risk, significantly related to the plasma metabolome at age 6 months. In particular, the amino acids tyrosine and citrulline, diacyl-phosphatidylcholine PCaaC34:4, and the lysophosphatidylcholine LPCaC14:0 were positively associated with weight gain in the first 6 months of life [16]. LPCaC14:0 at age 6 months also predicted obesity at early school age (6 years; OR 1.33; 95% CI: 1.04–1.69). However, there was considerable interindividual variation in metabolic response.

It was previously established that metabolic status of males and females differs in adults and in adolescents after puberty [17]. Of interest, we also found sex

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differences in more than 700 neonates regarding the relationship between cord blood metabolites and birth weight. Several lysophosphatidylcholines, glycerophospholipid fatty acids, and nonesterified fatty acids were highly associated with birth weight. However, these associations of nonesterified omega-3 fatty acids and of lysophosphatidylcholines containing omega-6 fatty acids with birth weight were stronger in females than males [18].

We also found variation in metabolic status among 183 breastfed infants who presented with 20 separate plasma metabolome clusters. The four major metabolite clusters predicted BMI evolution up to age 6 years [19]. Thus, breastfeeding exposure is not homogeneous. Rather, different effects evolve within breastfed populations. One predictive factor appears to be the variation in human milk protein content. Breast milk protein predicted the infant plasma concentration of LPCaC14:0, the metabolite that we previously identified as an early predictor of both rapid weight gain and later obesity [20].

This observation is in line with the Early Protein Hypothesis. It suggests high protein supply in infancy to increase plasma and tissue concentrations of amino acids, which can stimulate an enhanced secretion of the infant growth factors insulin-like growth factor-1 (IGF-1) and insulin, subsequently resulting in increased weight gain, enhanced body fat deposition, and increased long-term risk of later obesity and associated disorders [7]. We tested the Early Protein Hypothesis in a large, multicenter RCT funded by European Commission Framework Programmes, the CHOP trial [21, 22]. We enrolled 1,678 healthy term infants born with appropriate gestational age that were either exclusively breastfed for at least the first 3 months of life (nonrandomized reference group) or formula fed. If parents chose to formula feed, infants were randomized double blind at a median age of 2 weeks to isocaloric formulas with either conventionally high protein content or reduced protein content, more comparable to human milk levels. We found a marked effect of infant feeding on BMI, obesity prevalence, and body fatness at school age [22, 23], with lasting effects until early adolescence [24]. Children who had been fed reduced protein in infancy had a body weight and body fat mass similar to those who had been breastfed after birth. However, the effect sizes were quite different in subgroups. The effect size of the intervention was much greater in children with a high BMI at the 90th and the 95th percentile, as compared to children at a median BMI (Fig. 2) [22]. Therefore, the dietary intervention had a very large effect on obesity prevalence at school age (6 years). A reduced protein supply in infancy lowered the risk for obesity at early school age 2.43-fold (unadjusted; 95% CI: 1.12, 5.27; $p = 0.024$) or 2.87-fold (adjusted; 95% CI: 1.22, 6.75; $p = 0.016$), respectively, compared to conventionally high protein supply [7, 22].

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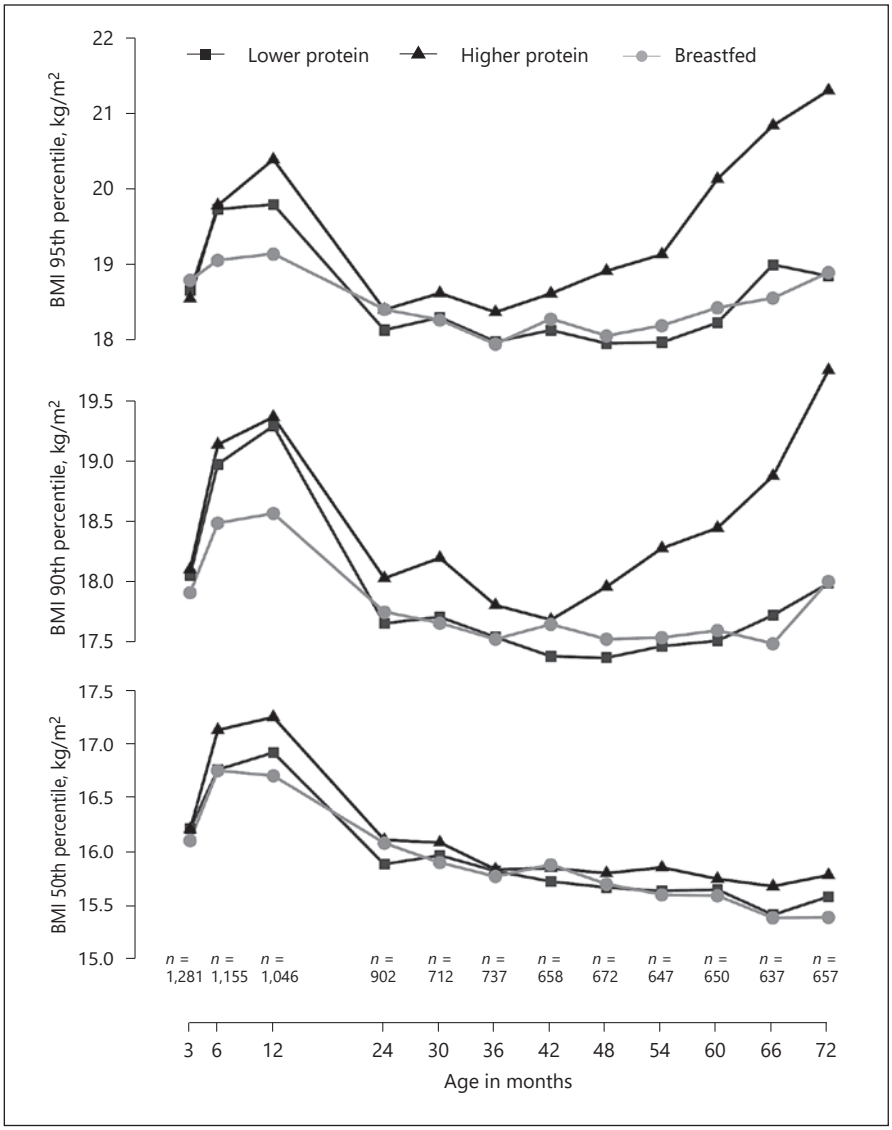

Fig. 2. Effect of infant feeding on BMI evolution from infancy to early school age. Higher protein supply with infant formula, compared to lower protein intakes, has a relatively modest effect on the mean BMI (mean BMI difference at the 50th percentile 0.29 kg/m^2), whereas there is a very large effect at the upper percentiles (mean BMI difference at the 95th percentile 2.50 kg/m^2). If the particularly susceptible subgroup with high obesity risk and large responsiveness to infant feeding can be identified early on, a targeted intervention (precision nutrition) could be applied with potentially much greater effectiveness. Modified with permission from Weber [22].

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We hypothesize that alterations in amino acid metabolism may be a key factor for triggering this very large effect on obesity. Higher protein intakes significantly elevated plasma concentrations of the branched chain amino acids (BCAA) leucine, isoleucine and valine (total BCAA 572.9 ± 173.2 μmol/L with higher vs. 413.5 ± 111.3 μmol/L with lower protein intake, $p < 0.0001$), along with an increase of other indispensable amino acids [25]. However, plasma concentrations of most other amino acids were unchanged, and they were even reduced for glutamine and glycine. Elevated concentrations of BCAA in response to protein supply may be causative for inducing excessive weight gain and higher body fat mass, as they can induce cellular anabolism, protein and fat deposition, and cell growth through activation of mammalian target of rapamycin (mTOR) [14]. However, again we found very marked interindividual variation of BCAA concentrations even within the same feeding group, which is not yet well explained.

The available data demonstrate that metabolic modulation of early growth can have a considerable impact on later obesity and health. Therefore, it is important to explore underlying mechanisms, key drivers, and predictors through which early metabolic exposure modulates child growth and health, as well as the observed interindividual variation in metabolic response to infant feeding, both in breastfed and bottle-fed babies. The relative roles of protein quantity and quality in modulating early growth and later obesity and the most sensitive time windows for preventive interventions need further exploration. The central pathways involved and the possibilities for best modulating them should be investigated and informative biomarkers characterized and evaluated. These elements may help develop and better evaluate targeted, preventive interventions (precision nutrition), as well as benefits and cost-effectiveness.

Endocrine Regulation

In the CHOP trial, higher protein intake notably increased the secretion of insulin and IGF-1, the key mediators of infant growth (Table 1) [25]. Insulin and IGF-1 contribute to activating mTOR. However, full activation of mTORC1 is only achieved with synergistic action of both insulin, IGF-1 and amino acids, while a low energy supply downregulates mTORC1 [14, 26].

We found IGF-1 to be the strongest predictor of BMI at age 1 year [25]. The effect size of diet in predicting IGF-1 is far greater than the impact of genotype variation. In 1,090 formula-fed infants in the CHOP trial, we assessed the degree of variation of IGF-1 axis parameters explained by eight single nucleotide polymorphisms of the IGF-1 and two of the Insulin-like Growth Factor Binding Protein-3 (IGBP3) genes. The combined genotype had a much lower effect com-

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Table 1. Serum concentrations of free and total IGF-1, IGFBP2 and IGFBP3, glucose and urea, and urinary C-peptide (median, IQR) in infants aged 6 months randomized to lower protein or conventional higher protein formulae, or being in a nonrandomized breastfed reference group

Parameter	Lower protein	Higher protein	*p*, lower vs. higher protein	Breastfed
IGF-1 free, ng/mL	0.43 (0.27, –0.77)[1]	0.60 (0.34, 1.11)[2]	<0.001	0.31 (0.21, 0.48)
IGF-1 total, ng/mL	34.7 (17.7, 57.5)[1]	48.4 (27.2, 81.8)[2]	<0.001	14.1 (5.1, 33.2)
IGFBP2, ng/mL	1,090 (865, 1,438)[1]	765 (575, 1,013)[2]	<0.001	1,370 (1,055, 1,740)
IGFBP3, ng/mL	2,908 (2,449, 3,440)[1]	2,969 (2,538, 3,483)[2]	0.248	2,454 (1,984, 2,794)
C-peptide/creatinine, ng/mg	107.3 (65.2, 194.7)[1]	140.6 (80.0, 203.8)[2]	0.030	57.0 (27.3, 119.3)
C-peptide, ng/mL	19.5 (9.4, 34.6)[1]	26.9 (13.3, 45.6)[2]	0.002	9.3 (3.5, 20.1)

p values were computed using Kruskal-Wallis rank test. [1]$p < 0.001$ lower protein versus breastfed. [2]$p < 0.001$ higher protein versus breastfed. Modified with permission from Elsevier [25].

Table 2. Degree of variation of IGF-1 axis parameters explained by eight single nucleotide polymorphisms (SNPs) of the IGF-1 and two of the IGFBP-3 genes, infant sex, and infant diet in 1,090 formula-fed infants in the European CHOP trial; nutritional regulation of IGF-I and IGFBP-3 is by far predominant

	Total IGF-1 (log10, R^2), %	Free IGF-1 (log10, R^2), %	IGF-BP3 (R^2), %	IGF-1/IGF-BP3 (R^2), %
Genotype only	3.8	3.6	0.78	5.0
Sex only	1.5	2.0	1.2	1.1
Diet only	15.1	6.8	10.4	13.1
Total R^2 explained with covariates	27.9	22.3	22.6	24.9

Modified with permission from Rzehak [27].

pared to that of the infant diet, which proved to be the predominant regulating factor (Table 2) [27].

Infant sex also played a distinct role in modulating the IGF-1 axis response to protein intake. Female infants had significantly higher concentrations of total and free IGF-1 and IGFBP3 than males. Higher protein supply increased total IGF-1 by 24.36 ng/mL ($p < 0.001$) compared to lower protein in females, but only by 11.22 ng/mL ($p = 0.140$) in males [28]. IGFBP2 differed between feeding groups by 410.84 ng/mL ($p < 0.001$) in females but only by 271.07 ng/mL in males ($p < 0.001$). Thus, infant females appear more sensitive to the effects of protein supply on endocrine response than males, although the effect on growth was not significantly different [28]. Also, females showed higher leptin concentrations which are correlated to IGF-1 axis parameters.

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The effects of dietary animal protein intake on the IGF-1 axis and subsequent health may also be relevant beyond early childhood. In adult organisms, diets high in protein are the most effective in increasing growth hormone signaling and IGF-1 levels, and in shortening lifespan [29]. Higher IGF-1 and lower IGFB-3 levels have been associated with the development of malignant diseases, including breast, prostate, and colorectal cancer [30]. Among participants aged 50–65 years of the NHANES III study, those reporting a high dietary protein intake had a 75% increase in overall mortality and a fourfold increase in the risk of cancer-associated deaths during the following 18 years. These associations were either abolished or attenuated, if the proteins were derived from plants. In contrast, study participants aged 65 years and older with a high protein intake showed reduced cancer and overall mortality, but a fivefold increase in diabetes mortality. Interestingly, high protein intake increased IGF-1 concentrations in subjects up to the age of 65 years, but not in the older age group. This observation suggests that the adverse effects of high protein diets on mortality at younger ages may be mediated via IGF-1 regulation.

To further evaluate the metabolic and endocrine response to dairy protein intake and the postprandial kinetics, we performed a randomized crossover study, examining the effects of toddler milk protein content on postprandial response in adult subjects. We found that higher protein supply markedly elevates plasma BCAA for at least 5 h after the formula meal, but again with very prominent inter-individual variation, also in plasma concentrations of insulin, glucose, urea, and triglycerides [31].

A better understanding of individual differences could pave the way to more targeted and efficient precision prevention. In addition, the development of strategies for early identification of susceptible subgroups, such as high risk infants, and those that respond most to dietary modifications, could be highly beneficial in establishing effective interventions.

Understanding Mechanisms Is Important

The description and analysis of growth patterns and their regulation through diet are of major relevance for public health and policy. We think this has the potential to contribute greatly to promoting population health and well-being. Improved awareness of underlying mechanisms of early nutrition programming is pivotal to establishing improved methods of effective health promotion. Effectiveness could be enhanced by precise interventions in susceptible subgroups, in order to achieve greater efficacy, efficiency, and cost-benefit ratios of early nutrition approaches. To reach these goals, close trans-disciplinary collabora-

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tion of clinicians, basic scientists and bioinformatics specialists is required. This can facilitate linking clinical characterization with state-of-the-art biomarkers and large dataset evaluation utilizing machine learning and artificial intelligence methodologies. One such attempt is the European BiomarKid collaboration that explores the body's response to the interplay of diet, activity, environment, and genetic predisposition. The project surveys metabolome and proteome, along with endocrine, genetic and epigenetic measures as well as biological and lifestyle assessments, physical activity and sedentary behavior, sleep habits, and their interplay in children and youth that participate in early life dietary intervention studies with long-term follow-up. The BiomarKid consortium aims to enhance the understanding of programming mechanisms, and to bring complex biomarker identification technology closer to practical application, including improved early-life prevention strategies. We need to invest further in groundbreaking research with novel and sophisticated methodology. Research collaboration of academic investigators and researchers from private sectors may help enhance outputs and translational application. If successful, the results of such endeavors could provide fundamental information on the regulation of growth. This should lead not only to great benefits for scientific understanding and opportunities for future research, but also to promotion of public health, nutrition recommendations, and the development of improved food products.

Conflict of Interest Statement

The participation and contribution of the corresponding author in and to the 99th NNI workshop was supported by the Nestlé Nutrition Institute. The authors declare no conflicts of interest in relation to the content of this manuscript, with no circumstances involving the risk that the professional judgment or acts of primary interest may be unduly influenced by a secondary interest.

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Author Contributions

B.K. wrote the first draft of the manuscript. H.D., V.G., J.H., G.K., E.N.-T., V.L., and M.T. contributed to generation of data, commented on the manuscript, and approved the final version.

References

1 Koletzko B, Brands B, Chourdakis M, Cramer S, Grote V, Hellmuth C, et al. The Power of Programming and the EarlyNutrition project: opportunities for health promotion by nutrition during the first thousand days of life and beyond. Ann Nutr Metab. 2014;64:141–50.
2 Koletzko B, Brands B, Grote V, Kirchberg FF, Prell C, Rzehak P, et al. Long-term health impact of early nutrition: the power of programming. Ann Nutr Metab. 2017;70:161–69.
3 Rzehak P, Oddy WH, Mearin ML, Grote V, Mori TA, Szajewska H, et al. Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood. Am J Clin Nutr. 2017;106(2):568–80.
4 Toschke AM, Grote V, Koletzko B, von Kries R. Identifying children at high risk for overweight at school entry by weight gain during the first 2 years. Arch Pediatr Adolesc Med. 2004;158(5):449–52.
5 Escribano J, Luque V, Ferre N, Mendez-Riera G, Koletzko B, Grote V, et al. Effect of protein intake and weight gain velocity on body fat mass at 6 months of age: the EU Childhood Obesity Programme. Int J Obes (Lond). 2012;36(4):548–53.
6 Gale C, Logan KM, Santhakumaran S, Parkinson JR, Hyde MJ, Modi N. Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis. Am J Clin Nutr. 2012;95(3):656–69.
7 Koletzko B, Demmelmair H, Grote V, Totzauer M. Optimized protein intakes in term infants support physiological growth and promote long-term health. Semin Perinatol. 2019;43(7):151153.
8 von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, et al. Breast feeding and obesity: cross sectional study. BMJ. 1999;319(7203):147–50.
9 Yan J, Liu L, Zhu Y, Huang G, Wang PP. The association between breastfeeding and childhood obesity: a meta-analysis. BMC Public Health. 2014;14:1267.
10 Koletzko B. Epigenetics, nutrition and growth. World Rev Nutr Diet. 2023;126:70–85.
11 Rzehak P, Covic M, Saffery R, Reischl E, Wahl S, Grote V, et al. DNA-methylation and body composition in preschool children: epigenome-wide-analysis in the European Childhood Obesity Project (CHOP)-Study. Sci Rep. 2017;7(1):14349.
12 Vehmeijer FOL, Kupers LK, Sharp GC, Salas LA, Lent S, Jima DD, et al. DNA methylation and body mass index from birth to adolescence: meta-analyses of epigenome-wide association studies. Genome Med. 2020;12(1):105.
13 Solomon O, Huen K, Yousefi P, Kupers LK, Gonzalez JR, Suderman M, et al. Meta-analysis of epigenome-wide association studies in newborns and children show widespread sex differences in blood DNA methylation. Mutat Res Rev Mutat Res. 2022;789:108415.
14 Kirchberg FF, Harder U, Weber M, Grote V, Demmelmair H, Peissner W, et al. Dietary protein intake affects amino acid and acylcarnitine metabolism in infants aged 6 months. J Clin Endocrinol Metab. 2015;100(1):149–58.
15 Voerman E, Jaddoe VWV, Shokry E, Ruijter GJG, Felix JF, Koletzko B, et al. Associations of maternal and infant metabolite profiles with foetal growth and the odds of adverse birth outcomes. Pediatr Obes. 2022;17(2):e12844.
16 Rzehak P, Hellmuth C, Uhl O, Kirchberg FF, Peissner W, Harder U, et al. Rapid growth and childhood obesity are strongly associated with LysoPC(14:0). Ann Nutr Metab. 2014;64(3–4):294–303.
17 Rauschert S, Uhl O, Koletzko B, Mori TA, Beilin LJ, Oddy WH, et al. Sex differences in the association of phospholipids with components of the metabolic syndrome in young adults. Biol Sex Differ. 2017;8:10.
18 Hellmuth C, Uhl O, Standl M, Heinrich J, Koletzko B, Thiering E. Cord blood metabolome is highly associated with birth weight, but less predictive for later weight development. Obes Facts. 2017;10:85–100.
19 Kirchberg FF, Grote V, Gruszfeld D, Socha P, Closa-Monasterolo R, Escribano J, et al. Are all breast-fed infants equal? Clustering metabolomics data to identify predictive risk clusters for childhood obesity. J Pediatr Gastroenterol Nutr. 2019;68(3):408–15.
20 Hellmuth C, Uhl O, Demmelmair H, Grunewald M, Auricchio R, Castillejo G, et al. The impact of human breast milk components on the infant metabolism. PLoS One. 2018;13(6):e0197713.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 1–13 (DOI: 10.1159/000534945)

21 Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, et al. Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. Am J Clin Nutr. 2009;89(6):1836–45.
22 Weber M, Grote V, Closa-Monasterolo R, Escribano J, Langhendries JP, Dain E, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. Am J Clin Nutr. 2014;99(5):1041–51.
23 Totzauer M, Luque V, Escribano J, Closa-Monasterolo R, Verduci E, ReDionigi A, et al. Effect of lower versus higher protein content in infant formula through the first year on body composition from 1 to 6 years: follow-up of a randomized clinical trial. Obesity (Silver Spring). 2018;26(7):1203–10.
24 Totzauer M, Escribano J, Closa-Monasterolo R, Luque V, Verduci E, ReDionigi A, et al. Different protein intake in the first year and its effects on adiposity rebound and obesity throughout childhood: 11 years follow-up of a randomized controlled trial. Pediatr Obes. 2022;17(12):e12961.
25 Socha P, Grote V, Gruszfeld D, Janas R, Demmelmair H, Closa-Monasterolo R, et al. Milk protein intake, the metabolic-endocrine response, and growth in infancy: data from a randomized clinical trial. Am J Clin Nutr. 2011;94(6 Suppl):1776S-84S.
26 Polak P, Hall MN. mTOR and the control of whole body metabolism. Curr Opin Cell Biol. 2009;21(2):209–18.
27 Rzehak P, Grote V, Lattka E, Weber M, Gruszfeld D, Socha P, et al. Associations of IGF-1 gene variants and milk protein intake with IGF-I concentrations in infants at age 6 months – results from a randomized clinical trial. Growth Horm IGF Res. 2013;23(5):149–58.
28 Closa-Monasterolo R, Ferre N, Luque V, Zaragoza-Jordana M, Grote V, Weber M, et al. Sex differences in the endocrine system in response to protein intake early in life. Am J Clin Nutr. 2011;94(6 Suppl):1920S-7S.
29 Longo VD, Anderson RM. Nutrition, longevity and disease: from molecular mechanisms to interventions. Cell. 2022;185(9):1455–70.
30 Boguszewski CL, Boguszewski M. Growth hormone's links to cancer. Endocr Rev. 2019;40(2):558–74.
31 Newton-Tanzer E, Demmelmair H, Horak J, Holdt L, Koletzko B, Grote V. Acute metabolic response in adults to toddler milk formulas with alternating higher and lower protein and fat contents, a randomized cross-over trial. Nutrients. 2021;13(9):3022.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 1–13 (DOI: 10.1159/000534945)

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COVID-19 Pandemic and Nutrition Status in Children: A Bidirectional Negative Relation

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Abstract

The rapid spread of severe acute respiratory syndrome coronavirus 2 causing a pandemic of human coronavirus disease 2019 (COVID-19), due to which most world countries instituted a lockdown, created conditions that could in many ways negatively affect population health besides the infection itself. The aim of this chapter is to present the latest data on the trends and possible causes of under and overnutrition occurring in children during the pandemic. Furthermore, the evidence on how the changes in nutrition status impair the prognosis of COVID-19 and the most recent recommendations on nutrition treatment strategies are emphasized. Undernutrition and nutritional deficiencies were expected to increase in less developed countries, but also in underprivileged societal groups in well-developed countries, due to an increase in poverty, unemployment, and food insecurity. On the other end of the spectrum, social distancing, a decrease in physical activity, an increase in screening time, and negative changes in eating habits are also fostered during the COVID-19 pandemic, and all of them are well-known causes of pediatric obesity. Both undernutrition and obesity, per se, negatively affect the severity of COVID-19, closing the bidirectional vicious circle of causes and consequences.

Introduction

In December 2019 in Wuhan, China, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a cause of COVID-19, spreading so quickly worldwide that on March 11, 2020, the WHO declared a pandemic which officially ended in May 2023 [1]. Soon after, 186 of 193 world countries adopted a lock-down policy which varied from almost complete movement restriction to a set of restrictive measures with quarantine and isolation of affected persons. By the time of finishing this manuscript, there were 761,071,826 confirmed cases of COVID-19 recorded, as well as 6,879,677 deaths [2]. Data on children are not as precise, and it is generally accepted that around 5% of infected cases are subjects below 20 years of age. This percentage is significantly higher in the COVerAGE database, in which from February 2020 to October 2022, 367 million COVID-19 cases were recorded from 105 countries, and among them were 75.3 million affected children with over 17,400 deaths which constitute 0.4% of the 4.4 million deaths reported in the same database [3]. This clearly shows that children are relatively spared by the infection itself, and the disease is often asymptomatic and of mild course.

Yet, the COVID-19 pandemic negatively impacts children's health in a wide array of indirect modes. Economies of even the most developed countries were affected in multiple ways, with the losses projected to be worse in fragile countries and vulnerable groups. At the beginning of the COVID-19 crisis, the projection of the relevant United Nations (UN) agencies was a 7.9% decrease in the gross national income relative to pre-COVID-19 projections for low- and middle-income countries (LMICs), resulting in a 14.3% increase in the prevalence of moderate and severe wasting in children younger than 5 years, which translates into 6.7 million of wasted children in 2020 more compared to pre-COVID-19 projections. Furthermore, an increase in the number of malnourished children and the expected 25%–30% reduction in nutrition and health coverage can translate into 128,605 additional deaths in children younger than 5 years – all that in a moderate case scenario [4, 5]. The projections of the expert team from Johns Hopkins University were even worse [6].

The potentially severe negative effect of the pandemic on child nutrition status and health in the LMIC is just one side of the coin. In more affluent societies, during the COVID-19 pandemic lockdown, a decrease in physical activities, an increase in screening time, and negative changes in eating habits and food intake could be expected, and all of them are well-known causes of pediatric obesity. Finally, both undernutrition and obesity might have life-long negative health consequences, and in that respect, children are the most vulnerable population group.

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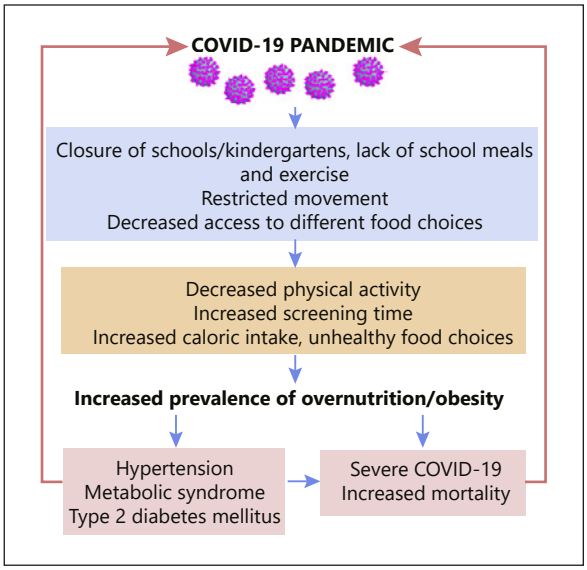

Fig. 1. Bidirectional relationship between the COVID-19 pandemic and obesity.

The projections presented above are hypothetical; however, it is now 3 years since the pandemic was proclaimed – a period that might be sufficient for relevant data to be published on the effect of the pandemic in general, and of the infection itself on the nutritional status of children. To summarize and present those data is the first aim of this chapter. The second goal is to investigate how both ends of the nutrition spectrum – undernutrition and obesity – per se, influence the severity of COVID-19 in children.

COVID-19 Pandemic and Obesity in Children (Fig. 1)

Closure of schools and kindergartens due to the COVID-19 pandemic lockdown occurred worldwide; instead of balanced school meals and a structured program of exercise, children were confined indoors. In the last 2 years, many studies were published on physical activity and screening time, comparing the periods before and during the pandemic lockdown, the majority of which consistently showed a significant decline in exercise time, physical performances, and an increase in the screening time [7–10]. However, this was not found in all studies [11] and was less present in LMIC compared to developed countries, and in younger children [12].

Equally well studied were changes in food selection and intake. Being at home, with family, could improve food quality and eating behavior, which was indeed shown in some studies [13, 14], but an overwhelming majority of evi-

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dence, originating mainly from developed countries, has shown an increase in the number of meals and unhealthy food choices such as sweet snacks, soft drinks, and bakery products [9, 10, 15–17]. Furthermore, using the national representative data on the quality of school-prepared and home-prepared lunches, with the latter having more calories and fewer valuable nutrients, and by comparing the number of school meals served from March to November 2020 with the same period in 2019, Hecht et al. found that 27–78 million fewer luncheons were served per week in the lockdown period. This huge number of missed school meals could be translated into the estimated increase of 3–10 billion additional calories per week consumed by students at the national level, and 640 calories per person per week [18].

Eight of ten studies included in the recently published systematic review reported that the changed pattern of food intake, increased screening time, and decreased physical activity resulted in a significant increase in BMI, body weight, and/or body fat [19]. The only two that did not detect the increase in obesity also reported improved adherence to healthier food choices during the pandemic [13, 14]. Finally, the multivariate regression analysis of Korean investigators identified changes in sedentary time and fast food consumption as the most important lifestyle variables associated with increased BMI in children and adolescents during the lockdown [10].

At the beginning of the COVID-19 pandemic, it has been hypothesized that the expected increase in the prevalence of obesity might have life-long consequences such as increased risks for metabolic syndrome and type 2 diabetes mellitus (T2DM). The above-cited Korean study, besides increased BMI, has already detected increased systolic and diastolic blood pressure and insulin resistance [10], and similar findings on the increased blood pressure were found also in Chinese school-aged children [20]. The narrative review of Capra et al. summarized results of several studies – all from the United States of America, reporting on the increased incidence of newly diagnosed T2DM in children during the pandemic in comparison with the prepandemic years [21].

The final issue in the possible bidirectional relationship between obesity and COVID-19 is whether children duplicate the well-documented risk of the worse clinical outcome in infected obese adult patients [22]. Early studies such as the one from China [23] already indicated that obesity in children could be associated with an increased risk of mortality, but much more evidence was provided by the systematic review and meta-analysis by Tsankov et al. who investigated the effect of comorbidities on the clinical outcome of COVID-19 in pediatric patients [24]. Summarizing the evidence from 42 pediatric case-control studies with 285,004 pediatric patients with laboratory-confirmed SARS-CoV-2 infection among which 9,353 (3.3%) had at least one comorbidity, the authors ob-

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tained the following results: (a) significantly increased risk for severe clinical presentation (RR 1.79, 95% CI: 1.27–2.51, $p < 0.001$) in COVID-19 patients with comorbidities; (b) significantly increased risk of mortality in children with comorbidities relative to pediatric patients without them (RR 2.81, 95% CI: 1.31–6.02, $p < 0.001$); (c) obesity was the most frequent comorbidity, and the obese infected children were more prone to develop severe COVID-19, although this difference was not significant (RR 2.87, 90% CI: 1.16–7.07, $p = 0.17$) [24]. Discussing the causal relationship between obesity and more severe clinical outcomes in COVID-19 patients, Steenblock et al. underlined the superposition of acute COVID-19–related inflammation on the obesity-driven chronic proinflammatory status, pulmonary consequences of adiposity resulting in reduced respiratory function, and the predisposing changes in SARS-CoV-2 entry receptors, namely at angiotensin-converting enzyme two domains [25].

In conclusion, dramatic changes in the daily routines of children during the COVID-19 pandemic, which affected feeding habits, food choices, and total energy intake, paralleled by a decrease in physical activity and an increase in screening time, are the most probable causes for the already detected increase in obesity prevalence. Further longitudinal studies will answer whether this will result in increased long-term consequences such as hypertension and T2DM/metabolic syndrome, but regrettably, the first published data indicate this scenario. Furthermore, the already published data do relate obesity to the worse clinical outcome of COVID-19 in children and this negative relationship is shown in Figure 1.

COVID-19 Pandemic and Undernutrition in Children (Fig. 2)

In the year 2020, all major UN agencies issued grave projections for the impact of COVID-19–related lockdowns on the nutrition status of children, mainly through its negative effects on the countries' economies and therefore reduced nutrition and health coverage [4–6]. Now – 3 years later – the relevant scientific data are expected to be available. Yet, authors of the systematic review on the impact of the COVID-19 pandemic on food security and quality, whose primary research goal was to investigate how it affected the nutrition status of children below 5 years and women/girls of childbearing age, could not find a single study designed to monitor this in LMIC (literature search done until January 2021) [26]. However, despite important heterogeneity of 35 included studies, the authors were able to summarize the detrimental effects of pandemic conditions on food security and diet quality across a wide range of LMIC, mainly associated with diminished income and purchasing power, unemployment, and failed

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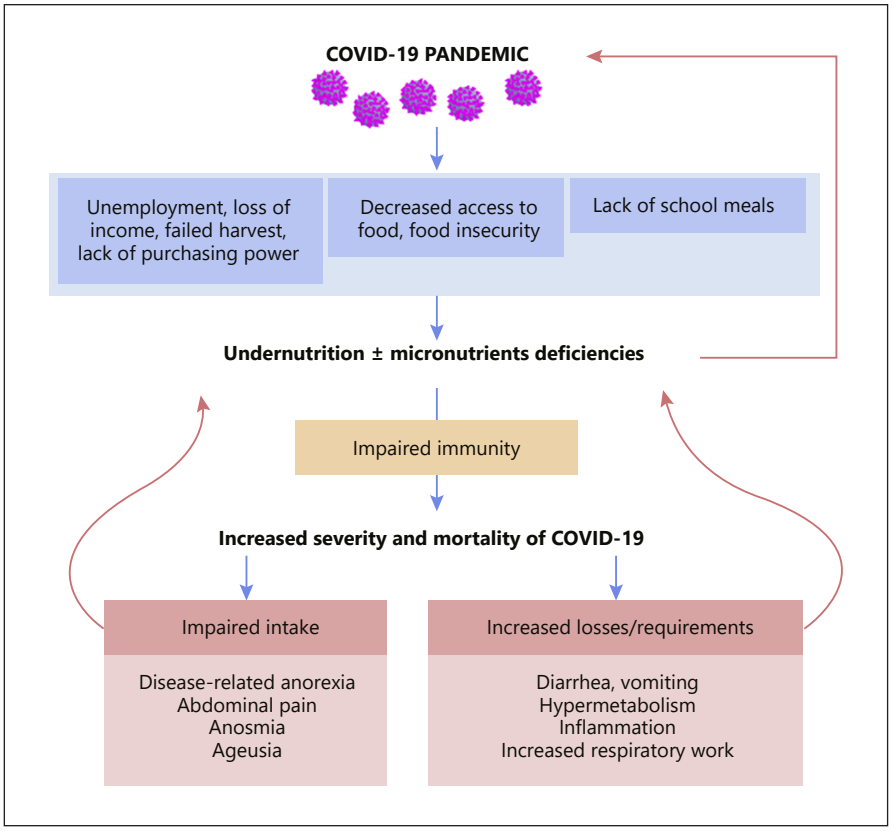

Fig. 2. Vicious circle of COVID-19 pandemic and undernutrition.

harvests, but also through lack of physical access and availability of foods. In countries where the prepandemic data were available, food insecurity increased from 51% to 77% in Nigeria, from 50% to 88% in Kenya, 43% to 87% in Uganda, and 6% to 36% in Bangladesh (summarized in Picchioni et al. [26]). Since then, a longitudinal study was recently published comparing the sanitation, hygiene, health, and nutrition status of 490 children 0–10 years from two different remote regions in Nepal, before the pandemic and during it (March–May 2018 and November–December 2021) [27]. The results have shown a significant improvement in sanitation/hygiene practices and water quality in the COVID-19 period, and a significant reduction in infectious diseases including diarrhea (19.6% to 9.5%, $p = 0.01$), respiratory illnesses (14.3% to 4.3%, $p = 0.002$), fever (41.1% to 16.8%, $p = 0.01$), and Giardia lamblia infection (34.2% to 6.5%, $p = 0.01$). Despite those positive results, data on the nutrition status in comparison to the prepandemic period were particularly grave: severe stunting increased from 26.6% to

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48.5% (p = 0.01), underweight increased from 19.0% to 54.9% (p = 0.01), frequency of Bitot's spots from 26.7% to 40.2% (p = 0.01), hair depigmentation from 13.3% to 41.1% (p = 0.01), dry cornea from 19.4% to 36.7% (p = 0.01), and bleeding gums increased from 17.8% to 66.7% (p = 0.01). The identified underlying causes were an increase in poverty and a lack of purchasing power due to inadequate harvests, unemployment, and loss of wages which occurred in 94.2% during the pandemic in comparison to 35% in the year 2018 [27]. Although this study is one of the first published and more results are awaited, it seems that the worst-case scenarios, predicted at the beginning of the pandemic, might be true. A further "brick in the wall" is the problem of missing school meals due to school closure; 369 million children missed meals only in April 2020, while in June 2021 the same occurred in 154 million children from 79 countries [28]. In contrast to fostering obesity development in developed countries where meals at home tend to be more caloric, in the LMIC the school meal might be the only proper food children are consuming during the day.

The next relevant question is, whether malnourished patients have an increased risk of acquiring infection with SARS-CoV-2 and if their clinical outcome is further impaired. It is very plausible to positively answer both questions as it is scientifically well established that undernutrition negatively affects immunity, particularly the cellular arm [29], increasing, therefore, the risk of acquiring infections [30] including those nosocomial [31], morbidity, mortality, length of hospital stay, and costs of health care [32]. With respect to the clinical outcome of COVID-19, Kurtz et al. retrieved data for 103,099 COVID-19 inpatients from 56 hospitals in the United States between March and June 2020 and found higher odds for severe outcomes for children between 6 and 17 years with a history of malnutrition: 1.5% of children with mild COVID-19 were malnourished compared to 7.5% among those with severe COVID-19 [33]. In the retrospective study of 1,024 children hospitalized in a tertiary care setting in Kerala, India, from March 2020 to September 2021, the most important comorbidities significantly associated with severe COVID-19 were neurological conditions (OR = 8.73), malnutrition (OR = 3.01), and prematurity (OR = 6.8) [34]. Reviewing the literature on the effects of malnutrition on the thymus and immunity in COVID-19 patients, it was suggested that malnutrition-induced thymic atrophy and immune dysfunction may increase the risk of progression of COVID-19 to more severe forms, slow the recovery, and increase the risk of other infections [35]. Furthermore, once the child acquires COVID-19, there are several pathways by which the disease itself initiates and/or further increases the risk of undernutrition [36] which are depicted in Figure 2.

In conclusion, the COVID-19 pandemic with the imposed restrictive measures affects the economic power of the country and the purchasing power of

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individual households. This inevitably results in food insecurity and decreased nutrition and health coverage in the LMIC, further impairing the nutrition status of vulnerable groups such as children and women of childbearing age. Undernutrition increases the risk of severe COVID-19 clinical presentation, while the disease itself in various ways increases the risk of further nutritional deterioration, closing thereby the vicious circle of causes and consequences as shown in Figure 2.

Nutrition Approach to Children with SARS-CoV-2 Infection, and during the COVID-19 Pandemic

Awareness of the negative immediate and long-term effects of malnutrition in children (both under, and overnutrition) and the necessity for an early evaluation of the nutritional status have a pivotal role, irrespective if this is during the COVID-19 pandemic or any other health condition [37]. This is also the initial step in the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for the nutritional management of individuals with SARS-CoV-2 infection, followed by the recommendation for stepwise nutritional interventions with respect to the severity of the disease: (a) advice for optimization of oral nutrition intake; (b) supplementation with vitamins and minerals in subjects with malnutrition; (c) regular physical activity; (d) addition of oral nutrition supplements if nutrition intake is still suboptimal; (e) enteral nutrition in subjects with a functioning gut who cannot have adequate oral intake; (f) addition of parenteral nutrition in cases when oral/enteral access is insufficient, which further varies with respect to the severity of COVID-19 (ICU patients ± intubated patients ± patients with dysphagia) [38].

With respect to children, the cited ESPEN recommendations do not differ from the "pyramid of nutrition interventions" recommended to pediatric patients in general [39], which can therefore also be applied to children infected with the SARS-CoV-2. In addition, public health measures such as age-appropriate physical activity, restriction of the screening time, and a balanced diet should be applied to all, otherwise "healthy" children, particularly those who are overweight/obese [40].

A special issue in the nutrition approach to the COVID-19 pandemic is whether to suggest supplementation with micronutrients, particularly those with antioxidant properties, and if yes, to whom – all exposed, only to diseased individuals or just for malnourished deficient pediatric patients? Micronutrients are involved in literally every arm of innate and adaptive immunity, and there is already a wealth of literature on their potential role in the pathogenicity of

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SARS-CoV-2 infection [36, 41]. However, randomized controlled trials on their use in the treatment of COVID-19 are scarce, and the scientific evidence for children is nonexistent. Authors of the systematic review on the role of nutrients in general, and vitamins and minerals in particular in COVID-19 treatment, concluded that the evidence for the use of high-dose supplementation of micronutrients for either prevention or treatment is too limited to be recommended [41]. It is therefore prudent to continue "Doing what we know, and doing it well," which is, to continue with the public health measures to prevent micronutrient deficiencies and to diagnose and treat them early, particularly in malnourished children. With respect to nondeficient children, there is no evidence that the supplementation can improve the clinical outcome of COVID-19 [36, 38, 41].

There are also global nutrition strategies proposed for exceptional situations such as the COVID-19 pandemic, created to prevent further deterioration in food insecurity and food shortage, but their presentation is beyond the scope of this review [42, 43].

Conclusion

The COVID-19 pandemic set the stage that fosters the development of undernutrition and obesity in children, depending on the economic power of the country and the socioeconomic strata of the individual patient. Furthermore, both obesity and undernutrition through different pathogenic mechanisms increase the risk of more severe clinical presentation of COVID-19, closing therefore a vicious circle of causes and consequences (Fig. 1 and 2). Awareness of the importance of nutrition status in children, early nutrition assessment, and timely instituted nutrition support at a more general population level, and also in individual patients with COVID-19, is the therapeutic milestone, while the future scientific evidence will indicate more detailed nutrition approaches.

Conflict of Interest Statement

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References

1 Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91(1):157–60.
2 World Health Organization. WHO Coronavirus (COVID-19) Dashboard; 2023. Available from: https://covid19.who.int/.
3 UNICEF. COVID-19 confirmed cases and deaths: age- and sex-disaggregated data; 2022. Available from: https://data.unicef.org/resources/covid-19-confirmed-cases-and-deaths-dashboard/.
4 Headey D, Heidkamp R, Osendarp S, Ruel M, Scott N, Black R, et al. Impacts of COVID-19 on childhood malnutrition and nutrition-related mortality. Lancet. 2020;396(10250):519–21.
5 UNICEF. Tracking the situation of children during COVID-19; 2021. Available from: https://data.unicef.org/resources/rapid-situation-tracking-covid-19-socioeconomic-impacts-data-viz/.
6 Roberton T, Carter ED, Chou VB, Stegmuller AR, Jackson BD, Tam Y, et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modeling study. Lancet Glob Health. 2020;8(7):e901–8.
7 Kidokoro T, Tomkinson GR, Lang JJ, Suzuki K. Physical fitness before and during the COVID-19 pandemic: results of annual national physical fitness surveillance among 16,647,699 Japanese children and adolescents between 2013 and 2021. J Sport Health Sci. 2022;12(2):246–54.
8 Ostermeier E, Tucker P, Clark A, Seabrook JA, Gilliland J. Parents' report of Canadian Elementary School children's physical activity and screen time during the COVID-19 pandemic: a longitudinal study. Int J Environ Res Public Health. 2021;18(23):12352.
9 Hanbazaza M, Wazzan H. Changes in eating habits and lifestyle during COVID-19 curfew in children in Saudi Arabia. Nutr Res Pract. 2021;15(Suppl 1):S41–52.
10 Woo S, Yang H, Kim Y, Lim H, Song HJ, Park KH. Sedentary time and fast-food consumption associated with weight gain during COVID-19 lockdown in children and adolescents with overweight or obesity. J Korean Med Sci. 2022;37(12):e103.
11 Kellstedt DK, Essay AM, Schenkelberg MA, Rosen MS, Von Seggern MJ, Idoate R, et al. COVID-19 pandemic and changes in children's physical activity in a rural US community: a mixed methods study. BMJ Open. 2022;12(10):e062987.
12 Okely AD, Kariippanon KE, Guan H, Taylor EK, Suesse T, Cross PL, et al. Global effect of COVID-19 pandemic on physical activity, sedentary behavior and sleep among 3- to 5-year-old children: a longitudinal study of 14 countries. BMC Public Health. 2021;21(1):940.
13 Łuszczki E, Bartosiewicz A, Pezdan-Śliż I, Kuchciak M, Jagielski P, Oleksy Ł, et al. Children's eating habits, physical activity, sleep, and media usage before and during COVID-19 pandemic in Poland. Nutrients. 2021;13(7):2447.
14 Medrano M, Cadenas-Sanchez C, Oses M, Arenaza L, Amasene M, Labayen I. Changes in lifestyle behaviors during the COVID-19 confinement in Spanish children: A longitudinal analysis from the MUGI project. Pediatr Obes. 2021;16(4):e12731.
15 Koletzko B, Holzapfel C, Schneider U, Hauner H. Lifestyle and body weight consequences of the COVID-19 pandemic in children: increasing disparity. Ann Nutr Metab. 2021;77(1):1–3.
16 Ruiz-Roso MB, de Carvalho Padilha P, Mantilla-Escalante DC, Ulloa N, Brun P, Acevedo-Correa D, et al. Covid-19 confinement and changes of adolescent's dietary trends in Italy, Spain, Chile, Colombia and Brazil. Nutrients. 2020;12(6):1807.
17 Pujia R, Ferro Y, Maurotti S, Khoory J, Gazzaruso C, Pujia A, et al. The effects of COVID-19 on the eating habits of children and adolescents in Italy: a pilot survey study. Nutrients. 2021;13(8):2641.
18 Hecht AA, Dunn CG, Kinsey EW, Read MA, Levi R, Richardson AS, et al. Estimates of the nutritional impact of non-participation in the National School Lunch Program during COVID-19 school closures. Nutrients. 2022;14(7):1387.
19 Karatzi K, Poulia K-A, Papakonstantinou E, Zampelas A. The impact of nutritional and lifestyle changes on body weight, body composition and cardiometabolic risk factors in children and adolescents during the pandemic of COVID-19: a systematic review. Children. 2021;8(12):1130.
20 Qiu N, He H, Qiao L, Ding Y, Ji S, Guo X, et al. Sex differences in changes in BMI and blood pressure in Chinese school-aged children during the COVID-19 quarantine. Int J Obes. 2021;45(9):2132–6.
21 Capra ME, Stanyevic B, Giudice A, Monopoli D, Decarolis NM, Esposito S, et al. The effects of COVID-19 pandemic and lockdown on pediatric nutritional and metabolic diseases: a narrative review. Nutrients. 2023;15(1):88.
22 Steenblock C, Schwarz PEH, Ludwig B, Linkermann A, Zimmet P, Kulebyakin K, et al. COVID-19 and metabolic disease: mechanisms and clinical management. Lancet Diabetes Endocrinol. 2021;9(11):786–98.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 14–24 (DOI: 10.1159/000534966)

23 Zhang F, Xiong Y, Wei Y, Hu Y, Wang F, Li G, et al. Obesity predisposes to the risk of higher mortality in young COVID-19 patients. J Med Virol. 2020;92(11):2536–42.
24 Tsankov BK, Allaire JM, Irvine MA, Lopez AA, Sauvé LJ, Vallance BA, et al. Severe COVID-19 infection and pediatric comorbidities: a systematic review and meta-analysis. Int J Infect Dis. 2021;103:246–56.
25 Steenblock C, Hassanein M, Khan E, Yaman M, Kamel M, Babir M, et al. Obesity and COVID-19:what are the consequences? Horm Metab Res. 2022;54:496–502.
26 Picchioni F, Goulao LF, Roberfroid D. The impact of COVID-19 on diet quality, food security and nutrition in low and middle income countries: a systematic review of the evidence. Clin Nutr. 2022;41(12):2955–64.
27 Shrestha A, Kunwar BM, Meierhofer R. Water, sanitation, hygiene practices, health and nutritional status among children before and during the COVID-19 pandemic: longitudinal evidence from remote areas of Dailekh and Achham districts in Nepal. BMC Public Health. 2022;22(1):2035.
28 World Food Programme. Global monitoring of school meals during COVID-19 school closures; 2023. Available from: https://cdn.wfp.org/2020/school-feeding-map/index.html.
29 Rytter MJH, Kolte L, Briend A, Friis H, Christensen VB. The immune system in children with malnutrition – a systematic review. PLoS One. 2014;9(8):e105017.
30 Kirolos A, Blacow RM, Parajuli A, Welton NJ, Khanna A, Allen SJ, et al. The impact of childhood malnutrition on mortality from pneumonia: a systematic review and network meta-analysis. BMJ Glob Health. 2021;6(11):e007411.
31 Niseteo T, Hojsak I, Kolaček S. Malnourished children acquire nosocomial infections more often and have significantly increased length of hospital stay. Clin Nutr. 2020;39(5):1560–3.
32 Guenter P, Abdelhadi R, Anthony P, Blackmer A, Malone A, Mirtallo JM, et al. Malnutrition diagnoses and associated outcomes in hospitalized patients: United States, 2018. Nutr Clin Pract. 2021;36(5):957–69.
33 Kurtz A, Grant K, Marano R, Arrieta A, Grant K, Feaster W, et al. Long-term effects of malnutrition on severity of COVID-19. Sci Rep. 2021;11(1):14974.
34 Muthusamy S, Sarojam B, Sugunan S, Krishna G, Bindusha S, Ajith Krishnan AK. Clinical profile and short-term outcome of children with acute SARS-CoV-2 infection during the first and second waves of the pandemic. Indian J Pediatr. 202390(5):443–9.
35 Chiang KC, Kalantar-Zadeh K, Gupta A. Thymic dysfunction and atrophy in COVID-19 disease complicated by inflammation, malnutrition and cachexia. Nutr Health. 2022;28(2):199–206.
36 Spolidoro GCI, Azzolino D, Shamir R, Cesari M, Agostoni C. Joint effort towards preventing nutritional deficiencies at the extremes of life during COVID-19. Nutrients. 2021;13(5):1616.
37 Hulst JM, Huysentruyt K, Gerasimidis K, Shamir R, Koletzko B, Chourdakis M, et al. A practical approach to identifying pediatric disease-associated undernutrition: a position statement from the ESPGHAN Special Interest Group on Clinical Malnutrition. J Pediatr Gastroenterol Nutr. 2022;74(5):693–705.
38 Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr. 2020;39(6):1631–8.
39 Koletzko Berthold GO. Nutrition support in infants, children, and adolescents. In: Luboš S, editor. Basics in clinical nutrition. Prague: Galen; 2019. Vol. 5.
40 Scapaticci S, Neri CR, Marseglia GL, Staiano A, Chiarelli F, Verduci E. The impact of the COVID-19 pandemic on lifestyle behaviors in children and adolescents: an international overview. Ital J Pediatr. 2022;48(1):22.
41 James PT, Ali Z, Armitage AE, Bonell A, Cerami C, Drakesmith H, et al. The role of nutrition in COVID-19 susceptibility and severity of disease: a systematic review. J Nutr. 2021;151(7):1854–78.
42 Sotiraki M, Malliou A, Tachirai N, Kellari N, Grammatikopoulou MG, Sergentanis TN, et al. Burden of childhood malnutrition: a roadmap of global and European policies promoting healthy nutrition for infants and young children. Children. 2022;9(8):1179.
43 Akseer N, Kandru G, Keats EC, Bhutta ZA. COVID-19 pandemic and mitigation strategies: implications for maternal and child health and nutrition. Am J Clin Nutr. 2020;112(2):251–6.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 14–24 (DOI: 10.1159/000534966)

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Breast Milk, Mother, and Infant Triad as a Biological Complex

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Abstract

Human milk is the optimal food for the growing infant and breastfeeding has been associated with short- and long-term benefits for both infant and mother. Human milk composition is adapted to stages of infant development from the immunologically rich colostrum to energy dense mature milk. Recent studies have shown that the time of lactation, circadian rhythm, maternal diet, genetics, and even presence of maternal or infant infection can influence milk composition. Human milk, however, is not just a sum of single nutrients but a complex biofluid rich and organized in potentially functional and not just nutritive structures like exosomes, bacteria, and eukaryotic cells. The complexity of human milk, its importance for infant health, and development call for future research investments to characterize deeper milk composition beyond single nutrients to understand their function. Building global and regional references for human milk will also enable a better insight in nutrition requirements, inform guidelines, and provide recommendations adapted to lactating mothers.

Introduction

Human milk is the optimal food for the growing infant as recognized by the World Health Organization and global recommendations aim to guide health practitioners and the public to adopt exclusive breastfeeding for at least the first 6 months of life and optimally continue breastfeeding until at least 2 years of age

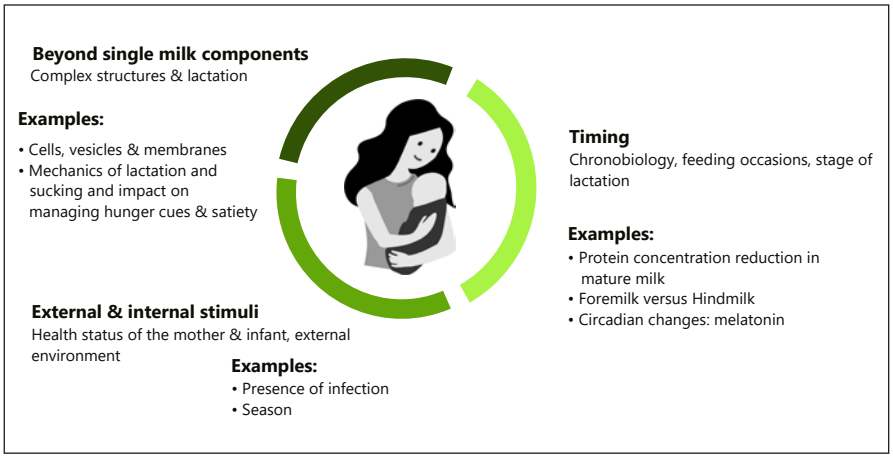

Fig. 1. Breast milk is a complex fluid reflecting mother and infant interaction and it is adapted to baby needs.

[1]. Exclusive breastfeeding is defined as infant feeding that includes only breast milk and no additional water, other liquids, and foods (excluding medications) during the first 6 months of life. Several health benefits have been associated with breastfeeding for both child and the lactating mother [2]. Breast milk is recommended food for optimal growth during infancy and beyond and several studies have reported a benefit in preventing overweight or obesity later in life [3, 4]. Heterogeneity exists among the published results due to differences in study design, time-points for samples, and data collection, while the observational nature of the studies needs to account for the role of confounders, effect modifiers, or reverse causality. Most recent meta-analyses confirm a protective effect against overweight or obesity even among those studies that are susceptible to positive confounding accounting for socioeconomic status [5]. Breastfed infants have less risk to common pediatric infections, like pneumonia, ear infections, and diarrhea compared to nonbreastfed [6]. Breastfeeding also confers short- and long-term health benefits for the lactating mother, reducing the risk for postpartum depression, both breast and ovarian cancer, and type 2 diabetes [7]. Breastfeeding can have an impact on behavioral components beyond delivery of infant feeding with recent epidemiological studies pointing out that breastfed infants develop healthier choices later in life than formula fed having more opportunities for flavor learning and preference development via exposure to maternal dietary flavors during breastfeeding. These effects may partly explain the protective role of breastfeeding against overweight and obesity [8].

Human milk carries probably thousands of nutrients or metabolites with a specific bioactivity defined by maternal exposures and infant developmental

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needs [9], transforming mother-milk-child as an active and dynamic triad delivering health benefits for both mother and infant. In order to better understand the biology and the functionality of human milk components, we need to look beyond single nutrients and concentrations and consider human milk as a bioactive system consisting of complex structures like macrovesicles, milk fat globules, and living cells (Fig. 1) [10]. Then, we need to account for human milk composition changes over the day, between feeding occasions and across lactation. Finally, considerations of both health status of the mother and infant as well as the external environment will inform the relationship between milk production, delivery, and perceived benefit by the growing infant. In the next sections, evidence on the role of these specific components will be discussed, as well directions for future research.

Time Defines Human Milk Composition

Temporal changes are clearly described in the literature for human milk composition per feeding occasion, during the day and along lactation. Differences between foremilk (the first fraction of milk after flow initiation, usually 2–3 min) and hindmilk (the remainder of the milk until breast emptying) have been described for the fat content and vitamins A and E [11, 12]. As milk is produced, milk fat globules aggregate and attach to the walls of the alveoli resulting in foremilk having a low-fat content. Breast emptying results into milk fat globules detaching and moving down milk ducts making hindmilk rich in fat. Recent studies have shown that hindmilk contains higher number of unique peptides compared to foremilk possibly due to longer exposure to intramammary gland proteolytic activity although total peptide abundance remains similar [13].

Human milk changes in relation to circadian, ultradian, or diurnal rhythms sometimes follow maternal hormonal variation. The most well-studied examples are hormones melatonin and cortisol. Milk melatonin peaks at night matching maternal serum levels [14], while cortisol is over 300% higher in morning milk (2.97 ng/mL) compared to late afternoon and evening milk (0.69 ng/mL) likely reflecting concentrations in maternal circulation [15, 16]. Exogenous melatonin administration in preterm infants has been studied to compensate for the reported deficiency and to protect from oxidative stress injury commonly reported in this population [17]. These large differences in melatonin concentration between day and night should be considered in both clinical and feeding protocols for infants, especially preterm, as providing mistimed milk may not deliver the full benefits for the growing infant.

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Changes in milk composition over lactation are the ones most commonly and comprehensively described. Fat content has been described to slightly increase over lactation, while protein concentration sharply decreases after colostrum and remains stable after 4 months of lactation [18–20]. Lactose remains stable, while human milk oligosaccharides (HMOs) present with specific trajectories influenced by maternal genetic polymorphisms on the fucosyltransferase 2 and 3 (FUT2 and FUT3) genes [21].

The studies discussed above can be used to highlight the limitations of current literature where absence of common or standardized milk collection protocols impacts results and their application on maternal and infant recommendations for staged-matched or circadian-matched milk feeding. Variability in milk composition over time established across multiple observational studies reflects infant developmental needs that may not be understood or met by not accounting for time and process of milk sampling.

More than Single Nutrients or Bioactives, Human Milk Includes Complex Structures

Human milk contains living cells both from bacterial and host origin [22]. Most eukaryotic cells consist of distinct epithelial lactocyte subpopulations, then blood cells mainly immune cells like monocytes, T and B cells, myoepithelial cells, and a proportion of progenitor and stem cells. A recent study by Nyquist et al. [23], using single-cell RNA-sequencing, identified how different cell populations evolve over lactation. Analyzing associations with maternal and infant meta-data showed that a specific group of lactocytes are increased over time and are associated with daycare attendance and the use of hormonal birth control. These first results are key to understand how mammary gland changes with time and what may be the influence of external stimuli to the milk production.

Another complex structure found abundantly in the milk are extracellular vesicles (approximately 100–1,000 nm) and specifically exosomes (approximately 40–150 nm) [24]. These are lipid bilayer particles secreted by predominantly mammary gland epithelial cells into extracellular space as a means of transport of cargos including lipids, proteins, and nucleic acids to recipient cells. Their importance for cellular communication and impact on physiological and cellular processes is studied in different biological aspects. Milk exosomes functions are not well understood; however, considering the bioactive component cargos renders them possibly as one of the functional structures found in human milk. One of the most prominent groups of molecules found in the exosomes are microRNAs, small, single stranded, noncoding RNA molecules (21–23 nu-

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cleotides long), known as major epigenetic regulators controlling posttranscriptional regulation of gene expression. A recent study has extracted and analyzed the profile of human milk exosomal miRNAs content from the second week until the third month after birth, reporting that they change over lactation and are mainly associated with innate and adaptive immunity pathways regulation [25]. Interestingly in this study, a stable core of 35 miRNAs consistently highly expressed was identified as well as a set of miRNA with a very dynamic and variable expression. The coauthors did not report any associations with maternal and infant meta-data.

Maternal and Infant Factors Modify Milk Composition

The impact or association of maternal characteristics and infant outcomes on human milk composition have been investigated and reviewed in recent publications [26]. Maternal diet can affect at least the fatty acid composition of human milk with omega-3 intake during lactation having a positive association with milk fatty acid profile across studies even with different design and methodological approaches. Maternal intake of certain vitamins and minerals like vitamins B1, B2, B3, B6, B12, C, A, D, and selenium and iodine, respectively, seems to influence their concentration in human milk. On the other hand, certain minerals like sodium, potassium, phosphorous and zinc, folate, and macronutrients like lactose remain stable and unaffected by dietary changes.

Body mass index, typically defined before pregnancy, the maternal age, parity, as well as gestational age and infant sex are common factors considered in most observational studies on human composition with little consistency on either the direction or strength of association with milk composition. Results from these reports may be challenging to interpret in light of study design, methodological differences, and also temporal changes described earlier in this review. Wherever possible, cell numbers, nutrients, or bioactive molecule concentrations need to be interpreted together with maternal and infant health metadata.

A study that aimed to describe the dynamics of leukocytes present in human milk discovered that both maternal and infant infection can modulate the number and profile of the cellular population [27]. The study reported that leukocyte number is higher in colostrum (13%–70% out of total cells) compared to mature milk (0%–2%) unless there is an infection for either mother or infant during which the number increases as expected (up to 94% leukocytes out of total cells, $p < 0.001$). Using maternal meta-data, a trend toward a specific leukocyte profile was seen in the presence of mastitis compared to other types of infections. With

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the resolution of the infection, cell numbers returned to baseline. Exclusive breastfeeding was also associated with a greater number of leukocytes in mature breast milk.

Geography has not been systematically used to compare human milk composition or concentration of milk components [28]. McGuire et al., reported that specific HMO like disialyllacto-*N*-tetraose and 3-fucosyllactose were significantly different in milk from Swedish mothers compared to milk of mothers living in rural Gambia [28]. Geography however may be a proxy for genetic variability, dietary differences and abundance of food, cultural practices during lactation, and even climate adaptation. Whereas in well-nourished populations of lactating mothers, seasonal differences seem to play little role in milk composition, in geographies with very distinctive climatic influence on food abundances this may not be the case. Human milk of Gambian mothers nursing during the wet season, characterized by reduced food availability, had significantly lower concentration of total measured HMOs compared to milk from mothers nursing during the dry season, when food abundance is higher [29]. These results show that the role of external factors human milk may be geography or population specific and it can definitely not be generalized.

Future Research Directions to Understand How Milk Adapts to Infant Needs via Maternal Interventions

Current literature on human milk provides with an overview of consistent and well-described milk composition variation over lactation mainly for macronutrients. Circadian, ultradian, or diurnal rhythms are studied for a limited number of milk components like hormones or sometimes minerals and macronutrients with limited consistency among studies. There is, therefore, a general lack of systematic approaches to assess or consider all types of temporal dynamics in human milk composition. Then, there is an evident heterogeneity among studies, protocols for milk collection, and methods used to analyze milk composition, making it hard to interpret the totality of evidence across different studies. Standardization among study protocols and perhaps proposition or at least recommendations for specific methodologies would reduce inconsistencies for results interpretation and favor a more systematic overview of human milk composition among researchers.

Observational studies on human milk composition remain, in most of the times, on the simple descriptive analyses of nutrient or bioactives concentrations without integrating available maternal and infant meta-data. Reporting on single molecules and single time-point associations does not allow to under-

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stand how these compositional changes likely reflect developmental needs of the growing baby or maternal health status. Dedicated studies with clear and well-captured maternal and infant health outcomes, as well as other epidemiological factors, may be more suitable to enable data mining exercises considering groups of nutrients or complex. In contrast, caution is needed when such approaches are used for analyses on limited or inadequately defined phenotypic data from studies with little power.

Most of the literature is based on studies with well-nourished, healthy mothers and infants recruited from limited geographies. Evidence, however, indicates that milk dynamically changes in the presence of infections, metabolic status of the mother, and in response to food scarcity, a prominent condition in certain parts of the world. As breastfeeding is the optimal and most affordable solution for infant feeding, understanding the compositional specificities in different health subgroups can inform better the recommendations for lactating mothers.

Future studies need to consider standardized approaches for the design, collection, and sample and data analyses for the deep characterization of both composition and function of milk components. Milk reference values, if feasible to construct considering limitations in study heterogeneity, need to account for expected variability across lactation stages, geographies, heath, and ethnic background. Ultimately, strong compositional evidence will facilitate the design of maternal interventions to further understand the impact on infant growth and development. The clinical significance of advancing the field of human milk research could be immense and applicable for children who are breastfed, infant formula fed, and human milk bottle fed. Refined nutritional needs for lactating mothers, adapted per stage and need, can be developed. Support to safe and efficacious human milk substitutes or infant supplements and an optimized use of donor and banked milk will be achievable. Overall, the knowledge will be used across for improved infant feeding and breastfeeding support.

Conflict of Interest Statement

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References

1 WHO/UNICEF. Breastfeeding counseling: a training course. Geneva: World Health Organization; 1993.
2 Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475–90.
3 Horta BL, de Lima NP. Breastfeeding and type 2 diabetes: systematic review and meta-analysis. Curr Diab Rep. 2019;19(1):1.
4 Horta BL, Loret de Mola C, Victora CG. Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. Acta Paediatr. 2015;104(467):30–7.
5 Horta BL, Rollins N, Dias MS, Garcez V, Pérez-Escamilla R. Systematic review and meta-analysis of breastfeeding and later overweight or obesity expands on previous study for World Health Organization. Acta Paediatr. 2023;112(1):34–41.
6 Horta BL, Victora CG. Short-term effects of breastfeeding: a systematic review of the benefits of breastfeeding on diarhoea and pneumonia mortality. Geneva: World Health Organization; 2013.
7 Chowdhury R, Sinha B, Sankar MJ, Taneja S, Bhandari N, Rollins N, et al. Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. Acta Paediatr. 2015;104(467):96–113.
8 Ventura AK. Does breastfeeding shape food preferences? Links to obesity. Ann Nutr Metab. 2017;70(Suppl 3):8–15.
9 Baumgartel K, Stevens M, Vijayakumar N, Saint Fleur A, Prescott S, Groer M. The human milk metabolome: a scoping literature review. J Hum Lact, 2023;39(2):255–77.
10 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.
11 Valentine CJ, Hurst NM, Schanler RJ. Hindmilk improves weight gain in low-birth-weight infants fed human milk. J Pediatr Gastroenterol Nutr. 1994;18(4):474–7.
12 Bishara R, Dunn MS, Merko SE, Darling P. Volume of foremilk, hindmilk, and total milk produced by mothers of very preterm infants born at less than 28 weeks of gestation. J Hum Lact. 2009;25(3):272–9.
13 Nielsen SD, Beverly RL, Dallas DC. Peptides released from foremilk and hindmilk proteins by breast milk proteases are highly similar. Front Nutr. 2017;4:54.
14 Illnerova H, Buresova M, Presl J. Melatonin rhythm in human milk. J Clin Endocrinol Metab. 1993;77(3):838–41.
15 Pundir S, Wall CR, Mitchell CJ, Thorstensen EB, Lai CT, Geddes DT, et al. Variation of human milk glucocorticoids over 24 hour period. J Mammary Gland Biol Neoplasia. 2017;22(1):85–92.
16 Italianer MF, Naninck EFG, Roelants JA, van der Horst GTJ, Reiss IKM, Goudoever JBV, et al. Circadian variation in human milk composition, a systematic review. Nutrients. 2020;12(8):2328.
17 Marseglia L, Gitto E, Laschi E, Giordano M, Romeo C, Cannavò L, et al. Antioxidant effect of melatonin in preterm newborns. Oxid Med Cell Longev. 2021;2021:6308255.
18 Lonnerdal B, Erdmann P, Thakkar SK, Sauser J, Destaillats F. Longitudinal evolution of true protein, amino acids and bioactive proteins in breast milk: a developmental perspective. J Nutr Biochem. 2017;41:1–11.
19 Giuffrida F, Cruz-Hernandez C, Bertschy E, Fontannaz P, Masserey Elmelegy I, Tavazzi I, et al. Temporal changes of human breast milk lipids of Chinese mothers. Nutrients. 2016;8(11):715.
20 Thakkar SK, De Castro CA, Beauport L, Tolsa JF, Fischer Fumeaux CJ, Affolter M, et al. Temporal progression of fatty acids in preterm and term human milk of mothers from Switzerland. Nutrients. 2019;11(1):112.
21 Samuel TM, Binia A, de Castro CA, Thakkar SK, Billeaud C, Agosti M, et al. Impact of maternal characteristics on human milk oligosaccharide composition over the first 4 months of lactation in a cohort of healthy European mothers. Sci Rep. 2019;9(1):11767.
22 Witkowska-Zimny M, Kaminska-El-Hassan E. Cells of human breast milk. Cell Mol Biol Lett. 2017;22:11.
23 Nyquist SK, Gao P, Haining TKJ, Retchin MR, Golan Y, Drake RS, et al. Cellular and transcriptional diversity over the course of human lactation. Proc Natl Acad Sci U S A. 2022;119(15):e2121720119.
24 Chutipongtanate S, Morrow AL, Newburg DS. Human milk extracellular vesicles: a biological system with clinical implications. Cells. 2022;11(15):2345.
25 Raymond F, Lefebvre G, Texari L, Pruvost S, Metairon S, Cottenet G, et al. Longitudinal human milk miRNA composition over the first 3 mo of lactation in a cohort of healthy mothers delivering term infants. J Nutr. 2022;152(1):94–106.
26 Samuel TM, Zhou Q, Giuffrida F, Munblit D, Verhasselt V, Thakkar SK. Nutritional and non-nutritional composition of human milk is modulated by maternal, infant, and methodological factors. Front Nutr. 2020;7:576133.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 25–33 (DOI: 10.1159/000534947)

27 Hassiotou F, Hepworth AR, Metzger P, Tat Lai C, Trengove N, Hartmann PE, et al. Maternal and infant infections stimulate a rapid leukocyte response in breastmilk. Clin Transl Immunology. 2013;2(4):e3.
28 McGuire MK, Meehan CL, McGuire MA, Williams JE, Foster J, Sellen DW, et al. What's normal? Oligosaccharide concentrations and profiles in milk produced by healthy women vary geographically. Am J Clin Nutr. 2017;105(5):1086–100.
29 Davis JC, Lewis ZT, Krishnan S, Bernstein RM, Moore SE, Prentice AM, et al. Growth and morbidity of Gambian infants are influenced by maternal milk oligosaccharides and infant gut microbiota. Sci Rep. 2017;7:40466.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 25–33 (DOI: 10.1159/000534947)

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Can Food Allergies in Children Be Prevented?

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Abstract

Food allergies pose a significant burden on individuals and families due to dietary restrictions, which carry the risk of nutritional deficiencies, social restrictions, and impacts on quality of life. Thus, prevention is critical. This chapter provides a brief overview of the magnitude of the food allergy problem and identifies factors contributing to this rising epidemic. It also reviews the current guidelines for preventing food allergies in children. Recently, there has been a clear shift in guidelines, which now emphasize the early introduction of potentially allergenic foods instead of avoidance. Findings from selected articles published between 2021 and 2023 are also briefly reviewed to complement these guidelines. There is a discussion about whether this shift in guidelines will lead to meaningful reductions in the prevalence of food allergies. Recent data on peanut allergies will be presented, as well as the rationale for the early introduction of peanuts in various risk groups, rather than focusing solely on the high-risk population. The relevance of the early introduction of cow milk protein (within the first weeks of life) for reducing the risk of cow milk allergies will also be discussed. However, many questions remain unanswered and further high-quality studies are needed.

Introduction

Food allergies are often a long-term condition affecting children and adults. While some allergies such as cow milk allergy or egg allergy, especially non-IgE-mediated, usually resolve gradually over time, allergy to peanuts and tree nuts may persist into adulthood (or develop only later in life). Regardless of the possible resolution over time, food allergies pose a significant burden on the individual and their family; this burden includes dietary restrictions, with a risk of nutritional deficiencies, social restrictions and impact on the quality of life, a financial burden for families, and limitations on healthcare resources [1]. Thus, prevention is crucial. This chapter discusses the problem of food allergies and factors contributing to its rise. It also reviews current guidelines for preventing food allergies in infants and children and briefly summarizes selected recent research.

Magnitude of Food Allergies

The prevalence of food allergies is difficult to determine and varies with the method used to diagnose food allergies and the population studied [2]. In high-income countries, a 2023 systematic review and meta-analysis found a threefold increase in the point prevalence of self-reported food allergies in 2012–2021 (14.9%) compared to 2000–2012 (5.9%) [3]. The most common allergens in children in the United States are peanuts, milk, shellfish, and tree nuts [4]. Australia has the highest worldwide rates of food allergies, with peanuts, egg, and sesame being the most prevalent allergens in children [5]. In low- and middle-income countries, data on the prevalence and trends of food allergies are limited. A 2022 meta-analysis of studies from China found that the self-reported prevalence rate of food allergies was higher than the hospital-diagnosed food allergy rate and that the prevalence of food allergies is increasing [6]. Overall, self-reported food allergy rates tend to overestimate the prevalence compared to diagnoses made using rigorous methods. The prevalence of allergic disease is higher in high-income countries, but it is also increasing in low- and middle-income countries.

Food Allergy Risk Factors and Hypotheses

The risk factors for food allergies can have a genetic component, and many genetic loci, genes, and gene variants have been associated with food allergy development [7]. However, the rise of food allergies cannot be explained by genetics

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alone – genetic predisposition might be permissive rather than decisive (critical). Thus, several hypotheses have been proposed to explain the rise [8]. These include:

- the hygiene hypothesis (Improved hygiene and reduced exposure of the immune system to microbial and parasitic stimuli during early life may lead to impaired immunoregulation in later life and an increased risk of developing Th2 diseases, such as allergies, or Th1 diseases, such as type 1 diabetes. This is because the immune system does not receive the necessary stimulus to develop tolerogenic responses.) [9];
- the biodiversity hypothesis (Biodiversity loss leads to immune dysfunction and disease.) [10];
- the vitamin D hypothesis (Vitamin D has been shown to affect several mechanisms that promote immunologic tolerance, including T regulatory cell function and the induction of tolerogenic dendritic cells. However, the relationship between vitamin D deficiency and the development of food allergies is contradictory, with lower exposure to sunlight associated with food allergies in some studies but higher vitamin D levels linked to allergic sensitization and food allergies in others.) [11];
- the short-chain fatty acid (SCFA) hypothesis (SCFAs such as butyrate, acetate, and propionate, which are the main bacterial metabolites, have been proposed as key mediators in microbiota-induced effects on the host contributing to food allergy protection.) [12, 13];
- the dual-allergen exposure hypothesis (The route of sensitization matters; early-life exposure to allergens through the skin, especially in the presence of eczema, promotes IgE sensitization and food allergy via T-cell skewing toward allergic type Th2 cells producing cytokines such as IL-4, IL-5, and IL-13. Conversely, early oral exposure to allergens through food consumption may induce oral tolerance via T-cell skewing toward Th1 cytokine production and tolerance [8]. This hypothesis is based on the need for oral tolerance to replace cutaneous (or possibly also respiratory, as recently proposed [14]) sensitization, and suggests that consistent and regular oral ingestion of potential allergens is necessary to induce and maintain tolerance).

Prevention of Food Allergy: Statements from Professional Societies

A 2021 systematic review (search date; August 2019) analyzed food allergy prevention guidelines and recommendations [15]. Additionally, the guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool. As there is no established quality threshold, it was subjectively

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Table 1. Comparison of recent (2020–2022) guidelines on prevention of food allergy through dietary modifications

	ASCIA 2020 [19]	AAAAI/ACAAI/CSACI 2021 [20]	EAACI 2021 [21]	CSACI/CPS 2022 [22]
Maternal diet (pregnancy/lactation)	No			
Breastfeeding	Yes (even if it does not reduce the risk of FA)			
Hydrolyzed formula (pHF/eHF)	No	No	No *for* or *against*	No
CMF	If BF is not possible, a standard CMF can be given	No clear statement	1st week of life: no After 2nd week of life: no *for* or *against*	If introduced, regular ingestion (10 mL daily) to prevent loss of tolerance
Peanut	In the first year of life (when an infant is ready, at around 6 months, but not before 4 months)	Around 6 months of life, but not before 4 months	In populations with a high prevalence of peanut allergy, from 4 to 6 months	High-risk infants: at about 6 months (not before 4 months) Low-risk infants: at around 6 months of age. Ongoing ingestion, regular
Egg	In the first year of life, cooked (not raw) egg (when an infant is ready, at around 6 months, but not before 4 months)	Around 6 months of life, but not before 4 months	Well-cooked hen's egg (not raw or uncooked pasteurized egg) as part of CF (from 4 to 6 months)	As above (cooked [not raw] egg)
Screening before introduction	N/A	No	N/A	No
Pro-/pre-/synbiotics	No	N/A	No *for* or *against*	No
Omega-3	N/A	N/A	No *for* or *against*	No
Vitamin D	N/A	N/A	No *for* or *against*	No

AAAAI/ACAAI/CSACI, American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology; ASCIA, Australasian Society of Clinical Immunology and Allergy; BF, breastfeeding; CF, complementary feeding; CMF, cow milk-based formula; CSACI/CPS, Canadian Society of Allergy and Clinical Immunology/Canadian Pediatric Society; EAACI, European Academy for Allergy and Clinical Immunology; FA, food allergy; N/A, not addressed.

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defined by the reviewers. Twenty-eight food allergy prevention documents, including 10 guidelines (8 met the reviewers' quality threshold) and 18 advice documents (none met the quality threshold) were identified. Overall, earlier documents (i.e., those published before two landmark trials, i.e., the Learning Early About Peanut [LEAP] [16] and the Enquiring about Tolerance [EAT] Study [17] were published) recommended avoidance of common food allergens during pregnancy and breastfeeding and delayed introduction of allergenic foods after the age of 1–3 years. Only more recent guidelines, including a 2019 American Academy of Pediatrics position paper [18], recommended the early introduction of allergenic foods such as peanuts or eggs. For a table comparing the guidelines published from 2020 to 2022 [19–22] (see Table 1). There is a clear paradigm shift in the guidelines for food allergy prevention. While some differences in the specific recommendations exist, overall, the guidelines emphasize the early introduction of potentially allergenic food.

Guideline Adoption

As the major change relates to peanut and/or egg allergy, studies have focused mainly on these foods. However, data are limited and come from countries where peanut allergy is a significant problem. In a 2020 survey of 1791 US pediatricians, only 30% reported implementing peanut allergy guidelines, whereas allergists were more likely to implement them [23, 24]. Adoption rates of guideline changes were low in a 2022 US survey, with almost half of caregivers not introducing peanuts by 1 year and a third not introducing eggs [25]. However, earlier introduction of peanuts and eggs was associated with a greater likelihood of introducing other food allergens. In contrast, Australia reported an increase in early peanut introduction following guideline changes [26, 27]. Adherence to evidence-based guidelines is necessary to improve outcomes, and further data on guideline adoption for peanuts and other allergens in various settings and populations are needed.

Impact of Updated Guidelines on Peanut Allergy Prevalence

At the time of the writing of this manuscript, only one study has evaluated the impact of the new guidelines on peanut allergy prevalence. Data from two large population-based studies conducted 10 years apart (i.e., 2007–2011 and 2018–2019) in Melbourne, Australia, using the same sampling frame and methods, were analyzed [28]. Over 7,000 participants (5,276 infants in the 2007–2011

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group and 1,933 infants in the 2018–2019 group) were evaluated. These two cohorts represented populations advised in line with the old guidelines (i.e., avoiding allergenic foods until children reach 1–3 years of age) and the new guidelines, respectively. Despite a large increase in parents introducing food early to infants [26, 27], the prevalence of peanut allergy among infants at 12 months did not change. After standardization for ancestry and other demographics, peanut allergy prevalence decreased among all infants in 2018–2019 compared to 2007–2011. However, the difference was not statistically significant (2.6%, 95% CI 1.9–3.4 vs. 3.1%, 95% CI −1.4 to 0.4, respectively). In 2018–2019, among infants of Australian ancestry, an earlier age of peanut introduction was associated with a lower risk for peanut allergy compared with 2007–2011. For infants of East Asian ancestry, no significant association between earlier introduction of peanuts in 2018–2019 compared with 2007–2011 was found.

The disappointing findings may prompt researchers and clinicians to question current advice, but the lack of information makes it hard to draw definitive conclusions. The exact dose and frequency of allergen exposure and why the effect of early peanut introduction differed among certain families remain unclear. The lack of an effect in the general population suggests that other factors may be at play, highlighting the complexity of the issue and the need for further research. Nevertheless, clinicians should still follow current guidance recommending early peanut introduction for infants, as the potential benefits outweigh the low risk of harm [29].

The Early Introduction of Peanuts in Various Risk Groups (High-Risk Groups or the General Population)

Current recommendations on the early introduction of peanuts are based on UK study data mainly from high-risk children (i.e., those with severe eczema, egg allergy, or both, which are well-known risk factors for peanut allergy [30]). However, it is still unclear whether the UK findings can be extrapolated to other populations and nonrisk groups. At least two recent reports suggest that the early introduction of peanuts is relevant to the general population and should not be limited to infants at high risk.

One of the recent reports comes from the PreventADALL (Preventing Atopic Dermatitis and Allergies) study in the general population from Norway and Sweden [31]. This factorial, cluster-randomized trial found that exposure to allergenic foods (peanut, cow's milk, wheat, and egg; $n = 641$) from age 3 months (once a week) reduced the risk of documented food allergies at age 36 months compared to the no intervention group ($n = 596$) (risk difference: −1.6%, 95%

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CI −2.7% to −0.5%). However, the number needed to treat was 63. On average, 63 children would have to receive early complementary feeding (early exposure to allergenic foods) for 1 additional child to *not* have food allergies. The effect was seen only for peanut allergy (risk difference: −1.2%, 95% CI −2.1 to −0.3), but not for other allergens.

Second, findings from an integrated meta-analysis [32] using individual patient data from a study in a high-risk population (the LEAP study) [16] and a study in a normal-risk population (the EAT study) [17] revealed that the early introduction of peanuts in infancy effectively reduces the risk of peanut allergy. This is true regardless of the presence or severity of eczema, sensitization to peanuts, and ethnicity (Caucasian and non-Caucasian). An intention-to-treat analysis of pooled data from the LEAP and EAT studies showed a 75% reduction in peanut allergy (risk difference: −5.65%, 95% CI −3.7 to −7.6; $p < 0.0001$) in the intervention group (consumption of peanuts from early infancy) compared to the control group (avoidance of peanuts). Furthermore, the timing of peanut introduction was found to be important, with earlier introduction of peanuts before 6 months of age being more effective in preventing peanut allergy than later introduction. As a result, the authors suggest that recommending the early introduction of peanut-containing foods for the primary prevention of peanut allergy could be considered for the entire population, regardless of the identifiable allergy risk. However, it is still unclear whether this is applicable to other food allergens. The authors also indicate that, except in resource-poor countries with high morbidity and mortality from infections, it is time to reappraise the recommendation that infants should be exclusively breastfed for 6 months. Importantly, at least two trials [31, 33] found that breastfeeding rates at 6 months were not affected by early food introduction and were higher than commonly reported.

The additional data support early peanut introduction as a safe and effective way to prevent peanut allergies in all infants, and not limited to high-risk infants. However, more evidence is needed in regard to the amount, formulation, timing, and duration of consumption. In real-world settings, the impact may be smaller or absent compared to that in UK studies, as previously discussed.

The Early Introduction of Cow Milk Protein

There is ongoing debate over the significance of brief exposure to or avoidance of cow milk proteins during early life, within hours or days after birth, and its relationship to the risk of cow milk protein allergy (CMPA) later in life. Table 2

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Table 2. Early introduction of cow milk protein for prevention of cow milk protein allergy: current recommendations [20, 21, 48, 49]

AAAAI/ACAAI/CSACI 2021 [20]	No clear statement
EAACI 2021 [21]	For infants who need a breastmilk substitute, EAACI suggests: In the 1st week of life Avoiding supplementing with CMF in breastfed infants After the 1st week of life No *for* or *against* the use of regular CMF
S3 Guideline Allergy Prevention Germany 2022 [48]	As EAACI
Spanish Association of Paediatrics 2022 [49]	Not possible to draw clear conclusions

CMF, cow milk-based formula.

provides an overview of current recommendations on the early introduction (within the first few days of life) of cow milk proteins (cow milk-based infant formula, CMF) in infants who could not be breastfed for the prevention of CMPA. The inconsistent recommendations result from a lack of clear evidence, which is summarized in Table 3, including data from both observational (non-randomized) studies [34–40] and randomized controlled trials [41–46]. Between 2021 and 2023, three studies were published after guideline publication that contribute to current knowledge.

The first study is an additional analysis of data from the SPADE (The Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy) trial. This was an open-label randomized controlled trial conducted in a general infant population in Japan [41]. The study found that daily ingestion of CMF at a minimum of 10 mL (equivalent to 150 mg of cow milk protein per day) between 1 and 2 months of age significantly reduced the risk of CMPA (risk difference: 6.0%, 95% CI 2.7–9.3). Most infants (431 out of 462, or 3%) received CMF within the first 3 days of life and were further evaluated. The follow-up observation revealed that early exposure and subsequent discontinuation of CMF, especially in the first month of life, was associated with the development of CMPA [before age 1 month: 7/17 (41.2%); between age 1 and 2 months: 3/26 (11.5%); between age 3 and 5 months: 7/69 (10.1%)] [46]. On the other hand, continuous intake of CMF over the first months of life (up to 6 months) was associated with the lowest number of children with CMPA: 2/319 (0.6%) [46]. It is important to note that, except for the latter group, the number of

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Table 3. Summary of the findings from randomized and nonrandomized studies on the early introduction of cow milk proteins and the risk of cow milk protein allergy

Randomized controlled trials			
Juvonen et al., 1996 [42]	Sweden	Quasi-RCT	NS
Saarinen et al., 1999 [43]	Finland	Quasi-RCT	↑ CMA
Urashima et al., 2019 [44]	Japan	Open RCT ABC study	In the first 3 days of life and subsequent removal ↑ On a regular basis – NS
Tachimoto et al., 2020 [45]	Japan	Open RCT, 2-year follow-up of ABC	↓ CMA
Sakihara et al., 2021 [41]	Japan	Open RCT SPADE study	CMF consistently 1–2 months of age, ↓ CMA
Sakihara et al., 2022 [46]	Japan	Data from SPADE study	CMF in the first 3 days of life and then stop, ↑ CMA
Nonrandomized studies			
Katz, 2010 [34]	Israel	Prospective cohort	First 14 days ↓ risk of CMA After 14 days ↑ risk of CMA
Koletzko et al., 2011 [35]	Germany	GINI study (Post hoc)	NS
Onizawa et al., 2016 [36]	Japan	Case-control study	Early vs. delayed (after 1 month) CMF or no formula, ↓ risk of CMA
Sakihara et al., 2016 [37]	Japan	Retrospective	CMF in the first 3 months, ↓ CMA
Peters et al., 2019 [38]	Australia	Prospective cohort HealthNuts	CMF in the first 3 months, ↓ CMA
Lachover-Roth et al., 2023 [39]	Israel	Prospective cohort	Early continuing CMF from birth, ↓ CMA
Switkowski et al., 2022 [40]	USA	Prospective cohort	Early consistent CMF, ↓ CMA

ABC, the Atopy Induced by Breastfeeding or Cow's Milk Formula trial; CMA, cow milk allergy; CMF, cow milk-based formula; GINI, German Infant Nutritional Interventional Study; RCT, randomized controlled trial; SPADE, The Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy.

children in other groups was small, the groups were not randomized, and the diagnosis of CMPA was not confirmed with an oral food challenge. Nevertheless, these findings highlight the importance of the continuous intake of CMF once it has been started.

The second study – a questionnaire study on nearly 1,300 US children (part of the Project Viva Cohort) – points to the importance of the timing of CMF administration [40]. The risk of a cow milk adverse reaction in early childhood (2–5 years) was *highest* in infants who were introduced to cow milk protein at or after 6 months of age or before 2 weeks of age. A neutral response seemed to be the result of the introduction of cow milk protein sometime between 2 weeks and 6 months of age. In infants who received CMF in the hospital, soon after birth, the intake of CMF at the age of less than 2 weeks contributed to the lower risk of a later adverse reaction to cow milk. The findings from this observational study suggest that both timing and likely regular intake matter. However, the lack of randomization and parental reporting of adverse reactions are among the study limitations and preclude the formation of firm conclusions.

The third study, the COMEET (Cow's Milk Early Exposure Trial), found that early and consistent exposure to CMF in the first 2 months of life is associated with a lower risk of developing IgE-mediated CMPA compared to exclusive breastfeeding. This nonrandomized study enrolled 1,992 newborns and divided them into two groups based on their parents' feeding preferences. The group who was exclusively breastfed until 2 months of age had a higher prevalence of IgE-mediated CMPA compared to the group who received at least one meal of CMF daily (17/1,073, 1.58% vs. 0/919, 0%, respectively, $p < 0.001$, RR 30 [95% CI 1.8–500]). Post-hoc analysis showed that the risk of IgE-mediated CMPA was higher among breastfed infants who were exposed to small amounts of CMF compared to exclusively breastfed infants. These results suggest that early and consistent exposure to CMF has the potential to prevent the development of IgE-mediated CMPA, but occasional exposure increases the risk and should be avoided. A propensity score analysis was used as randomization was not feasible [39].

Overall, these recent studies contribute to the ongoing debate about the early introduction of cow's milk as a means of preventing CMPA. However, the conclusions drawn from these studies are limited due to a lack of randomization and/or the absence of a confirmed diagnosis of CMPA using strict criteria. Despite the trend toward using the early introduction of CMF to prevent CMPA, more data are needed to determine the optimal approach. At this point, it is premature to make specific recommendations.

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Quantity of Allergenic Foods

The data from the EAT study suggest that the amount of allergen consumed is important [17]. The study found that consuming 2 g of peanut protein or 4 g of egg protein per week was associated with a significantly lower prevalence of peanut or egg allergies, respectively, compared to consuming less. The Prevent-ADALL study also found that increased adherence to peanut intake was associated with a lower incidence of peanut allergy [31]. While more research is needed on the optimal doses of allergens [21], these findings point to the significance of food allergen dose in preventing food allergies. New guidelines for preventing food allergies have led to the availability of products containing allergenic foods, but a 2021 study found significant variability in allergen levels and composition of these products, highlighting the need for more stringent quality control [47].

Conclusions and Future Research

Food allergies pose a significant burden on individuals, families, and society, making prevention crucial.

Assessing the exact prevalence of food allergies can be difficult. However, there are reports of an increase in food allergies in some regions. Accurate estimates of food allergy prevalence, based on well-established criteria, are essential for promoting prevention and evaluating current strategies.

The increase in food allergies is likely due to a combination of genetic and environmental factors, but the exact cause is still unknown. Further research is needed to better understand the environmental risk factors that may contribute to the development of food allergies.

Guidelines on food allergy prevention may differ in their specific recommendations for the age of introduction and target populations. However, overall, the paradigm has shifted from allergen avoidance to the early introduction of potentially allergenic foods such as egg and peanut (in an age-appropriate format) based on evidence showing that this approach can lower the risk of developing allergies to these foods.

Data on the adoption of these guidelines are limited. However, in settings with high guideline adoption rates, such as Australia, recent evidence indicates that earlier introduction of peanuts may not lower peanut allergy risk at the population level. Further research is needed to gain a better understanding of why this is the case and what additional factors may be necessary to minimize the risk of food allergies.

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Many research questions about specific food allergens remain unanswered. To address these questions, further research should focus on a wider range of populations with regard to their risk of allergy and/or ethnicity. The optimal (minimal) amount of allergenic foods, as well as the importance of regular versus irregular ingestion of food allergens, needs to be clarified. In addition to peanuts, eggs and cow's milk proteins, which have been studied but require more data, other food allergens should be evaluated as well.

Conflict of Interest Statement

H.S. has participated as a consultant and/or speaker for companies manufacturing infant formulas, i.e., Danone, Else Nutrition, Hipp, Mead Johnson/RB Health, Nestlé, the Nestlé Nutrition Institute.

Author Contributions

The author confirms sole responsibility for all aspects of the manuscript preparation.

References

1 Muraro A, de Silva D, Halken S, Worm M, Khaleva E, Arasi S, et al. Managing food allergy: GA(2)LEN guideline 2022. World Allergy Organ J. 2022;15:100687.
2 Woods RK, Stoney RM, Raven J, Walters EH, Abramson M, Thien FCK. Reported adverse food reactions overestimate true food allergy in the community. Eur J Clin Nutr. 2002;56:31–6.
3 Spolidoro GCI, Amera YT, Ali MM, Nyassi S, Lisik D, Ioannidou A, et al. Frequency of food allergy in Europe: an updated systematic review and meta-analysis. Allergy. 2023;78:351–68.
4 Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics. 2018;142(6):e20181235.
5 Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. J Allergy Clin Immunol. 2017;140:145–53.e148.
6 Luo J, Zhang Q, Gu Y, Wang J, Liu G, He T, et al. Meta-analysis: prevalence of food allergy and food allergens – China, 2000–2021. China CDC Wkly. 2022;4:766–70.
7 Kanchan K, Clay S, Irizar H, Bunyavanich S, Mathias RA. Current insights into the genetics of food allergy. J Allergy Clin Immunol. 2021;147:15–28.
8 Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol. 2008;121:1331–6.
9 Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax. 2000;55(Suppl 1):S2–10.
10 Hanski I, von Hertzen L, Fyhrquist N, Koskinen K, Torppa K, Laatikainen T, et al. Environmental biodiversity, human microbiota, and allergy are interrelated. Proc Natl Acad Sci U S A. 2012;109:8334–9.
11 Giannetti A, Bernardini L, Cangemi J, Gallucci M, Masetti R, Ricci G. Role of vitamin D in prevention of food allergy in infants. Front Pediatr. 2020;8:447.
12 Tan J, McKenzie C, Vuillermin PJ, Goverse G, Vinuesa CG, Mebius RE, et al. Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. Cell Rep. 2016;15:2809–24.
13 Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. Adv Immunol. 2014;121:91–119.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 34–47 (DOI: 10.1159/000534957)

14 Kulis MD, Smeekens JM, Immormino RM, Moran TP. The airway as a route of sensitization to peanut: an update to the dual allergen exposure hypothesis. J Allergy Clin Immunol. 2021;148:689–93.
15 Vale SL, Lobb M, Netting MJ, Murray K, Clifford R, Campbell DE, et al. A systematic review of infant feeding food allergy prevention guidelines – can we AGREE? World Allergy Organ J. 2021;14:100550.
16 Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803–13.
17 Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016;374:1733–43.
18 Greer FR, Sicherer SH, Burks AW. The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. Pediatrics. 2019;143(4):e20190281.
19 Infant feeding and allergy prevention. Available from: https://www.allergy.org.au/images/pcc/ASCIA_Guidelines_Infant_Feeding_and_Allergy_Prevention_2020.pdf. Accessed 2 January 2024.
20 Fleischer DM, Chan ES, Venter C, Spergel JM, Abrams EM, Stukus D, et al. A consensus approach to the primary prevention of food allergy through nutrition: guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology. J Allergy Clin Immunol Pract. 2021;9:22–43.e24.
21 Halken S, Muraro A, de Silva D, Khaleva E, Angier E, Arasi S, et al. EAACI guideline: preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol. 2021;32:843–58.
22 Abrams EM, Watson W, Vander Leek TK, Atkinson A, Primeau MN, Francoeur MJ, et al. Dietary exposures and allergy prevention in high-risk infants. Allergy Asthma Clin Immunol. 2022;18:36.
23 Gupta RS, Bilaver LA, Johnson JL, Hu JW, Jiang J, Bozen A, et al. Assessment of pediatrician awareness and implementation of the addendum guidelines for the prevention of peanut allergy in the United States. JAMA Netw Open. 2020;3:e2010511.
24 Johnson JL, Gupta RS, Bilaver LA, Hu JW, Martin J, Jiang J, et al. Implementation of the Addendum Guidelines for Peanut Allergy Prevention by US allergists, a survey conducted by the NIAID, in collaboration with the AAAAI. J Allergy Clin Immunol. 2020;146:875–83.
25 Venter C, Warren C, Samady W, Nimmagadda SR, Vincent E, Zaslavsky J, et al. Food allergen introduction patterns in the first year of life: a US nationwide survey. Pediatr Allergy Immunol. 2022;33:e13896.
26 O'Sullivan M, Vale S, Loh RK, Metcalfe J, Orlemann K, Salter S, et al. SmartStartAllergy: a novel tool for monitoring food allergen introduction in infants. Med J Aust. 2020;212:271–5.
27 Soriano VX, Peters RL, Ponsonby AL, Dharmage SC, Perrett KP, Field MJ, et al. Earlier ingestion of peanut after changes to infant feeding guidelines: the EarlyNuts study. J Allergy Clin Immunol. 2019;144:1327–35.e1325.
28 Soriano VX, Peters RL, Moreno-Betancur M, Ponsonby AL, Gell G, Odoi A, et al. Association between earlier introduction of peanut and prevalence of peanut allergy in infants in Australia. JAMA. 2022;328:48–56.
29 Dantzer J, Wood RA. Can peanut allergy prevention be translated to the pediatric population? JAMA. 2022;328:25–6.
30 Du Toit G, Roberts G, Sayre PH, Plaut M, Bahnson HT, Mitchell H, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. J Allergy Clin Immunol. 2013;131:135–43.e1–12.
31 Skjerven HO, Lie A, Vettukattil R, Rehbinder EM, LeBlanc M, Asarnoj A, et al. Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet. 2022;399:2398–411.
32 Logan K, Bahnson HT, Ylescupidez A, Beyer K, Bellach J, Campbell DE, et al. Early introduction of peanut reduces peanut allergy across risk groups in pooled and causal inference analyses. Allergy. 2022;78(5):1307–18.
33 Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Flohr C, et al. Enquiring About Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. J Allergy Clin Immunol. 2016;137:1477–86.e1478.
34 Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. J Allergy Clin Immunol. 2010;126:77–82.e71.
35 Koletzko S, Filipiak-Pittroff B, von Berg A, Grübl A, Heinrich J, Krämer U, et al. Supplementation with cow's milk at birth is not recommended. J Allergy Clin Immunol. 2011;127:836–8; author reply 839–40.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 34–47 (DOI: 10.1159/000534957)

36 Onizawa Y, Noguchi E, Okada M, Sumazaki R, Hayashi D. The association of the delayed introduction of cow's milk with IgE-mediated cow's milk allergies. J Allergy Clin Immunol Pract. 2016;4:481–8.e482.
37 Sakihara T, Sugiura S, Ito K. The ingestion of cow's milk formula in the first 3 months of life prevents the development of cow's milk allergy. Asia Pac Allergy. 2016;6:207–12.
38 Peters RL, Koplin JJ, Dharmage SC, Tang MLK, McWilliam VL, Gurrin LC, et al. Early exposure to cow's milk protein is associated with a reduced risk of cow's milk allergic outcomes. J Allergy Clin Immunol Pract. 2019;7:462–70.e461.
39 Lachover-Roth I, Cohen-Engler A, Furman Y, Shachar I, Rosman Y, Meir-Shafrir K, et al. Early, continuing exposure to cow's milk formula and cow's milk allergy: the COMEET study, a single center, prospective interventional study. Ann Allergy Asthma Immunol. 2023;130:233–9.e234.
40 Switkowski KM, Oken E, Rifas-Shiman SL, Camargo CA Jr, Gold DR, Sordillo JE, et al. Timing of cow's milk protein introduction and childhood adverse reactions to cow's milk. J Allergy Clin Immunol Pract. 2022;10:2713–21.e2712.
41 Sakihara T, Otsuji K, Arakaki Y, Hamada K, Sugiura S, Ito K. Randomized trial of early infant formula introduction to prevent cow's milk allergy. J Allergy Clin Immunol. 2021;147:224–32.e228.
42 Juvonen P, Månsson M, Andersson C, Jakobsson I. Allergy development and macromolecular absorption in infants with different feeding regimens during the first three days of life. A three-year prospective follow-up. Acta Paediatr. 1996;85:1047–52.
43 Saarinen KM, Juntunen-Backman K, Järvenpää AL, Kuitunen P, Lope L, Renlund M, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. J Allergy Clin Immunol. 1999;104:457–61.
44 Urashima M, Mezawa H, Okuyama M, Urashima T, Hirano D, Gocho N, et al. Primary prevention of cow's milk sensitization and food allergy by avoiding supplementation with cow's milk formula at birth: a randomized clinical trial. JAMA Pediatr. 2019;173:1137–45.
45 Tachimoto H, Imanari E, Mezawa H, Okuyama M, Urashima T, Hirano D, et al. Effect of avoiding cow's milk formula at birth on prevention of asthma or recurrent wheeze among young children: extended follow-up from the ABC randomized clinical trial. JAMA Netw Open. 2020;3:e2018534.
46 Sakihara T, Otsuji K, Arakaki Y, Hamada K, Sugiura S, Ito K. Early discontinuation of cow's milk protein ingestion is associated with the development of cow's milk allergy. J Allergy Clin Immunol Pract. 2022;10:172–9.
47 Filep S, Chapman MD. Doses of specific allergens in early introduction foods for prevention of food allergy. J Allergy Clin Immunol Pract. 2022;10:150–8.e153.
48 Kopp MV, Muche-Borowski C, Abou-Dakn M, Ahrens B, Beyer K, Blümchen K, et al. S3 guideline Allergy Prevention. Allergol Select. 2022;6:61–97.
49 Díaz Martín JJ, Blesa Baviera L, Campoy Folgoso C, Espín Jaime B, Leis Trabazo MR, Mesa Del Castillo M, et al. Consensus document on the primary prevention of cow's milk protein allergy in infants aged less than 7 days. An Pediatr (Engl Ed). 2022;97(1):59.e1–59.e7.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 34–47 (DOI: 10.1159/000534957)

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Diet and Microbiome: The Link to Allergy

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Abstract

Over the past century, there has been a rapid rise in the prevalence of allergic disorders in parallel with industrialization and urbanization. The development of allergic disorders is now known to be the end result of complex interactions between host genetic factors and exposure to various environmental factors. Among them, dietary factors and exposure to microbes have been found to be pivotal. Dietary fiber intake and exposure to microbes in the environment will affect the intestinal microbiome which in turn produces metabolites interacting with different components of our immune system. Short-chain fatty acids produced by beneficial microbes are some of the most important candidates which can interact with G-protein-coupled receptors leading to modulation of the immune system and enhanced intestinal integrity. Such interactions result in a lower risk of future development of allergies. Early prospective trials are encouraging in showing the benefits of such intervention including the use of minimally processed milk or bacterial lysate. With the development of safe and effective primary prevention, we may be able to reverse the increasing trend of allergic disease worldwide.

Introduction

Over the past century, we have witnessed a gradual increase in the prevalence of different allergic conditions such as allergic rhinitis, asthma, atopic eczema, and food allergy in parallel with industrialization and urbanization. The rapid increase in the prevalence of food allergies in Western countries has been observed in the past 20 years. Although the exact reasons for the rise in allergic conditions are not known, it appears that the changes in our diet and our exposures to microbes are likely to be crucial players in the process. Over the past 3 decades, there have been significant advances in the understanding of the early development of the human immune system and its relationship with various allergic conditions. It is now known that the manifestations of allergic disorders are the results of complex interactions between host genetic factors and a variety of environmental factors including dietary factors, environmental microbial exposure, drug or chemical exposures, as well as environmental air pollutants [1]. Figure 1 shows the complex relationship of genetics, the environment, and the immune system. Recent hospital data from Australia and other parts of the world clearly documented a dramatic increase in food-induced anaphylaxis leading to hospitalization and the highest increase was found in children [2, 3]. No effective curative treatments are available for most allergic conditions. One of the most consistent epidemiological findings is that children growing up in a rural environment are protected from developing allergic diseases [4]. Such protection has been attributed to exposure in a traditional environment which includes dietary exposure and microbial stimulation starting at an early age. These factors may shape the early maturation of the immune system mediated by various active microbial metabolites such as different short-chain fatty acids (SCFAs) [5]. In this chapter, we review the potential role of diet and microbial exposure and discuss how these factors may link to the development of various allergic disorders. Understanding the underlying mechanisms will lead to the development of effective primary preventive strategies against the development of allergies.

In the 60s and 70s, allergens were believed to be the major factors resulting in the manifestations of different allergic conditions. For example, exposure to a higher level of house dust mite allergens was believed to be a major factor causing asthma, while early exposure to food allergens might lead to food allergies [6]. Therefore, avoidance has been the recommendation as one of the strategies for the prevention of allergic conditions [6]. Similarly, nonevidence-based recommendations of avoidance of food allergens early in life might have contributed to the increase in the prevalence of food allergies in the 80s to the turn of the century. Research directions started to change with comparative epidemiol-

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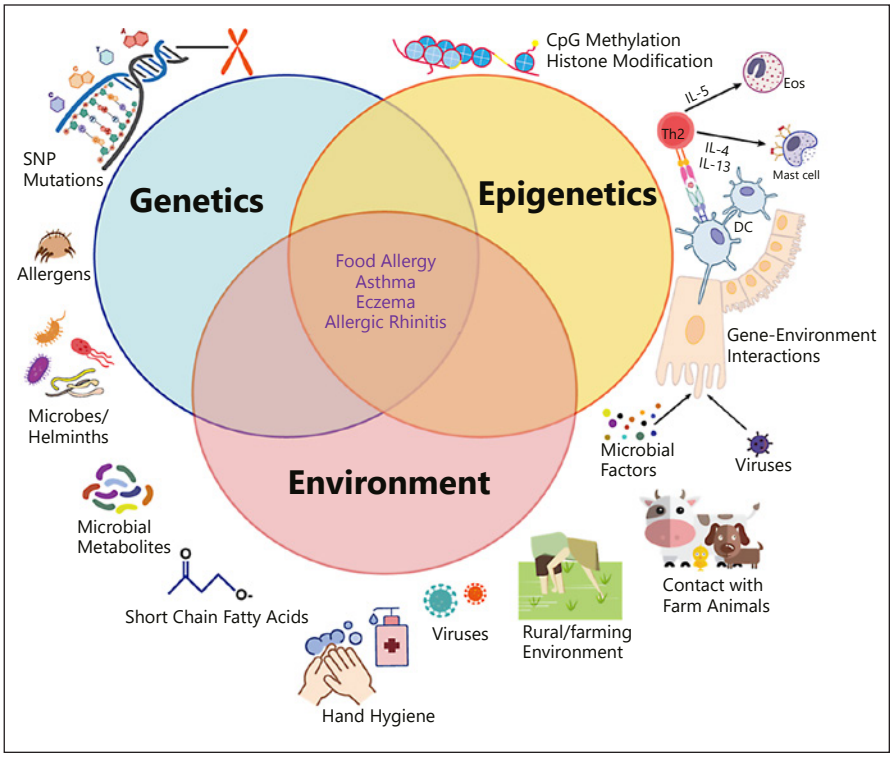

Fig. 1. Interactions between genetics, environmental factors, microbiome, and the manifestations of allergies.

ogy studies especially those from the rural areas showing other possible causes for the rise in allergies. Children born and raised in a rural or farming environment have much a lower prevalence of allergies [7, 8]. At the same time, a better understanding of the immune response regarding the roles of T-helper 1 and T-helper 2 response in the manifestations of allergic disorders leads to further mechanistic studies of how rural exposure may protect against the development of allergies [9]. Subsequently, there have been many landmark birth cohort studies and large cross-sectional studies investigating the effects of allergen exposures, rural exposure, and microbial exposures on the subsequent development of allergies [10–13].

The Tucson Children's Respiratory Study was a longitudinal birth cohort recruited over 1,200 subjects from the community to investigate the role of early viral respiratory infections in the subsequent development of asthma. Children were evaluated by their pediatrician whenever they developed symptoms suggestive of lower respiratory infections. Not surprisingly, those who had attended

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daycare or exposure to other older children at home were more likely to have frequent episodes of wheezing in the first 2 years of life [10]. However, they were less likely to have frequent wheezing episodes compatible with allergic asthma by 6 years of age. Strachan evaluated a large British birth cohort with 17,414 subjects born in 1958 and they were evaluated for symptoms of allergic rhinitis within the past 12 months at age 23 years. Those with one or more older siblings were less likely to have symptoms of allergic rhinitis at the age of 23 years [14]. These studies demonstrated that early unhygienic contact with older siblings or other children at daycare was associated with protection against the subsequent development of allergic asthma. Further studies in rural Bavaria, Germany, demonstrated that exposure to environmental microbes and consumption of unpasteurized farm milk were the main factors conferring protection against allergies. These early studies have led to a plethora of studies across the world in search of the relationship between exposure to environmental microbes and the development of allergies.

Among the studies performed in rural central Europe, exposure to microbes through contact with large farm animals and consumption of unpasteurized farm milk were suspected to modulate the early immune system such that excessive immune responses to innocuous proteins were suppressed [11, 12]. Interestingly, the increase in diversity of dietary food intake in the first year of life was found to be protective against the subsequent development of asthma in a dose–response effect [13]. An early observational study suggested early intake of peanuts might be associated with protection against peanut allergy later on [15]. Such observation has led to the LEAP (Learning Early About Peanut) trial which demonstrated early consumption rather than avoidance leading to the development of tolerance to peanuts. Infants consuming peanuts regularly from 6 months of age had an 80% reduction in their risk of having peanut allergy by 5 years of age when compared with those who avoided peanuts [16, 17]. A similar subsequent EAT (Enquiry About Tolerance) study evaluating a similar early introduction strategy in standard-risk infants in the United Kingdom employed a very ambitious protocol [18]. Infants were fed six allergenic foods including peanuts, cow's milk, boiled hen's egg, sesame, white fish, and wheat starting at 6 months of age. Compared to the control group, a significant reduction of any of the six allergenic foods between 1 and 3 years of age was observed in the per-protocol group. Less than half of the parents or guardians were able to adhere to the very ambitious protocol of feeding young infants so much food on a regular basis. Both the LEAP and EAT studies clearly demonstrated avoidance is harmful and would not result in the reduction of subsequent food allergies.

Although exposure to large animals in Europe was found to be an important protective factor, the prevalence of allergies was equally low in rural Chinese

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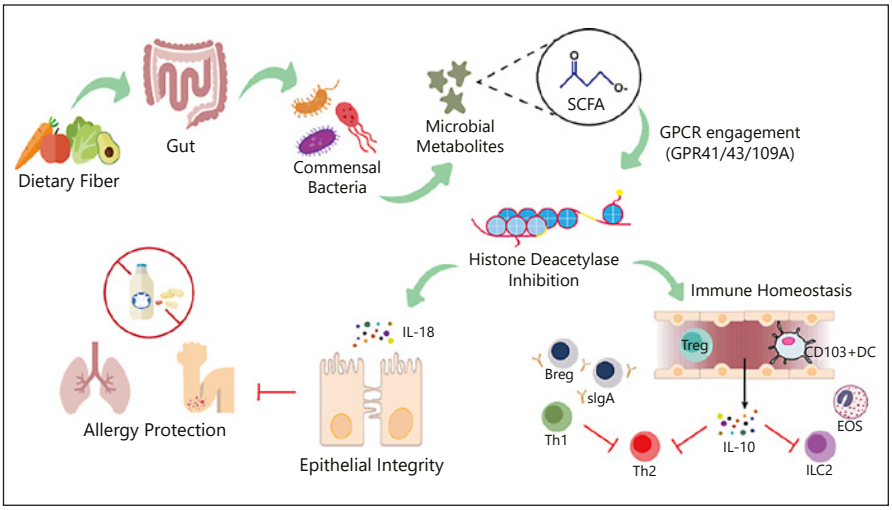

Fig. 2. Dietary and environmental microbial exposures affect the intestinal microbiome leading to the production of metabolites such as SCFAs which interact with the intestinal mucosa and immune system leading to protection against the development of allergies.

children and these farms are primarily agricultural in nature [8]. Detailed epidemiological analyses in rural China revealed that domestic exposure to poultry was a strong factor explaining protection against the development of allergy [19]. Dust extracts from such rural environments were tested in an asthma murine model and showed exposed mice in the early-life period resulted in a marked reduction of airway eosinophilia and bronchial hyperreactivity. Such protective effects appeared to be mediated through modulation of the gut microbiome [20]. Understanding the biological mechanisms explaining the relationship between microbial exposure and the host microbiome leading to protection against development is crucial if we were to develop effective primary prevention against allergies. One possible mechanism is that alternation in the host gut microbiome may result in a proliferation of certain beneficial organisms which in turn produce specific metabolites with important biological functions. The diet in the rural environment is characterized by higher fiber content and increased diversity as compared to the typical urban diet [21]. The link between dietary intake, microbiome, and the development of allergy may be mediated by specific metabolites produced by specific microbes, and these metabolites in turn interact with the immune system leading to protection against the development of allergies. Figure 2 illustrates how diet and microbiome exposure may lead to changes in the intestinal microbiome and related metabolic changes which results in allergy protection.

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The higher fiber intake together with exposure to various environmental microbes may facilitate higher production of various SCFAs such as acetate, butyrate, and propionate [21]. Among the SCFAs, butyrate has been extensively studied. Observational studies have confirmed that reduced levels of SCFA butyrate in stool samples early in life are associated with increased food allergy and food sensitizations [22]. These SCFAs are known to influence gut mucosal immunity such as stimulation of G-protein–coupled receptors (GPCRs); inhibition of histone deacetylases; and induction of various intracellular metabolic changes; all would lead to enhanced gut epithelial integrity and regulatory T-cell activities as well as reduction of inflammatory cytokines [23]. Studies from the PASTURE study revealed that children who had the highest levels of butyrate and propionate in their feces at 1 year had significantly less atopic sensitization and had a lower risk of asthma between 3 and 6 years [24]. SCFAs are produced in the colon where the concentration of microbes is the highest. These compounds are released following the fermentation of dietary fibers or other complex carbohydrates. The human gut microbiome represents the largest portion of microbes inside or on our body and the most common phyla are Bacteroidota and Bacillota. Species from the Phylum Bacteroidetes are responsible for degrading dietary fibers to yield various SCFAs. SCFAs have been found to interact with a variety of GPCRs [25]. These receptors are found in many cell types within the intestinal tract and immune cells including eosinophils, basophils, mast cells, neutrophils, monocytes, dendritic cells, T and B cells, and innate lymphoid cells [25–28]. Interaction with these immunoactive cells through GPCRs results in multiple downstream protective effects including modulation of inflammation and promotion of gut barrier function.

Studies of the link between the diet, microbiome, and the subsequent manifestations of allergies have provided us a deeper understanding of the role of various factors in the environment which may interact with the early immune system. It is now clear that there may be a window of opportunity to reduce the future risk of allergies through effective early interventions. There are ongoing trials using minimally processed milk and bacterial lysate as early intervention strategies to protect against subsequent allergies [29, 30]. The Milk Against Respiratory Tract Infections and Asthma (MARTHA) trial was a prospective study comparing the consumption of minimally processed full cream milk compared against ultrahigh heat-treated milk. Infants will be fed with these milk preparations at 11 months to 3 years of age and they will be assessed for the frequency and respiratory illness and asthma at 5 years of age. The use of bacterial lysates has also been documented to reduce wheezing episodes in preschool children and asthma exacerbations in school children. Studies will be needed to define the dosage and timing of the use of these dietary manipulations.

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Conclusion

As we begin to understand clearly the underlying biological mechanisms linking these dietary factors and microbiome with the modulation of the immune system, we will be able to develop effective primary preventive treatment to reverse the increasing trend of allergic disease on a population basis.

Conflict of Interest Statement

Gary Wong has served as the chair and speaker of the Nestlé Nutrition Institute. Yuhan Xing has no conflict of interest to declare.

Author Contributions

Gary Wong: conceptualization; project administration; supervision; validation; visualization; writing: original draft; writing: review and editing. Yuhan Xing: data curation; formal analysis; writing: original draft; writing: review and editing.

References

1 Xing Y, Wong GW. Environmental influences and allergic diseases in the Asia-Pacific region: what will happen in next 30 years? Allergy Asthma Immunol Res. 2022 Jan;14(1):21–39.
2 Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998–1999 to 2011–2012. J Allergy Clin Immunol. 2015 Aug;136(2):367–75.
3 Leung ASY, Li RMY, Au AWS, Rosa Duque JS, Ho PK, Chua GT, et al. Changing pattern of pediatric anaphylaxis in Hong Kong, 2010–2019. Pediatr Allergy Immunol. 2022 Jan;33(1):e13685.
4 Deckers J, Marsland BJ, von Mutius E. Protection against allergies: microbes, immunity, and the farming effect. Eur J Immunol. 2021 Oct;51(10):2387–98.
5 Tan JK, Macia L, Mackay CR. Dietary fiber and SCFAs in the regulation of mucosal immunity. J Allergy Clin Immunol. 2023 Feb;151(2):361–70.
6 Sporik R, Holgate ST, Platts-Mills TA, Cogswell J. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med. 1990 Aug 23;323(8):502–7.
7 Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Böhm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy. 2000 Feb;30(2):187–93.
8 Ma Y, Zhao J, Han ZR, Chen Y, Leung TF, Wong GW. Very low prevalence of asthma and allergies in schoolchildren from rural Beijing, China. Pediatr Pulmonol. 2009 Aug;44(8):793–9.
9 Romagnani S. Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. Int Arch Allergy Immunol. 1992;98(4):279–85.
10 Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med. 2000 Aug 24;343(8):538–43.
11 Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C, et al. Exposure to environmental microorganisms and childhood asthma. N Engl J Med. 2011 Feb 24;364(8):701–9.
12 Riedler J, Braun-Fahrländer C, Eder W, Schreuer M, Waser M, Maisch S, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet. 2001 Oct 6;358(9288):1129–33.
13 Roduit C, Frei R, Depner M, Schaub B, Loss G, Genuneit J, et al. Increased food diversity in the first year of life is inversely associated with allergic diseases. J Allergy Clin Immunol. 2014 Apr;133(4):1056–64.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 48–55 (DOI: 10.1159/000534948)

14 Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989 Nov 18;299(6710):1259–60.
15 Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008 Nov;122(5):984–91.
16 Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med. 2016 Apr 14;374(15):1435–43.
17 Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015 Feb 26;372(9):803–13.
18 Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016 May 5;374(18):1733–43.
19 Xing Y, Wang MH, Leung TF, Wong CK, Roponen M, Schaub B, et al. Poultry exposure and environmental protection against asthma in rural children. Allergy. 2022 Oct;77(10):2949–60.
20 Yang Z, Chen Z, Lin X, Yao S, Xian M, Ning X, et al. Rural environment reduces allergic inflammation by modulating the gut microbiota. Gut Microbes. 2022 Jan-Dec;14(1):2125733.
21 Tan JK, Macia L, Mackay CR. Dietary fiber and SCFAs in the regulation of mucosal immunity. J Allergy Clin Immunol. 2023 Feb;151(2):361–70.
22 Roduit C, Frei R, Ferstl R, Loeliger S, Westermann P, Rhyner C, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. Allergy. 2019 Apr;74(4):799–809.
23 Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therap Adv Gastroenterol. 2013 Jul;6(4):295–308.
24 Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016 Aug 19;14(8):e1002533.
25 Tan JK, McKenzie C, Mariño E, Macia L, Mackay CR. Metabolite-sensing G protein-coupled receptors-facilitators of diet-related immune regulation. Annu Rev Immunol. 2017 Apr 26;35:371–402.
26 Di Costanzo M, De Paulis N, Biasucci G. Butyrate: a link between early life nutrition and gut microbiome in the development of food allergy. Life. 2021 Apr 23;11(5):384.
27 Cait A, Cardenas E, Dimitriu PA, Amenyogbe N, Dai D, Cait J, et al. Reduced genetic potential for butyrate fermentation in the gut microbiome of infants who develop allergic sensitization. J Allergy Clin Immunol. 2019 Dec;144(6):1638–47.
28 Sandin A, Bråbäck L, Norin E, Björkstén B. Faecal short chain fatty acid pattern and allergy in early childhood. Acta Paediatr. 2009 May;98(5):823–7.
29 Brick T, Hettinga K, Kirchner B, Pfaffl MW, Ege MJ. The beneficial effect of farm milk consumption on asthma, allergies, and infections: from meta-analysis of evidence to clinical trial. J Allergy Clin Immunol Pract. 2020 Mar;8(3):878–89.
30 de Boer GM, Żółkiewicz J, Strzelec KP, Ruszczyński M, Hendriks RW, Braunstahl GJ, et al. Bacterial lysate therapy for the prevention of wheezing episodes and asthma exacerbations: a systematic review and meta-analysis. Eur Respir Rev. 2020 Nov 27;29(158):190175.

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Personalized Nutrition: The Role of Genetics, Microbiome, and Digitalization

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Abstract

Personalized nutrition describes the adaptation of general dietary principles to the traits and state of a group or individual. Single gene polymorphisms can mandate specific dietary alterations while multiple genes, with more subtle effects, may combine to justify tailored approaches. Such combined effects can be measured with polygenic risk scores. The microbiome, genetic material present in microorganisms (microbiota) colonizing the gut, confers traits relevant for nutrition but also adapts during the life course and may be a modifiable factor in digestive function. Microbiome features are associated with variable responses to diet, but it is not yet clear how to harness this association to improve health. Microbiome variation in carbohydrate digestion capability (CAZymes) represents an opportunity to enhance health effects through dietary choices. In early life, this capability is immature so dietary glycan intake may influence microbiome development. Forming actionable recommendations from multiple complex biological parameters requires data integration. Appropriate capture and characterization of dietary data is a key challenge. Digital tools can enhance standard dietary assessment. Ultimately, personalized nutrition complements human expert judgement to advise an individual on their specific needs. New technologies can improve information synthesis and accessibility to support better judgements and dietary choices.

Introduction

Personalization of nutrition can be expressed as a cycle: dietary and health data are evaluated and interpreted to formulate a recommendation for behavior such as choices of food item, meal composition, or supplement use. Effects on diet and health are then re-measured. Adoption of such recommendations will depend on how well they align with consumers' motivations and preferences, and how continuing cycles of personalization can reinforce adherence.

Just as personalized medicine aims to move beyond the "one-size-fits-all" approach to treatment, personalized nutrition can be understood in a hierarchy. The term "personalized" and related terms are used differently in different settings, sometimes with overlap. Table 1 provides definitions of some key terms as they are used in this chapter. The first level of personalization reflects approaches for specific populations or subpopulations, as might be referenced in a subsection of general guidelines. "Personalized nutrition" is more often taken to consider variation between individuals within a population such as demographic, lifestyle, and behavioral factors. "Precision nutrition" proposes to incorporate molecular data beyond current standard clinical testing such as genetic polymorphisms, gut microbiota and the genes within the bacterial ecosystem, and the metabolites produced by dietary interactions with both the genome and the "metagenome" in the microbiome.

Table 1. Definition of key terms used in this chapter

Personalized	The overarching concept of adapting general recommendations to an individual's traits, state, circumstances, and priorities. This can be based on clinical inquiry, physiological measurement, or laboratory evaluation
Precision	The area of personalization that focuses on new and advanced measurement of factors, such as the genome and metagenome, to achieve greater suitability of recommendation for the individual concerned
Genome	The totality of genetic material in an individual. Human cells contain distinct genomes in the nucleus and the mitochondria
Metagenome	The totality of genetic material in microorganisms colonizing an individual. Characteristic subsets of the metagenome occur in distinct ecological niches (gut, lung, skin, etc.)
Single-nucleotide polymorphism (SNP)	A specific point in the genome where the coding base (A,C,T,G) varies between individuals with measurable frequencies across the population. Variation may, or may not, affect RNA coding, protein formation, and physiological function
Polygenic risk score	An expression of the cumulative effects of SNPs affecting the same physiological trait

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This chapter will consider some of the challenges and the opportunities for analysis of genetics and/or the gut microbiome to add value to nutrition personalization, and also how digital approaches can make dietary recommendations more accessible and easier to adopt.

Personalization through Genetics

A sufficient supply of nutrients is essential to ensure the maintenance of health in an individual. Regulatory authorities in most countries have established dietary reference values (DRVs) or recommended dietary allowance (RDA) as estimates of the average amount of a nutrient that a person needs to maintain their health. As averaged values, based on dietary intake data in a population assumed to be healthy, RDAs can properly be used to assess intake inadequacies in a population. They cannot, however, be used to evaluate a specific individual for micronutrient deficiency or to provide individual recommendations for nutrient intake thresholds.

Figure 1 demonstrates this point by plotting data from the US National Health and Nutrition Examination Study (NHANES) on vitamin B12 intake against vitamin B12 blood concentrations (data from NHANES). Thirty percent of the people sampled do not reach sufficiently high vitamin B12 blood levels despite intake levels at the national RDA level and above. The effort required for any one individual to identify their own nutrient intake requirements through recurrent testing at various doses is cumbersome and unrealistic. This raises the opportunity to identify methods to support such an individual in choosing a relevant level of intake.

One such method is genetic testing, where genetics are known to influence nutrient bioavailability through digestion, absorption, metabolism, or excretion. In rare cases, a single gene defect can be sufficient to disrupt a nutrient's metabolism and cause serious clinical effects. An example is phenylketonuria (PKU) where a single mutation in the phenylalanine hydroxylase gene is sufficient to disrupt the conversion of phenylalanine to tyrosine. This leads to a steep increase in phenylalanine in the blood and, if untreated, to the development of cognitive disabilities in early childhood. The condition can be treated with a low-protein diet that decreases the intake of phenylalanine.

Borel and Desmarchelier provide a theoretical framework on how to adjust RDAs for vitamins based on different genetic backgrounds [1]. The genetic contribution to bioavailability of most micronutrients is more complex than for PKU: many genetic variants in multiple genes contribute to each micronutrient's bioavailability in an additive fashion. Gene loci that contribute to the ge-

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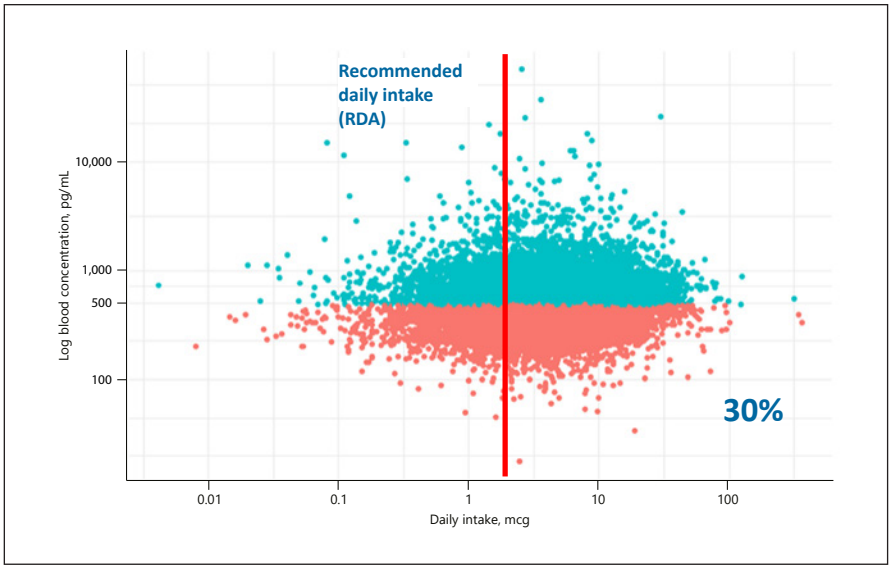

Fig. 1. Distribution of blood concentrations of vitamin B12 (after log transformation, pg/mL) according to reported daily intake (micrograms) in data from the National Health and Nutrition Examination Survey. The vertical line indicates the recommended daily intake of B12 in the United States. Red data points to the right of this line represent individuals with suboptimal levels of B12 despite meeting intake recommendations.

netic effects can be identified using large-scale genome-wide association studies (GWAS). Many such studies have identified genetic variants, usually single-nucleotide polymorphisms (SNPs), associated with changes in blood concentration of nutrients such as vitamins, fatty acids, and minerals.

While PKU can result from a variety of mutations in the single phenylalanine hydroxylase gene, for most nutrients the effects of each relevant SNP, both direction and magnitude, must be combined to establish a polygenic risk score (PRS) [2]. PRSs are currently the gold standard for estimating the genetic effect on a trait of interest and estimate (predict) an individual's risk for that trait. Just as such a combination of gene effects can be used to prognosticate the severity of early-onset Crohn's disease [3], so the combined score can inform on the relative likelihood of low or high nutrient levels.

The polygenic effect size for a quantitative trait such as vitamin blood levels is the change in blood concentration of that trait due to the risk alleles present in an individual. Publicly available databases like the GWAS catalogue provide access to summary statistics of these data that can be used to calculate PRS. This genetic predisposition can then be accounted for when calculating a recommendation for an individual's nutrient requirements, thus establishing a "personal-

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ized RDA," as recently demonstrated in school-age children in Brazil by Fuzo et al. [4].

In order to calculate the actual intake needs of a vitamin for an individual, one needs to establish the dose–response relationship between intake of said vitamin and factors that influence its bioavailability, including the genetic effects to achieve a specific blood threshold (i.e., nutrient sufficiency). As with all tests, the result of such genetic profiles should be considered in combination with, not isolation from, clinically observable features. Figure 2 provides an example for the calculation of intake needs based on a PRS for vitamin D. Figure 2a shows the average decrease of vitamin D blood concentration for each additional SNP, with stratification of the PRS into "low-," "medium-," and "high"-risk categories. The horizontal line delineates blood levels considered to reflect vitamin D sufficiency. Figure 2b then shows the interaction between the genetic stratification and the known effect of skin pigmentation on vitamin D requirements. Propositions of personalized advice on intake will then need validation to confirm that they support the achievement of adequate intake.

The proliferation of publicly available genetic profiling services is rapidly increasing the feasibility of applying PRS for nutrition applications, along with others. The next challenge for consumers and clinicians will be to ensure that advice based on the results provided by such services is reliable and relevant.

Personalization through Microbiome Characterization

As with the human genome, "the metagenome" of the gut microbiota is now recognized to influence health. Large observational studies have identified associations between variations in the microbiome and variations in health status according to diet [5, 6].

Proof of concept studies have shown how diet can change the microbiota and its metabolite output in a manner that should influence health, and that dominant features of habitual diet can determine how the microbiome responds to such specific dietary inputs [7]. One of the most cited examples is the variation between meat consumers and excluders in the production of tri-methylamine *N*-oxide, a microbial metabolite associated with cardiovascular complications, following ingestion of L-carnitine [8]. It remains challenging, however, to demonstrate that dietary alteration based on personal microbiome characterization can clearly impact hard health outcomes. For instance, recent efforts have aimed to identify associations between microbiome profiles and the impact of sweeteners on responses to glucose challenge but the interpretation is complicated by the within-individual test-retest variability of response to a standard challenge,

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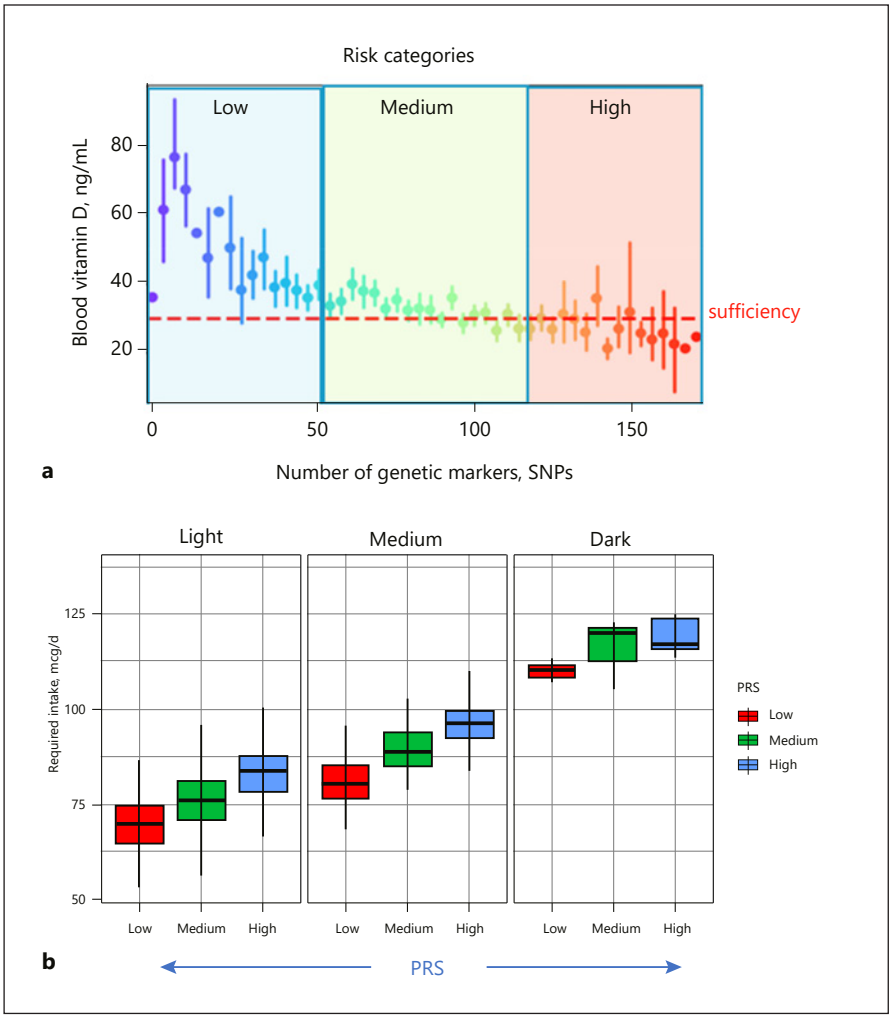

Fig. 2. Representative data illustrating the interaction between genetic and phenotypic characteristics in the example of vitamin D requirements, using Nestlé internal data [unpublished]. **a** Blood vitamin D levels of adult subjects according to the number of single-nucleotide polymorphisms known to influence vitamin D absorption. The horizontal dashed line indicates a low threshold of blood levels considered to indicate vitamin sufficiency. **b** Average and distribution (box and whiskers plot represents median and interquartile range) of recommended intake according to the degree of skin pigmentation, adjusted for polygenic risk score.

illustrating that separation of the factors that influence individual responses will require huge sample sizes of exquisitely characterized subjects [9].

The example of carbohydrate digestion demonstrates the issues well. It is established that individuals vary in the number of copies of the amylase gene that

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they carry, and that this alters the expression of amylase in the saliva and most likely digestive tract. Such variation will influence the ease of digestion of starches and glucose absorption kinetics. Maldigested carbohydrates, starch or otherwise, represent a significant nutrient source for the microbiota of the colon. Bacteria within the microbiota vary in their ability to use different carbohydrates as sources of energy according to their expression of carbohydrate-active enzymes, or CAZymes. Genetic variation in carbohydrate digestion has been shown to influence microbiome composition and functional capacity for carbohydrate metabolism when diet intake is standardized [10]. Variation in the expression of lactase with geography and age may have similar effects.

Nevertheless, there are good reasons to believe in the importance of matching carbohydrate intake to an individual's microbiome. While dietary fiber can support optimal gastrointestinal transit, many of the benefits of fiber derive from its fermentation in the colon. Metabolites such as short-chain fatty acids not only act as an energy source for the gut epithelium but also signal to the immune system and, through entry into the systemic circulation, modulate various physiological functions including insulin secretion. A mismatch between CAZymes in the microbiota and dietary carbohydrate intake risks losing these benefits and increasing discomfort through colonic bulk. We recently investigated how diet can be used to predict patterns of carbohydrate metabolism in the microbiome, reducing the need for fecal testing (manuscript in preparation).

The concept of matching carbohydrate intake with digestion capabilities has even greater relevance in early life when children's microbiomes are still developing. Bhattacharya et al. identified CAZyme pattern differences between infants under 1 year of age, children between one and five, and adults [11]. This is consistent with the recognized sequential development of the microbiome in the first 3 years of life. The first exogenous glycans to reach the gut microbiota are the human milk oligosaccharides, the breastmilk profile of which is recognized to vary over time after parturition. The subsequent introduction of a complementary diet represents the first exposure to plant glycans, stimulating further diversification of the species present.

The concept of a standard trajectory for microbiome maturation against which to benchmark a child's progress is attractive, but will rely on advanced modelling methods [12]. There is increasing evidence that variations in early microbiome development are associated with later health outcomes, either reduced growth through delayed maturation or increased risk of immune-mediated disorders through premature maturation. Where individuals are diverted from the standard trajectory, for instance through caesarean section delivery, antibiotic exposure or other factors, supplemental probiotics may have a role in supporting appropriate early establishment of keystone species such as Bifido-

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bacteria. It remains to be clarified whether microbiome testing, to confirm probiotic engraftment or persistence of desirable resident strains, can help to guide individual use of such supplemental support.

Personalization of Recommendations through Digital Technology

Digital platforms can be an effective medium through which to enable effective personalization. Their success relies on careful attention to the user experience so that interactions are easy and relevant data are readily accessible through personal devices. These interactions include data recording/capture, and expression of any resulting recommendations in a form that is engaging and motivating for adoption.

Nutrition and lifestyle changes take time so solutions or programs offered through digital platforms must engage users, and remain relevant to them, throughout their health journey. An ideal situation occurs with the creation of a virtuous cycle of data sharing, evaluation, interpretation, updated recommendations, and renewed adoption. Successful measurement is crucial to establish such improvement cycles. Measuring nutrition and lifestyle can increase the personalization of advice on how to improve, in any particular aspect of health. It should be noted that it may be possible to provide useful advice without perfect accuracy in measurement; rather, recommendation to adopt one of several possible regimens can be driven by a few key prognostic features.

Distinguishing between accurate measurement and relevant measurement may be particularly important for the evaluation of the role of digital sensors in nutrition personalization. Parameters such as physical activity, sleep, heart rate, and others are measured using smartphones and smartwatches. The increasing accessibility of such sensors enables research in free-living settings – the "lab at home" approach – and increases their assimilation into everyday life. Nevertheless, the measurement performance of each such sensor is still being established. Each parameter they measure needs validation, along with characterization of precision, trueness, and variation between similar sensors and other factors.

Of the relevant factors to measure, nutritional intake remains one of the hardest. People's eating behavior is intrinsically complex, including the interactions between levels of analysis such as nutrient, ingredient, food, meal, and diet. The consensus for the gold standard of dietary data capture still defaults to traditional methods such as 24-h recalls, food frequency questionnaires, or multiple-day food diaries. These should be administered and reviewed by a trained nutritionist or dietitian, as is common practice in nutritional epidemiology. Fur-

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ther complexity arises when considering the impact of diet on the microbiome, where novel approaches such as food-tree analysis may be needed [13].

Digitalization of food logging has significantly progressed through popular self-assessment applications like MyFitnessPal, Noom, Insidetracker, or the Tibay Calculator used by parents in the Philippines to assess their child's nutrition status (https://www.bearbrand.com.ph/tibay-calculator). Evaluation of one application showed that its measurements are comparable to those of the 24-recall gold standard [14]. Digitalization may also assist standardization of subjective measures such as portion size estimation. Predictive models for recognizing foods based on e.g., MyFoodRepo data [15] as well as models for automatic portion size estimation from food images are active areas of research.

Data acquisition requires interpretation to add value. This relies on databases of food composition and diet characteristics. Public food composition databases can be connected to compile isolated sources of knowledge. Additional data from other sources can supplement these compilations and then machine learning models can enrich and standardize the interactions between datasets. One such example is the food and nutrition data platform managed by Nestlé Research [16].

Communicating the output of data interpretation requires a translation step: to make the message usable and useful for users. Summary terms can help; examples include healthy diet scores, risk scores, and different biological age concepts. Healthy eating scores make it simple for the user to understand how they can improve their situation by following dietary advice [17]. Such scores are based on precise knowledge of food nutrient composition, precise food intake data, and dietary reference values for a relevant set of nutrients (e.g., RDAs, DRVs). In some cases, the dietary reference intakes can be personalized using genetic data or adapted using recommendations based on a medical condition. Generally, healthy eating scores need validation to prove their sensitivity and utility in guiding any health status change. Further work is needed to determine the format and narratives that most effectively balance information precision with an attractive "call to action."

Recommendation systems ultimately require clinical evidence of efficacy and impact. An example of such a system is the recent launch of "Gut Friendly Recipes," an activity led by the Crohn's and Colitis Foundation (www.crohnscolitisfoundation.org/gutfriendlyrecipes), to offer a large choice of recipes that can be filtered and browsed according to dietary restrictions adopted by people living with inflammatory bowel disease. Recipes can be assembled into a weekly meal plan that ensures nutritional balance and dietary diversity according to individual taste. Usage, users' nutritional status, and symptom burden can all be considered as patient-centered outcome measures for future evaluation of efficacy.

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Beyond efficacy, maintenance of privacy and equity of access are key considerations for digital health applications, along with clear routes of liability once they are implemented in care pathways. Many operational, technical, and clinical challenges remain to be tackled to ensure that digital applications add value for users. Nevertheless, the mounting interest in the sector will drive continued integration of evolving datasets, underpinned by parallel development of the relevant decision algorithms and user interfaces.

Conclusion

The goal of nutritional advice tailored to an individual's dynamic requirements remains highly attractive. Integrating factors such as an individual's genomic profile, and the metagenomic profile of their microbiome, may improve evaluation of dietary needs; wearable sensors may facilitate time-sensitive adjustment of advice. The more that relevant data can be collected without conscious action by the individual, the more such advice systems could be managed automatically. Such systems will need to account for two other sources of innovation. Firstly, the digestive tract has evolved over 550 million years to harvest nutrients according to the organism's requirements. Secondly, expert clinical judgement has developed to integrate information on a person's situation and needs, and produce a coherent, actionable message for the individual concerned. This judgement includes emotional and human factors and is a key component of the relationship between clinical practitioners and patients that may not be easily recreated with technology. Thus, personalized nutrition extends and broadens the classic model of expert consultation, offering new opportunities to support health through diet.

Conflict of Interest Statement

All authors are employees of Société des Produits Nestlé S.A.

Author Contributions

G.M. conceived the article. All authors contributed to the development of the article structure and content. G.M. is the final guarantor of the content.

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References

1 Borel P, Desmarchelier C. Bioavailability of fat-soluble vitamins and phytochemicals in humans: effects of genetic variation. Annu Rev Nutr. 2018;38:69–96.
2 Wand H, Lambert SA, Tamburro C, Iacocca MA, O'Sullivan JW, Sillari C, et al. Improving reporting standards for polygenic scores in risk prediction studies. Nature. 2021;591(7849):211–9.
3 Gettler K, Levantovsky R, Moscati A, Giri M, Wu Y, Hsu NY, et al. Common and rare variant prediction and penetrance of IBD in a large, multi-ethnic, health system-based biobank cohort. Gastroenterology. 2021;160(5):1546–57.
4 Fuzo CA, da Veiga Ued F, Moco S, Cominetti O, Métairon S, Pruvost S, et al. Contribution of genetic ancestry and polygenic risk score in meeting vitamin B12 needs in healthy Brazilian children and adolescents. Sci Rep. 2021;11(1):11992.
5 Asnicar F, Berry SE, Valdes AM, Nguyen LH, Piccinno G, Drew DA, et al. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. Nat Med. 2021;27(2):321–32.
6 Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163(5):1079–94.
7 David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559–63.
8 Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576–85.
9 Suez J, Cohen Y, Valdes-Mas R, Mor U, Dori-Bachash M, Federici S, et al. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. Cell. 2022;185(18):3307–28.e19.
10 Poole AC, Goodrich JK, Youngblut ND, Luque GG, Ruaud A, Sutter JL, et al. Human salivary amylase gene copy number impacts oral and gut microbiomes. Cell Host Microbe. 2019;25(4):553–64.e7.
11 Bhattacharya T, Ghosh TS, Mande SS. Global profiling of carbohydrate active enzymes in human gut microbiome. PLoS One. 2015;10(11):e0142038.
12 Banjac J, Sprenger N, Dogra SK. Microbiome toolbox: methodological approaches to derive and visualize microbiome trajectories. Bioinformatics. 2023;39(1):btac781.
13 Johnson AJ, Zheng JJ, Kang JW, Saboe A, Knights D, Zivkovic AM. A guide to diet-microbiome study design. Front Nutr. 2020;7:79.
14 Blanchard CM, Chin MK, Gilhooly CH, Barger K, Matuszek G, Miki AJ, et al. Evaluation of PIQ-NIQ, a novel mobile application for capturing dietary intake. J Nutr. 2021;151(5):1347–56.
15 Mohanty SP, Singhal G, Scuccimarra EA, Kebaili D, Heritier H, Boulanger V, et al. The food recognition benchmark: using deep learning to recognize food in images. Front Nutr. 2022;9:875143.
16 Plestina R. Food & Nutrition data platform – an enabler for digital nutrition transformation. 2021.
17 Mainardi F, Drewnowski A, Green H. Personalized nutrient profiling of food patterns: Nestle's nutrition algorithm applied to dietary intakes from NHANES. Nutrients. 2019;11(2):379.

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Diet-Microbiome Interactions in Pediatric Gastrointestinal Disease

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Abstract

Our gut harbors a highly dense community of microorganisms which play an important role in the maintenance of human health. Perturbation of this microbial community is believed to cause or influence the risk of development of diseases, including noncommunicable diseases such as those of the gastrointestinal tract. This review presents recent literature on the role of the gut microbial community and its interaction with diet in the etiology, progression, and outcomes of gastrointestinal diseases in children. We allude that even though the gut microbiome is commonly altered in pediatric conditions like inflammatory bowel disease, celiac disease, intestinal failure, and necrotizing enterocolitis, it is still unclear the implications these findings have for the underlying etiology of these conditions or in informing clinical and nutritional practices. It is possible that in the future, the gut microbiome may help in disease diagnosis, prediction of clinical outcomes, or comprise a target for dietary therapy.

Introduction

The human gut is home to a complex microbiome which is composed of a multitude of different fungi, viruses, and archaea with bacteria representing the dominant kingdom [1]. Under normal, healthy, conditions, the microbiome in our gut is predominantly comprised of bacteria belonging to the Firmicutes and

Bacteroidetes phyla such as *Clostridium*, *Ruminococcus*, and *Bacteroides*. However, in certain diseases, the composition of the microbiome shifts from the usual profile, which we normally see in healthy people, to a state commonly referred to us as microbial dysbiosis, which is believed to be a major contributing factor toward noncommunicable disease. This microbial dysbiosis in many gastrointestinal diseases arises due to one of two shifts: a decline in beneficial members of the microbiome or an increase in potentially pathogenic or pathobiont organisms [2]. It is also important to note that this microbial dysbiosis does not refer only to compositional shifts but also to changes to the functionality of the microbial community which also have considerable implications for human health [3].

This dense microbial community is of crucial importance to human health. Bacteria, in particular, are capable of producing a myriad of metabolites the majority of which our human eukaryotic cells do not bear the genes to encode for. The most typical class of these metabolites are the short-chain fatty acids (SCFAs) originating from the fermentation of indigestible carbohydrates and fiber by specialized bacterial enzymes such as glycoside hydrolase. Other microbial metabolites that are important for human health include conjugated linoleic acid, which some *Bifidobacterium* spp. have shown an ability to produce and trimethylamine, the precursor of trimethylamine-*N*-oxide which is derived from the metabolism of choline, and choline-containing compounds present in the dietary food by gut bacteria [4, 5]. The gut microbiome also produces vitamins for the host, regulates local and whole-body inflammatory responses, facilitates absorption of electrolytes and calcium at the distal colon, and produces an array of metabolites which can both protect us from diseases, or cause it.

The role of diet in the modulation of the gut microbiome is well-documented whereby individuals following diets rich in animal products and processed foods, such as we see in the modern Western diet, have microbiome compositions different from those who eat other diets such as the Mediterranean diet which is more focused on whole grains, nuts, and vegetables [6].

The diet we consume can be utilized in several different ways to address the onset or progression of gastrointestinal disease (Fig. 1). This can be through complete or partial replacement of habitual diet such as the administration of exclusive enteral nutrition (EEN) in Crohn's disease (CD) or through diet supplementation with fiber or prebiotics and probiotics [7] (Fig. 2). As the role of the gut microbiome in health and disease becomes more apparent, methods to restore microbial dysbiosis and revert the microbiome back to its normal state are of great interest. Herein, we aim to provide a synopsis of current affairs in ways that the dysbiosis of the gut microbiome can be addressed via dietary interventions and how this can influence our gut microbiome in the context of

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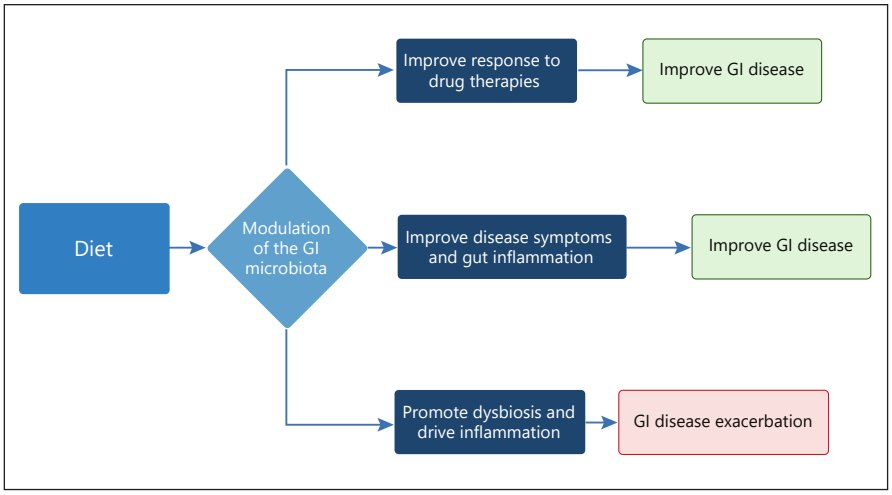

Fig. 1. Schematic displaying the complex interplay between diet and the human microbiome in the onset and management of gastrointestinal disease.

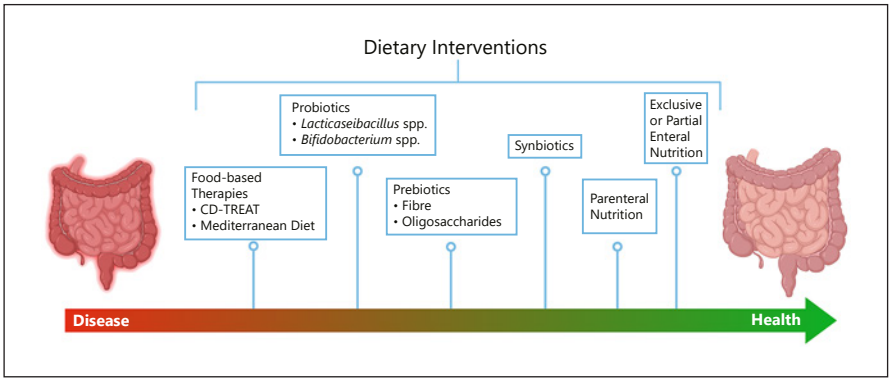

Fig. 2. Microbiota modifying dietary interventions with relevance to the management of gastrointestinal diseases and their potential effect on the gut microbiota.

noninfectious, noncommunicable gastrointestinal diseases in children. We focus on four important gastrointestinal conditions, namely inflammatory bowel disease (IBD), celiac disease (CoD), intestinal failure (IF), and necrotizing enterocolitis (NEC).

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Inflammatory Bowel Disease

Ulcerative colitis (UC) and CD both fall under the umbrella of IBD. Both are chronic inflammatory conditions where CD can affect any part of the gastrointestinal tract from the mouth to the anus, whereas UC is confined to the colon only. Both conditions are characterized by extensive microbial dysbiosis; however, these differences are less apparent in UC compared to CD [2]. Most commonly seen in IBD are increases in the abundance of Proteobacteria and decreases in Firmicutes, a large number of which are fiber-fermenting organisms [2]. To date, one of the largest studies investigating the microbiome in CD, performed by Gevers and colleagues, in pediatric patients, observed enriched levels of Neisseriaceae, Gemellaceae, Fusobacteriaceae, Veillonellaceae, Pasteurellaceae, Enterobacteriaceae, and a decrease in Bacteroidales, Clostridiales, Erysipelotrichaceae and Bifidobacteriaceae in feces and mucosal biopsies of patients with CD [8]. *Escherichia coli* strains with adherent and invasive properties have also been implicated in IBD cause, particularly in ileal CD [9]. Despite our deep knowledge from studies profiling the composition of the gut microbiome in IBD and how it differs from that of health, the extent to which microbial changes arise because of the disease itself or if it is a driving factor behind disease onset is yet unclear. However, what is clear is that the dysbiotic nature of the gut microbiome in IBD is accompanied by a shift in the functional profile as well, with studies reporting alterations in SCFA concentrations and other metabolites [10].

Prebiotics and probiotics have gained interest within the field of IBD research and therapy over the past 3 decades and promising results have been reported mainly with animal models and in vitro [11]. However, these encouraging results do not commonly translate to clinical research in humans except for certain pre- and probiotics mixtures in UC, albeit the quality of evidence remains low [12, 13]. The effectiveness of intestinal material transplantation from healthy donors has produced mixed results from patients with CD and in general positive signals in patients with UC [14] but what remains to be addressed is if combining intestinal material transplantation with dietary therapies aiming to enhance gut colonization can improve overall treatment response rates.

Diet is a major modulator of the gut microbiome with differences in microbial composition observed across countries and different dietary habits [15]. EEN, the treatment of choice in pediatric CD, improves symptom severity and induces clinical remission [16]. Therapy with EEN involves the intake of a complete nutritional formula as a replacement for a person's habitual diet and has been shown to induce clinical remission in patients at a rate equal to that of corticosteroids as well as promoting mucosal healing [17]. The way in which EEN induces remission is thought to occur through the modulation of the gut micro-

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biome [18]. Previous evidence shows that the use of EEN decreases bacterial diversity and reduces microbial load [19]; yet the evidence remains inconsistent. This may seem counterintuitive as reduced bacterial diversity is often associated with disease; however, this decrease in diversity along with reductions in beneficial bacteria and metabolites such as *Faecalibacterium prausnitzii* and butyrate, respectively, aligned with decreases in intestinal inflammation and the onset of clinical remission [19]. Nonetheless, what remains unclear is if these microbial shifts are brought on as a direct result of the dietary therapy or due to inflammation reduction from successful EEN therapy. To address this, a recent study showed that EEN targets a specific panel of microbes in the gut and acts more as a means to disrupt the dysbiotic and harmful microbiome in CD [20]. This study identified a population of organisms being suppressed, allowing another to grow into a new niche. These findings suggest that EEN prompts the gut microbiome in CD to transition away from its stable, harmful state where it is composed of organisms that have adapted to survive in the CD gut, causing a shift in the host–microbe interactions and therefore reducing the inflammatory profile of the host.

Despite the well-documented efficacy, treatment with EEN is accompanied by some limitations, particularly regarding compliance and palatability issues. This has led to greater interest in the use of food exclusion diets such as the Crohn's Disease Exclusion Diet (CDED) plus partial enteral nutrition (PEN) which allows patients to eat certain types of foods while ameliorating intestinal inflammation and reducing exposure to presumably dietary triggers that may cause dysbiosis and interact with the innate and adaptive immune system [21]. Other mechanisms include the modulation of the intestinal microbiome by reducing bacterial adhesion and translocation and increasing intestinal permeability [21]. CDED is coadministered with five daily mandatory foods, and 50% of a person's energy requirements from PEN [21]. In their flagship study, this combination approach resulted in an increase in *Ruminococcus*, *Roseburia*, *Anaerotruncus*, and *Oscillibacter* [21] and both dietary interventions (CDED + PEN and EEN) induced a decrease in the abundance of Proteobacteria, suggesting that targeting this phylum might be key in effectively reducing intestinal inflammation. This observed decrease in Proteobacteria, in theory, provides a niche for the recovery of Firmicutes, indicating that the microbiome is transitioning toward a less dysbiotic state. A follow-up report from the same study showed that not only does dietary therapy with CDED + PEN and EEN correct dysbiosis in CD microbiome through decreasing Proteobacteria, but also influences the functionality of the microbiome. This was demonstrated through the identification of a metabolomic phenotype of the microbiome during EEN being associated with that of healthy patients [22].

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The observation that EEN extensively modifies the gut microbiome of patients with CD parallels with a reduction in gut inflammation contributed to the development of the CD treatment-with-eating (CD-TREAT) diet [23]. The diet aims to address CD symptoms through the use of a real food diet with a similar nutritional composition to the EEN formula, tailored to the food preferences and nutrient requirements of patients. In preclinical data in animal models and healthy individuals, CD-TREAT produced similar results to EEN, including a reduction in the abundance of beneficial taxa such as *Faecalibacterium* and *Bifidobacterium* [23]. These microbial effects observed in animal models of IBD were paralleled with the improvement of histopathological scores of ileitis and downregulation in the mucosal expression of inflammatory cytokines. Although microbiome composition was not assessed, CD-TREAT induced remission in 60% of children which was accompanied by significant decreases in fecal calprotectin levels, an objective marker of gut inflammation. To date, this is the only study whereby direct dietary modification of the gut microbiome ameliorated gut inflammation in children with CD.

Thus far, the ineffectiveness of treatment strategies to establish a healthy microbiome, and in contrast, the effectiveness of dietary therapies aiming to suppress the gut microbiome, as well as antibiotics, support the doctrine that suppression of inflammatory members of the gut microbiome may be required to alleviate gut inflammation in CD. In contrast, strategies aiming to promote a normal gut microbiome composition such as probiotics and prebiotics hold better promise in UC.

Intestinal Failure

Patients with IF require intravenous feeding with parenteral nutrition (PN) to survive and grow as their peers. The microbiome in people with IF is probably the most extensively dysbiotic microbiome ever described in the literature [24]. Consistent data from various studies show that patients with IF present with significant reductions in microbial diversity and excessively high increases in Enterobacteriaceae family members, a normally subdominant family of the human gut microbiome [24]. The reduced flux of nutrient substrates from the host diet to the distal gut is likely to be the driving influence for this increase in Enterobacteriaceae which is accompanied by marked decreases in Bacteroidetes and Firmicutes due to a deficiency in fermentable substrates to support their growth. Overgrowth of aerotolerant anaerobic bacteria, such as *Lactobacillus* spp., in the small intestine in IF is also common. In patients with compromised gut barrier function, such as in IF, this leads to increased production of D-lactic

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acid, which the human body is unable to metabolize. In turn, this can result in the patient developing D-lactic acidosis which can have life-threatening downstream effects such as altered mental status and ataxia [25].

Early data from low-quality studies with dietary supplementation of fiber, SCFAs, or probiotics showed promising results [26]. However, some of these results can be conflicting, with results from a randomized control trial with probiotic combinations of *Lacticaseibacillus rhamnosus* and *Lactobacillus johnsonii* did not observe any notable changes in microbiome composition [27]. Despite this, the use of synbiotics in IF produced more efficacious results [28]; however, replication in additional high-quality studies is needed. Authors reported that synbiotic supplementation increased the levels of butyrate, propionate, and acetate in feces as well as restoring the microbiome by increasing Bifidobacteria abundance and decreasing that of Enterobacteriaceae. Nonetheless, the implications of these effects on the clinical outcomes of patients are unclear.

Use of PN is a life-saving treatment for infants and children affected by IF, and recently, interest in the effects of PN on the composition and functionality of the gut microbiome has increased. However, as IF is a rare condition, many studies have small sample sizes or have been performed in animal models rather than in pediatric patient populations [29]. Some studies have described the differences in the microbiome of patients who successfully weaned off PN compared to those still on PN [30]. These previous studies showed that patients who had not successfully completed PN had a significantly less diverse microbiome compared to those who were weaned off, and this microbiome was dominated by Enterobacteriaceae [24]. Another study observed similar results where patients receiving PN a over long duration were associated with increased abundances of Enterobacteriaceae, and *Lactobacillus* abundance correlated with short PN durations [31]. Taken together, these results show that patients with IF who end up successfully weaning off PN have a less dysbiotic gut microbiome, suggesting that the gut microbiome in IF patients could be used as a biomarker to determine PN outcome. Future research is now exploring whether microbial dysbiosis in patients with IF is predictive of adverse disease outcomes, including small intestinal bacterial overgrowth, liver disease, and D-lactic-acidosis.

Coeliac Disease

CoD, a condition that more commonly occurs in children, is an autoimmune disorder triggered by an abnormal immune reaction to gluten from cereals in food. Although approximately 30%–40% of the general population have a genetic predisposition to CoD, the disease only develops in approximately 1%–2%

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of individuals [32]. Much like IBD, the prevalence of CoD has increased in recent years with a particular increase in Western countries, suggesting that an environmental trigger is at play.

It is well established that the gut microbiome plays a crucial role in digestion along the gastrointestinal tract as well as in the development, regulation, and homeostasis of innate immune cells in the gut. Therefore, it is perhaps unsurprising that there is evidence of microbial dysbiosis in the gastrointestinal tract of individuals with CoD. Overall, the microbiome in children with CoD presents with a higher microbial diversity than that of healthy children and this increased diversity is associated with higher abundances of *Bacteroides* and *Prevotella*, whereas *Clostridium* spp. and *F. prausnitzii* are found in higher abundances in healthy controls [32]. CoD is typically managed with a gluten-free diet (GFD). Studies have shown that the duration of GFD negatively correlates with the abundance of the opportunistic pathogens *Haemophilus parainfluenzae* and *Streptococcus sanguinis* while altering host–microbe cross-talk by influencing miRNA expression [33].

Current and recent evidence found a reduction in *Bifidobacterium* abundance in CoD, most likely due to reduction of fiber from exclusion of gluten-containing food from the diet. This genus, *Bifidobacterium*, has gained attention as a potential microbial culprit for modulating the aberrant immune response to gluten in CoD-afflicted individuals. Studies investigating the efficacy of probiotics in CoD in humans have been limited; however, one study sought to explore the effect of supplementing CoD patients with *Bifidobacterium breve* compared to placebo [34]. The results of this study showed that the gut microbiome of CoD patients receiving the probiotic underwent a shift toward a more balanced composition with an increase of Actinobacteria as well as restoring a healthy Firmicutes–Bacteroidetes ratio.

Despite some promising results arising from studies investigating the role of probiotics in the management of CoD, a large-scale, multicenter study which enrolled 6,000 participants that were genetically susceptible to developing CoD found no difference in CoD risk following administration of probiotics in the form of *L. rhamnosus* and *Limosilactobacillus reuteri* [35].

In CoD, it currently remains unclear whether a perturbed gut microbiome is causal to CoD development, or if this is an effect of changes in gastrointestinal physiology and motility, increased luminal substrate availability from nutrient malabsorption, and in those with diagnosed disease, the effect of dietary alterations during GFD.

In a recent study, using next-generation sequencing of the gut microbiome and targeted metabolomics, authors identified 11 bacterial taxa which composed a unique microbe signature distinctive of CoD with high diagnostic ac-

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curacy [36]. Nonetheless, most of the microbial alterations observed in children with CoD on treatment with GFD were attributed to differences in their dietary intake compared with the diet of healthy children on an unrestricted diet. In the same study, patients with GFD had a reduced production of beneficial fecal butyrate which is most likely explained by the reduced intake of fermentable fiber from gluten-containing cereals and not substituting them with other sources of fiber (e.g., fruits, vegetables, pulses).

Necrotizing Enterocolitis

NEC is a debilitating disease seen in preterm neonates [37]. Infants with NEC typically present with feeding intolerance, abdominal distention, and bloody stools which commence shortly after birth. The exact cause of NEC is not fully understood; however, an abnormal microbiome composition is thought to be a major contributing factor as the disease is commonly seen in preterm infants who are often fed with infant formula and low breast milk, which is rich with human milk oligosaccharides (HMOs) [7]. HMOs possess prebiotic and antimicrobial properties; however, they are absent from preterm milk formulas; albeit some synthetic analogues have entered the market in the last decade.

It is believed that lack of HMO intake by preterm infants results in them developing an abnormally colonized gastrointestinal tract which is less diverse than healthy controls and dominated by *Staphylococcus*, *Klebsiella*, *Escherichia*, *Enterobacter*, and *Enterococcus*. In preterm infants, disialyllacto-*N*-tetraose alone could predict the risk of NEC with 90% sensitivity/specificity, whereas the gut microbiome of preterm infants receiving high levels of this specific HMO in mothers' milk was more likely to transition into a *Bifidobacterium*-rich gut microbiome [38]. A recent randomized controlled trial (RCT) showed that HMO supplementation (2′-fucosyllactose and lacto-*N*-neotetraose) was safe and well-tolerated in preterm infants [39].

The use of probiotics in the treatment of NEC has been gaining attention as increased levels of Bifidobacteria have been associated with lower disease severity and lower risk of NEC development. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition provides advice on which specific strains might potentially be used and which strains should not be used for preterm neonates, considering safety profiling is met [39]. It is crucial to determine the optimal probiotic strains, concentrations, and delivery methods to best implement their use in NEC management. The use of prebiotics and less so HMOs in preterm milk formulas has exhibited some, encouraging data, indicating that

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the use of such prebiotics increases the abundance of beneficial bacteria such as *Bifidobacterium* [40, 41].

Oral administration of *Bifidobacterium* has subsequently increased the abundance of both *Bifidobacterium* and *Enterococcus* in recipient stool samples, contributing to colonic acetic acid production [42]. This shift in microbiome composition could result in increased growth of SCFA-producing bacteria as seen in an RCT where supplementation with probiotics caused an increase in butyrate and propionate [43].

With prebiotics and probiotics providing exciting targets for therapeutic intervention in infants, it is important that selection of health care professionals is driven by strong evidence, which is unlikely to be the same for all infants, suggesting a precision nutritional therapy approach may be required.

Conclusion

More recently, food and dietary therapy have become a focal point in people's lives with this being particularly true for those with gastrointestinal diseases, such as those discussed above. With the prevalence of these noncommunicable conditions increasing worldwide, particularly in areas following a Western diet, affected individuals and clinicians continue to search for alternative methods to aid in their management. Dietary interventions offer a promising alternative with the option to easily tailor these to the needs of the individual and are often free of negative side effects. Herein, we described recent evidence on the role of gut microbiome and its interaction in pediatric gastrointestinal diseases. Although it is not yet apparent if the shifts observed in gastrointestinal diseases are the cause of these conditions, there are various dietary treatments and supplements, such as prebiotics and probiotics with microbiome-modifying diets, which can influence the microbiome and disease outcomes in those with diseases such as IBD, IF, and CoD. It is also possible that several of these microbiome-modifying therapies may be used in conjunction with pharmacological agents to improve overall patient treatment outcomes and their quality of life.

Conflict of Interest Statement

K.G. received research funding, speaker's fees, and consultancy from Nestle Health Science, Nutricia-Danone, Baxter, Abbott, Janssen, Abbvie, Servier, Mylan, and Bristol-Myers Squibb. B.S. has no conflicts of interest to declare.

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Author Contributions

K.G. and B.S. both contributed to the writing and editing of the manuscript.

References

1 Kho ZY, Lal SK. The human gut microbiome – a potential controller of wellness and disease. Front Microbiol. 2018;9:1835.
2 Duvallet C, Gibbons SM, Gurry T, Irizarry RA, Alm EJ. Meta-analysis of gut microbiome studies identifies disease-specific and shared responses. Nat Commun. 2017;8(1):1784.
3 Das B, Nair GB. Homeostasis and dysbiosis of the gut microbiome in health and disease. J Biosci. 2019;44(5):117.
4 Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576–85.
5 Lehnen TE, da Silva MR, Camacho A, Marcadenti A, Lehnen AM. A review on effects of conjugated linoleic fatty acid (CLA) upon body composition and energetic metabolism. J Int Soc Sports Nutr. 2015;12:36.
6 García-Montero C, Fraile-Martínez O, Gómez-Lahoz AM, Pekarek L, Castellanos AJ, Noguerales-Fraguas F, et al. Nutritional components in western diet versus mediterranean diet at the gut microbiota–immune system interplay. Implications for health and disease. Nutrients. 2021;13(2):699.
7 Gerasimidis K, Gkikas K, Stewart C, Neelis E, Svolos V. Microbiome and paediatric gut diseases. Arch Dis Child. 2022;107(9):784–9.
8 Gevers D, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014;15(3):382–92.
9 Ormsby MJ, Johnson SA, Carpena N, Meikle LM, Goldstone RJ, McIntosh A, et al. Propionic acid promotes the virulent phenotype of Crohn's disease-associated adherent-invasive *Escherichia coli*. Cell Rep. 2020;30(7):2297–305.
10 Alghamdi A, Gerasimidis K, Blackburn G, Akinci D, Edwards C, Russell RK, et al. Untargeted metabolomics of extracts from faecal samples demonstrates distinct differences between paediatric Crohn's disease patients and healthy controls but no significant changes resulting from exclusive enteral nutrition treatment. Metabolites. 2018;8(4):82.
11 Liu N, Wang H, Yang Z, Zhao K, Li S, He N. The role of functional oligosaccharides as prebiotics in ulcerative colitis. Food Funct. 2022;13(13):6875–93.
12 Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut. 2011;60(7):923–9.
13 Chermesh I, Tamir A, Reshef R, Chowers Y, Suissa A, Katz D, et al. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. Dig Dis Sci. 2007;52:385–9.
14 Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Aliment Pharmacol Ther. 2017;46(5):479–93.
15 David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559–63.
16 van Rheenen PF, Aloi M, Assa A, Bronsky J, Escher JC, Fagerberg UL, et al. The medical management of paediatric Crohn's disease: an ECCO-ESPGHAN guideline update. J Crohns Colitis. 2020:jjaa161.
17 Yu Y, Chen K-C, Chen J. Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. World J Pediatr. 2019;15(1):26–36.
18 Svolos V, Gkikas K, Gerasimidis K. Diet and gut microbiota manipulation for the management of Crohn's disease and ulcerative colitis. Proc Nutr Soc. 2021:1–15.
19 Gerasimidis K, Bertz M, Hanske L, Junick J, Biskou O, Aguilera M, et al. Decline in presumptively protective gut bacterial species and metabolites are paradoxically associated with disease improvement in pediatric Crohn's disease during enteral nutrition. Inflamm Bowel Dis. 2014;20(5):861–71.
20 Runde J, Veseli I, Fogarty EC, Watson AR, Clayssen Q, Yosef M, et al. Transient suppression of bacterial populations associated with gut health is critical in success of exclusive enteral nutrition for children with Crohn's disease. J Crohns Colitis. 2023;17(7):1103–13.
21 Levine A, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. Gastroenterology. 2019;157(2):440–50.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 67–78 (DOI: 10.1159/000534950)

22 Verburgt CM, Dunn KA, Ghiboub M, Lewis JD, Wine E, Sigall Boneh R, et al. Successful dietary therapy in paediatric Crohn's disease is associated with shifts in bacterial dysbiosis and inflammatory metabotype towards healthy controls. J Crohns Colitis. 2022;17(1):61–72.
23 Svolos V, Hansen R, Nichols B, Quince C, Ijaz UZ, Papadopoulou RT, et al. Treatment of active Crohn's disease with an ordinary food-based diet that replicates exclusive enteral nutrition. Gastroenterology. 2019;156(5):1354–67.
24 Neelis E, de Koning B, Rings E, Wijnen R, Nichols B, Hulst J, et al. The gut microbiome in patients with intestinal failure: current evidence and implications for clinical practice. JPEN J Parenter Enteral Nutr. 2019;43(2):194–205.
25 Kowlgi NG, Chhabra L. D-Lactic acidosis: an underrecognized complication of short bowel syndrome. Gastroenterol Res Pract. 2015;2015:476215.
26 Reddy VS, Patole SK, Rao S. Role of probiotics in short bowel syndrome in infants and children – a systematic review. Nutrients. 2013;5(3):679–99.
27 Piper HG, Coughlin LA, Hussain S, Nguyen V, Channabasappa N, Koh AY. The impact of *Lactobacillus* probiotics on the gut microbiota in children with short bowel syndrome. J Surg Res, 2020;251:112–8.
28 Uchida K. Takahashi T, Inoue M, Morotomi M, Otake K, Nakazawa M, et al. Immunonutritional effects during synbiotics therapy in pediatric patients with short bowel syndrome. Pediatr Surg Int. 2007;23(3):243–8.
29 Heneghan AF, Pierre JF, Tandee K, Shanmuganayagam D, Wang X, Reed JD, et al. Parenteral nutrition decreases paneth cell function and intestinal bactericidal activity while increasing susceptibility to bacterial enteroinvasion. JPEN J Parenter Enteral Nutr. 2014;38(7):817–24.
30 Engstrand Lilja H. Wefer H, Nyström N, Finkel Y, Engstrand L. Intestinal dysbiosis in children with short bowel syndrome is associated with impaired outcome. Microbiome. 2015;3(1):18.
31 Huang Y, Guo F, Li Y, Wang J, Li J. Fecal microbiota signatures of adult patients with different types of short bowel syndrome. J Gastroenterol Hepatol, 2017;32(12):1949–57.
32 Valitutti F, Cucchiara S, Fasano A. Celiac disease and the microbiome. Nutrients. 2019;11(10):2403.
33 Francavilla A, Ferrero G, Pardini B, Tarallo S, Zanatto L, Caviglia GP, et al. Gluten-free diet affects fecal small non-coding RNA profiles and microbiome composition in celiac disease supporting a host-gut microbiota crosstalk. Gut Microbes. 2023;15(1):2172955.
34 Quagliariello A, Aloisio I, Bozzi Cionci N, Luiselli D, D'Auria G, Martinez-Priego L, et al. Effect of *Bifidobacterium* breve on the intestinal microbiota of coeliac children on a gluten free diet: a pilot study. Nutrients. 2016;8(10):660.
35 Uusitalo U, Andren Aronsson C, Liu X, Kurppa K, Yang J, Liu E, et al. Early probiotic supplementation and the risk of celiac disease in children at genetic risk. Nutrients. 2019;11(8):1790.
36 Zafeiropoulou K, Nichols B, Mackinder M, Biskou O, Rizou E, Karanikolou A, et al. Alterations in intestinal microbiota of children with celiac disease at the time of diagnosis and on a gluten-free diet. Gastroenterology. 2020;159(6):2039–51.
37 Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011;364(3):255–64.
38 Masi AC, Embleton ND, Lamb CA, Young G, Granger CL, Najera J, et al. Human milk oligosaccharide DSLNT and gut microbiome in preterm infants predicts necrotising enterocolitis. Gut. 2021;70(12):2273–82.
39 van den Akker CH, van Goudoever JB, Shamir R, Domellöf M, Embleton ND, Hojsak I, et al. Probiotics and preterm infants: a position paper by the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2020;70(5):664–80.
40 Borewicz K, Suarez-Diez M, Hechler C, Beijers R, de Weerth C, Arts I, et al. The effect of prebiotic fortified infant formulas on microbiota composition and dynamics in early life. Sci Rep. 2019;9(1):2434.
41 Thomson P, Medina DA, Garrido D. Human milk oligosaccharides and infant gut bifidobacteria: molecular strategies for their utilization. Food Microbiol. 2018;75:37–46.
42 Horigome A, Hisata K, Odamaki T, Iwabuchi N, Xiao JZ, Shimizu T. Colonization of supplemented *Bifidobacterium breve* M-16V in low birth weight infants and its effects on their gut microbiota weeks post-administration. Front Microbiol. 2021;12:610080.
43 Athalye-Jape G, Esvaran M, Patole S, Simmer K, Nathan E, Doherty D, et al. Effect of single versus multistrain probiotic in extremely preterm infants: a randomised trial. BMJ Open Gastroenterol. 2022;9(1):e000811.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 67–78 (DOI: 10.1159/000534950)

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New Dietary Patterns across the World and Their Consequences on Growth and Development

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Abstract

In the past, studies linking diet to health have mainly concentrated on individual nutrients and specific health outcomes. However, humans consume food as a whole, not just isolated nutrients. Since the early 2000s, there has been a shift in assessing dietary exposures, moving away from singular nutrients or foods and toward analyzing dietary patterns. This approach aims to capture the entirety of the diet and its nutrient profiles. Identifying dietary patterns may reveal stronger associations with specific health indicators and provide a more comprehensive understanding of how nutrients and other bioactive substances in food are consumed, and how consumption patterns affect health outcomes. Consequently, dietary patterns that include foods and beverages associated with improved health and reduced risk of chronic diseases are often considered indicators of a high-quality diet. Dietary patterns can also be influenced by environmental, cultural, and social factors. However, with changing times, new dietary patterns have emerged, some of which have spread globally due to factors such as immigration, technology, and media. Unfortunately, some of these patterns come with misleading health claims. This chapter aims to identify current trendy dietary patterns and examine their effects on the growth and development of children.

Introduction

Since nutrients are related to one another, the center of interest of nutrition studies is more focused lately on the types of foods we eat, the interactions between the nutrients in meals, the diversity of foods, amount of food consumed over a day, a week, a month, or a year, as well as how this might affect an individual's health outcomes [1–4]. Apparently, the changes between the first Dietary Guidelines for Americans in 1980 and the guidelines in 2015 demonstrate that nutritional epidemiology has gradually shifted from focusing on nutrients to focusing on dietary patterns [4].

Dietary patterns are defined as "The quantities, proportions, variety, or combination of different foods, drinks, and nutrients in diets, and the frequency with which they are habitually consumed" [3, 5, 6]. Indeed, dietary patterns have been linked to environmental, cultural, social, as well as health consequences [3]. In addition, they are used as an evaluation tool for diet quality which is a useful bridge for spreading messages meant to encourage high-quality diets [7]. Therefore, dietary patterns allow researchers to analyze and understand how people are eating besides examine the relationship between diet and the risk of chronic diseases.

The following sections will detail the impact of diet patterns on children's development, standard global guidelines for addressing their dietary needs, the benefits of a plant-based diet, and considerations for administering such diets to children.

Modern Shift toward Dietary Considerations

Since Paleolithic times, humans' dietary and physical activity patterns and body composition have undergone major changes. In the past 3 decades, these changes accelerated in different regions worldwide due to many factors including the globalization of food processing, marketing, and distribution techniques, most commonly linked to westernization of the world diets. Also, technology innovations such as transportations affect activities and energy expenditure. Last but not least is the spread of the global mass media which can have either negative or positive impact in health outcomes [8].

However, as education expands and information becomes more accessible, there has been a notable rise in interest in diet and nutrition. People are now better equipped with knowledge about the impact of food choices on their health, leading to a growing desire for healthier eating habits. From nutrition courses in schools to the influence of media and social platforms, the awareness

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of the importance of diet has increased significantly. This expanding interest reflects a societal shift toward prioritizing well-being and making informed dietary decisions. There are various reasons for this, but the advent of the Internet is a big one [9]. The Internet can offer users a good way to access content for free through blogs, YouTube, magazines, websites, and academic literature.

As such, there has been new evidence on the prevalence of different diet types, such as vegan, plant-based, and paleo, while people are becoming increasingly interested in such dieting "fads" for their children, there are mixed reviews on whether these diets are productive or healthy for children.

Diet and Impact on Children

Nutritional intake has a massive impact on children. According to Proia et al. [10], who conducted a literature review on the requirements for children's bone health and the long-term impacts that good or bad nutrition may have on children, food intake uniquely influences bone tissue formation. To adapt to various mechanical stresses and compensate for bone loss, bones expand in cross-section even after they cease growing in length. Physical exercise and adequate diet are two external factors that lead to the development of good bone mass during childhood growth, contributing to the growth of skeletal mass and foundation. The consumption of carbohydrates, fat, and protein is important for this goal.

Furthermore, Wilson et al. [11] revealed how breakfast consumption affected the nutritional intake of 5- to 14-year-old New Zealand youth. Children received only 16.2% of their daily energy intake from breakfast, but it still accounted for significant portions of iron, zinc, calcium, folate, riboflavin, and thiamin. Nutritionists consider breakfast the most important meal of the day that can positively impact children's cognitive functioning and development.

Healthy Dietary Patterns

According to Mayo Clinic, certain foods and food types are important for children to consume, and that promote healthy living. The ideal nutrition schedule for a child's growth and development considers the child's age, degree of exercise, and other aspects. Parents can cater diets according to the child's needs and preferences if they meet key standards [12].

There are controversies surrounding milk intake and other nutritional components that many view as "common sense." According to Verduci et al. [13], there are controversies surrounding which milk parents should feed toddlers.

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While protein consumption typically exceeds the required level, iron, zinc, and vitamin D intake are frequently inadequate. Between the ages of 1 and 3, 35%–40% of the daily recommended energy intake should come from fat. The best sources of lipids are polyunsaturated fatty acids and monounsaturated fatty acids. At 12 months of age, children should be adapting to a diet with diverse foods that can include ingredients other family members also consume, this includes cow's milk, whereas year two for children is a transitional period regarding nutrition, and children begin to change dietary patterns [13].

Parents should prioritize some nutritional categories over others while maintaining nutrient-dense or rich foods in their children's diets. Protein-rich foods include seeds, nuts, seafood, eggs, peas, soy, beans, and poultry. Parents should ensure that their children eat fruits, including dried, frozen, canned, or fresh. Optimal canned fruits are labeled as "light" or are packed in their own juice which indicates that there would be very little or no sugar added. ¼ of dried fruit would count as a fruit serving, which is important to understand for parents [12].

In addition, children should consume vegetables, dairy, and grains. Vegetables should be frozen, dried, canned, or fresh. Parents should choose beans and vegetables that are high in color. They should seek out products that have a low amount of sodium. Parents can choose oatmeal, popcorn, quinoa, whole-wheat bread, pasta, and brown or wild rice for grains. They may urge their kids to consume minimal or no-fat dairy products like yogurt, milk, and cheese. Dairy drinks that have been fortified also qualify [12]. Nutrient-dense foods are those that have very low saturated fat and salt, with limitations on sugar. They would be nutrient dense because the concentration of nutrients is higher than the number of harmful ingredients.

Guidelines for Children

Table 1 from the U.S. Department of Agriculture (USDA) shows approximately what types of food groups and subgroups children should eat between the ages of 2 and 8, including weekly and daily amounts. The chart shows that based on a 2,000-a-day calorie diet (closer to the age of 8), children should eat 2½ cups of vegetables daily. This should involve a combination of orange and red vegetables, starchy vegetables, dark greens, beans, lentils, and peas. Children should also be getting a minimum of 2 cups of fruit per day and 6 ounces of whole grains or refined grains. Children should consume 2½ cups of dairy and 5½ cups of protein-rich foods such as seafood, poultry, and meat [14].

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Table 1. Healthy US-style dietary pattern for children ages 2 through 8 years, with daily amounts from food groups (from the U.S. Department of Agriculture [USDA])

Calorie	1,000	1,200	1,400	1,600	1,800	2,000
Female	2–4 years					
		5–8 years				
Male	2–4 years					
		5–8 years				
Food groups	**Daily amount of food from each group**					
Vegetables (cup eq/day)	1	1½	1½	2	2½	2½
Fruits (cup eq/day)	1	1	1½	1½	1½	2
Grains (ounce eq/day)	3	4	5	5	6	6
Dairy (cup eq/day)	2	2½	2½	2½	2½	2½
Protein (ounce eq/day)	2	3	4	5	5	5½
Oils (g/day)	15	17	17	22	22	24

Providing balanced food to children is mostly the responsibility of the parents. Parents may encourage wholesome and healthy eating habits by emphasizing food categories, including vegetables, whole grains, and dairy products as seen in Figure 1. A well-rounded diet may benefit from including whole grains, a range of colorful vegetables, and canned or frozen foods with reduced salt. Encouragement of the intake of low-fat or fat-free dairy, products, as well as consideration of fortified soy drinks, might help provide vital nutrients. These decisions allow parents to assist their children's general well-being by promoting the development of wholesome eating habits. Figure 2 shows an example of healthy plate suggested by USDA.

New Dietary "Fads" for Children

There are now many new diet fads for kids, such as plant-based, gluten-free, paleo, ketogenic, Atkins diet, detox, or cleanse diets. In fact, there are a growing number of parents who are adopting alternative dietary patterns and behaviors. Actually, about 80% of people who choose to follow one of these dietary patterns relay on the internet as the main source of information [15]. While some of these tendencies could be beneficial, parents should proceed cautiously. Before implementing restricted or imbalanced diets, it is crucial to ensure that kids get enough nutrients and speak with medical specialists. Children's growth, development, and general health are supported by a balanced, diverse diet that contains foods high in nutrients.

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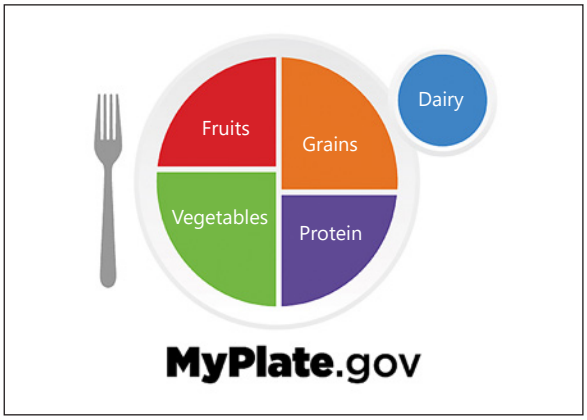

Fig. 1. MyPlate.gov from "U.S. Department of Agriculture" that supports healthy dietary patterns (U.S. Department of Agriculture).

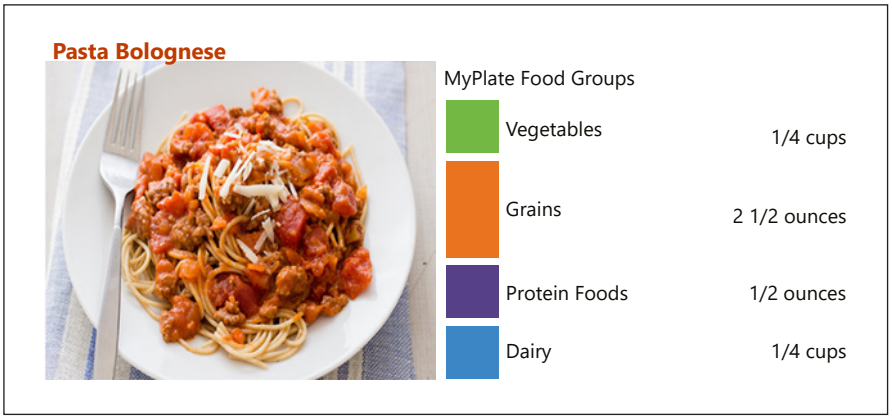

Fig. 2. An example of healthy plate suggested by USDA (U.S. Department of Agriculture).

Gluten-Free Diet

Over the last 30 years, gluten-free foods have grown significantly in popularity, showing strong economic growth in this sector where a wide and varied range of products are available. A gluten-free diet has been shown to be effective for treating gluten-related disorders, but there is no evidence that gluten-free diets are superior to a standard diet for the general population. In fact, celiac disease patients following gluten-free diets have been found to have deficiencies of fiber, iron, calcium, vitamin D, magnesium, folate, niacin, vitamin B12, and riboflavin [15].

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Ketogenic Diet

Recently, ketogenic diets have gained a lot of popularity. It is a strict diet that consists of high fat, low protein, and minimal carbohydrate intake. Following such a diet will induce ketosis by using fat as the primary energy source [15]. Diets low in carbohydrates may lack phytochemicals, vitamins, minerals, fiber that affect the microbiota, as well as other nutrients, like vitamin A, vitamin E, and vitamin B6. Moreover, the high ingestion of certain foods in ketogenic diets such as red meat, processed meat, and saturated fat may cause some health issues. There is no evidence on the use of a ketogenic diet on healthy children; in fact, it may impact their future health by increasing the risk of developing chronic diseases [15].

Plant-Based Diets

Plant-based diets – which focus on solely consuming fruits, vegetables, nuts, and seeds while excluding animal products, such as dairy, fish, poultry, meat, and eggs – are becoming popularized for younger populations, while there may be justified concerns about this phenomenon. There has been a growing fad among some parents to adopt a plant-based diet for their children. This trend involves feeding children a diet primarily of plant-derived foods while excluding or limiting animal products. Parents may believe this dietary choice promotes better health, environmental sustainability, and ethics.

Cultural Considerations

With increased cultural and global diversity, according to Kiely [16], plant-based diets have been considered healthy practices for millennia in different parts of the world. Up to ½ of the Indian population in India does not eat fish or meat for spiritual reasons. They are also influenced by Greek philosophers, who believed that humans are there to offer animals protection rather than eat them. Along with health, environmental and animal protection are key causes for the current increase in vegetarianism and veganism.

Health Benefits

An important study against administering a vegan diet to children comes from Kiely [16], who published his findings in a symposium, which raises some controversies. According to the author, the debate over whether vegetarian and vegan diets are suitable for kids has persisted for a long time. Increased diet restriction and the child's younger age generally contribute to poorer nutritional and

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overall health outcomes. Nutrients of potential concern are protein quantity and quality, essential fatty acids, vitamins A, D, and B12, calcium, riboflavin, iron, zinc, and selenium. Although children tend to exhibit deficiencies in iron and vitamin D, vegan children may have even poorer supplies of these vitamins and nutrients. They may excessively consume fiber – as a supplement food – which could limit other foods' bioavailability. Controversies emerged between European and North American guidelines. European guidelines strongly advise parents to only administer a vegan diet to children with medical supervision [16]. Kiely iterates and warns that there have been histories of B12 deficiency-facilitated neurological damage for vegan children who were not adequately supplemented.

The German Society also raised concerns for Pediatric and Adolescent Medicine. This organization proposed caution for restrictive childhood diets, suggesting "the stricter the diet, the greater the risk" [16]. Recommendations were for a balanced and omnivorous diet that includes plant foods and others. Caregivers were advised to pay attention to the intake of nutrients like iodine, DHA, protein, calcium, zinc, and iron in children to prevent neurological damage, anemia, and faltering or stifling growth. In addition, pregnant women were advised to supplement B12.

On the other hand, plant-based diets have many benefits, including eradication or mitigation of chronic illnesses. According to a study by Craig et al. [17], plant-based diets are more ecologically sustainable than meat-based diets and have a lower environmental effect. Observational studies show that vegans and those who eat a plant-based diet have lower BMI (body mass index) than omnivores, a positive impact on the gut microbiome and decreased risk of developing type 2 diabetes and decreased heart and circulatory ailments like stroke, hypertension, and ischemic heart disease.

While Kiely presents evidence "against" plant-based and vegan diets for children, this seems to be a problem only insofar as inadequate supplementation is available. In contrast, plant-based diets still confer many benefits, even for children. The possible exposure to a broad range of plant foods, decreased risk of obesity, and increased intake of vegetables and fruits are all health advantages of vegetarian diets in childhood and adolescence. Vegan children tend to have lower total and saturated fat and cholesterol consumption than nonvegan children. Craig et al. [17] present a study indicating that low-fat vegan diets have been used to combat childhood obesity.

Environmental Impacts

There may be cultural reasons why someone would want to retain or follow a vegan, vegetarian, or plant-based diet, particularly with new considerations for

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the impacts of climate change on the environment. Plant-based diets are generally considered more sustainable [17].

Plant-based diets are also praised for their lower impact on climate change. In today's world, much land is required for livestock growth and development. In addition, animals expel certain gasses, like carbon dioxide, into the air, further exacerbating greenhouse gas emissions. There are many harmful consequences of large-scale agricultural corporations. Veganism and plant-based diets offer an alternative to the kind of agribusinesses that tend to harm the environment. Children are increasingly entering the political playing field through education and increased awareness of changing global circumstances. With this, there is a natural inclination to want to involve them in alternative diets [17].

Supplementation for Children

There are opportunities for supplementing children's diet if they eat a vegan, vegetarian, or plant-based diet. Craig et al. [17] note that some nutrients that may present as deficient for younger vegetarians include calcium, vitamin D, iodine, zinc, B12, and iron. Protein requirements for vegan children/adolescents may be somewhat greater than normal guidelines due to considerations such as protein digestion and amino acid content. Zinc supplements may be needed if supplemented meals are predominantly zinc deficient. Infants, children, and adolescents should be monitored for iron and zinc levels and given fortified foods and supplements. Parents may also need to supplement iodized salt for iodine and B12. Children should consume plant-based milk, dairy products, and leafy greens for calcium. In addition, the authors recommend keeping children under medical supervision to monitor their nutritional intake and needs [17].

The nutrients mentioned by Craig et al. [17] are of vital importance to children because of the functions they conduct where red blood cells need B12; vitamin D facilitates calcium absorption in the gut, bone mineralization regulation, and bone differentiation. Iodine is necessary for thyroid hormones, which control metabolism, while zinc is a coenzyme associated with cognitive functionality, gene expression regulation, immunity, bone functioning, and growth. This zinc deficiency can cause alopecia, dermatitis, slow growth, and poor appetite [16]. It is thus vital that caregivers supplement these as much as possible.

Supplementation is important because evidence shows that vegan diets can be effective and safe [18]. According to a response to a BMJ study about veganism for children, the vegan children (participants) from Poland are within the predicted age range despite their shorter height and reduced bone density. The author's response details that almost no evidence shows that vegan children have stunted height. Regarding the issue of bone health, only about 1/3 of this sample used vitamin D supplements, and 1/3 did not use B12 supplements. The median

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Table 2. Some parameters associated with a vegan/vegetarian diet

Factor	Vegan children	Omnivorous children
Height	Within the predicted age range	N/A
Bone density	Reduced (only 1/3 using Vitamin D supplement)	N/A
Vitamin B12	1/3 not using B12 supplement	N/A
Calcium intake	Median consumption 376 mg/d (compared to 550 mg recommended)	N/A
Diet planning	Must be planned	N/A
Blood cholesterol	Lower	Higher
Glucose levels	Lower	Higher
Fat	Lower	Higher
Vitamin C	Higher	Lower
Magnesium	Higher	Lower
Carotenoids	Higher	Lower
Fiber	Higher	Lower
Folate	Higher	Lower
Sugar	Lower	Higher

calcium consumption was 376 mg per day, compared to 550 mg recommended in the United Kingdom for this age range. Vegan diets, like any diet, must be planned [19]. Here, the author responds to challenges by another author about the lack of nutrients that emerges with vegan diets. Some benefits of the vegan diet for children include lower blood cholesterol, glucose levels, and fat. They also consumed more vitamin C, magnesium, carotenoids, fiber, and folate. At the same time, omnivorous children were eating high amounts of sugar and fat, with insufficient fiber [19]. Table 2 summarizes some parameters associated with a vegan/vegetarian diet.

Recommendations and Conclusions

The analysis of the most popular diets worldwide indicates that their use in healthy children has no evidence, and their use should be limited to specific therapeutic cases, such as celiac disease or intractable epilepsy, where their efficacy is more clearly demonstrated.

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According to the available data, it would be prudent to approach a vegan diet for kids with care and under qualified medical supervision. While eating a plant-based diet may be good for one's health and the environment, there may be issues with nutritional deficiencies, especially in the areas of iron, iodine, vitamin B12, zinc, and vitamin D. To avoid developmental problems and guarantee healthy development and well-being, supplementation and careful attention to dietary demands must be paid. As a result, it is crucial to coordinate closely with medical experts and trained dietitians to produce a well-planned and balanced vegan diet that covers any possible nutritional deficiencies and promotes the child's general health and development.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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References

1 Jacobs DR, Temple NJ. Food synergy: a paradigm shift in nutrition science. In: Temple N, Wilson T, Jacobs D Jr, editors. Nutritional health. Part of the Nutrition and health book series. Totowa (NJ): Humana Press; 2012.
2 Jacobs DR Jr, Tapsell LC. Food, not nutrients, is the fundamental unit in nutrition. Nutr Rev. 2007 Oct;65(10):439–50.
3 Ćatović A. Dietary patterns. In: Jáuregui-Lobera I, Martínez-Quiñones JV, editors. Recent updates in eating disorders. London: IntechOpen; 2023.
4 Zhao J, Li Z, Gao Q, Zhao H, Chen S, Huang L, et al. A review of statistical methods for dietary pattern analysis. Nutr J. 2021;20:37.
5 Boushey C, Ard J, Bazzano L, Heymsfield S, Mayer-Davis E, Sabaté J, et al. Dietary patterns and growth, size, body composition, and/or risk of overweight or obesity: a systematic review. Alexandria (VA): USDA Nutrition Evidence Systematic Review; 2020.
6 Schulze MB, Martínez-González MA, Fung TT, Lichtenstein AH, Forouhi NG. Food based dietary patterns and chronic disease prevention. BMJ. 2018;361:k2396.
7 Liese AD, Krebs-Smith SM, Subar AF, George SM, Harmon BE, Neuhouser ML, et al. The dietary patterns methods project: synthesis of findings across cohorts and relevance to dietary guidance. J Nutr. 2015;145(3):393–402.
8 Popkin B. Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases. Am J Clin Nutr. 2006;84:289–98.
9 Marquis M, Dubeau C. Potential of the internet to address topics of interest in nutrition. Nutr Food Sci. 2006 Jul;36(4):218–24.
10 Proia P, Amato A, Drid P, Korovljev D, Vasto S, Baldassano S. The impact of diet and physical activity on bone health in children and adolescents. Front Endocrinol. 2021 Sep 13;12:704647.
11 Wilson NC, Parnell WR, Wohlers M, Shirley PM. Eating breakfast and its impact on children's daily diet. Nutr Diet. 2006;63(1):15–20.
12 Mayo Clinic. What nutrients does your child need now?; 2023. Available from: https://www.mayoclinic.org/healthy-lifestyle/childrens-health/in-depth/nutrition-for-kids/art-20049335.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 79–90 (DOI: 10.1159/000534949)

13 Verduci E, Di Profio E, Corsello A, Scatigno L, Fiore G, Bosetti A, et al. Which milk during the second year of life: a personalized choice for a healthy future? Nutrients. 2021 Sep 27;13(10):3412.
14 USDA. Make every bite count with the dietary guidelines. Rockville (MD): Dietary Guidelines for Americans; 2020. Available from: https://www.dietaryguidelines.gov/sites/default/files/2021-03/Dietary_Guidelines_for_Americans-2020-2025.pdf.
15 Martín-Rodríguez A, Bustamante-Sánchez Á, Martínez-Guardado I, Navarro-Jiménez E, Plata-SanJuan E, Tornero-Aguilera JF, et al. Infancy dietary patterns, development, and health: an extensive narrative review. Children (Basel). 2022 Jul 18;9(7):1072.
16 Kiely ME. Risks and benefits of vegan and vegetarian diets in children. Proc Nutr Soc. 2021 Jan 28;80(2):159–64.
17 Craig WJ, Mangels AR, Fresán U, Marsh K, Miles FL, Saunders AV, et al. The safe and effective use of plant-based diets with guidelines for health professionals. Nutrients. 2021 Nov 19;13(11):4144.
18 Richards L. Is a vegan diet healthy and safe for kids? What the evidence says. Plant-Based News; 2023. Available from: https://plantbasednews.org/your-health/health-wellbeing/is-vegan-diet-safe-healthy-for-children/.
19 Mahase E. What does the evidence say about vegan diets in children? BMJ. 2023 May 31;375:n2792.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 79–90 (DOI: 10.1159/000534949)

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Children's Diets and Their Sustainability in a Changing World

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Abstract

The last 5 decades have witnessed major reductions in hunger, child mortality, wasting, and stunting, despite the exponential growth of the world population. Technological advances in food production outpaced population growth, and together with socio-economic changes led to increases in energy supply and a decrease in the time cost of food. Thus, the evolution of how we produce and procure food was accompanied by an inflection in energy intake and expenditure, and a dietary transition that profoundly impacts health. Thus, this period was marked by an accelerated increase in body mass index worldwide, first evident in high-income countries and now globally ubiquitous, which disproportionally affects lower-income populations. While undernutrition persists, diet excesses and imbalances are increasing, and nutritional factors are now most of the leading causes of global death and disability worldwide, further widening global disparities. Moreover, these changes have significantly affected Earth's land, water, and atmosphere, threatening the gains made thus far. In particular, animal food sources disproportionally impact the environment. Food systems will need to evolve to decrease and protect resources. And diets will need to improve, in ways that make them both healthy and sustainable. Correcting course will require reorienting and collectively focusing efforts on social, economic, technological, and educational changes that simultaneously promote adequate nutrition, human health, and the health of the planet.

Introduction

We are living longer than at any time in human history, with a life expectancy of about 70 years. However, of those living now, more than 10% (around 820 million) go to bed hungry every night, 4% of children (about 15,000 children a day) die before their fifth birthday, and 14% cannot read. This seems a far from desirable global situation. However, today is a product of our past; only 200 years ago, 84% of the world's population lived in extreme poverty, 88% of people could not read, 43% of children died before 5 years of age, and life expectancy was about 30 years [1]. So even if today's situation may appear gloomy, by almost any measure related to global nutrition, morbidity, mortality, and wealth, today is the best time for a child to be born. Nevertheless, despite this progress and having the tools to improve people's health and well-being, we are far from what could or should be accomplished.

Since the beginning of humankind, available food and population growth have been intrinsically linked. For the first 200,000 years following the appearance of *Homo sapiens*, only a few hundred thousand humans populated the world. These numbers changed very little until the advent of agriculture about 10,000 years ago. Estimates place the world population at about 190 million inhabitants at the beginning of the Common Era, reaching 1 billion by 1800. It took hundreds of thousands of years to reach 1 billion, but only 200 more years to reach 8 billion [2, 3]. The 1800s witnessed the beginning of this exponential population growth and the advances of the Industrial Revolution, including technological progress that allowed for producing enough food for the world's inhabitants and for improving nutrition and health.

However, the advances in how we produce and procure food were also accompanied by changes in our diets and health. These changes are now challenging our health itself and widening disparities among people. Furthermore, these changes have significantly affected Earth's land, water, and atmospheric composition in ways that may alter the planet's ecological balance, threatening the gains made thus far. This chapter takes a historical look at how global diet and nutrition have changed and examines our current diets, their effect on human health, and how the food systems that support these diets impact the health of our planet.

Changes in Nutrition over Time

Child Mortality

It is impossible to directly assess children's nutritional status decades or hundreds of years ago. Child mortality, however, could be used as a proxy. Using data from a wide range of geographic locations, cultures, and times, it is esti-

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mated that in hunter–gatherer and early agricultural societies, about 30% of infants did not survive their first year. Moreover, about 47% did not survive till adulthood. These numbers appear remarkably constant for the last 10,000 years, up to the 1850s. Estimates show that whether in ancient Greece, the Roman Empire, Medieval Japan or England, Imperial China, or Pre-Columbian America, one in four newborns died in their first year, and one in two died in childhood [4, 5].

In the last two centuries, all this changed. From 1850 to today, child mortality under 5 years of age has decreased from about 46.2% to 4.6%, and infant mortality from 29.9% to 2.9%. Examining a shorter time window, in the last 30 years alone (1990–2020), the number of under 5 child deaths decreased from 9.3% (12.6 million or 1 in 11 children dying before age 5) to 3.7% (5 million or 1 in 27 dying before age 5). This is a remarkable accomplishment, in great part related to improved maternal and child nutrition and antenatal and perinatal care; however, it remains distant from the target of 2.5% mortality for children under 5 years, set as a sustainable development goal (SDG) by the United Nations for 2030. More importantly, the difference in mortality rates between high-income countries (0.49%) and low- and middle-income countries (LMICs) (3.98%) remains regrettably large [4, 6].

Height

Height can also serve as a good proxy for nutrition. Estimates of the average height of multiple populations over the last 2,000 years show that, with regional variations, global height remained relatively unchanged [7]. Through most of this time, height likely reflected changes in environmental factors (climate, infectious disease, food availability, and population density) which influenced physical growth, which were not optimal nor consistent for extended periods; thus, height rarely approached individuals' maximal genetic potential [8].

However, the 1800s marked a major inflection point, and global height trends started increasing significantly. In just the last 150 years, the average global height has increased in every population and every country. Today's average young adult is 8–9 cm taller than his ancestors [9]. Gains in height are very strongly correlated with living standards, in particular food security. Historically, height gains are associated with access to increased energy and protein, especially animal protein availability [7].

Nevertheless, continued height gains may be coming to an end. While most country populations today are still gaining in height, gains in high-income countries have slowed down, and some have stopped gaining height altogether. In the Netherlands, the tallest population in the world, after 150 years of height increases, the Dutch have not gotten taller for the last 25 years. Nutrition and

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health delivery may have allowed them to reach their maximum genetic potential [10].

Height reflects current differences in populations' social, economic, and nutritional standards. Today, the difference between the tallest population (the Netherlands) and the shortest populations (e.g., Guatemala) is 19 cm for men to 20 cm for women. That is, while all populations have gained height, the difference between the tallest and the shortest today is still more than what we as a species have gained in the last 100 years [9, 10].

Children's Nutritional Status Today: Progress and Disparities

While still suboptimal, we have better data on the changes in children's nutrition over the last few decades. Severe undernutrition and wasting of children under 5 years of age have decreased but remain at 6.7% or 45.4 million children. Global stunting of children under 5 years has decreased by 66%, or 54 million less stunted children in just the last 20 years (2000–2020), standing today at 21% prevalence. These figures are still far from the SDG targets of 3% wasting and 12% stunting by 2030 and remain unevenly distributed. Today, more than 90% of stunted children and 97% of children with severe undernutrition under 5 years of age live in Asia and Africa. In addition, overweight and obesity in children under 5 have increased to 6% in the same time frame, far from the SDG target of 3%. Today, we have 5.4 million more overweight young children under 5 than 20 years ago; of these, more than 75% of children live in Asia and Africa [11].

Overweight and obesity prevalence in infants and toddlers is increasing, but school-age children, 5–19 years of age, show even more dramatic increases, from 10.3% to 18.4% in the last 20 years [11]. While the increase in overweight children appears to be plateauing in some high-income countries, the increase in overweight continues to rise in low-income countries. It was estimated in 2017 that if trends continued, child and adolescent obesity would be expected to surpass moderate and severe underweight by 2022 [12, 13]. The intervening effect of the COVID pandemic, which may have increased both overweight and underweight prevalence, is yet to be determined.

Anthropometric markers of nutrition over time, and in the present, reflect disparities associated with social and income inequality and living standards, which are also reflected in people's diets. The highest gains in decreasing undernutrition and height in the last few decades have been seen in rapidly emerging economies. As mentioned above, the difference between the tallest and the shortest populations in the world today is about 20 cm, equivalent to a 6- to

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8-year growth gap between them, reflecting a huge lag in living standards between countries. In 19-year-old adolescents today, the country difference between the highest and lowest BMI is about 10 kg/m^2, which is more than two standard deviations in the reference BMI curves [12, 13].

Moreover, the great majority of stunted and overweight children live in low-income countries and regions. Furthermore, recent trends show a widening of these disparities in the overall picture of nutritional health. As an example, over the last 3 decades, the populations of most countries have seen simultaneous increases in both height and BMI; however, school-aged children in Sub-Saharan Africa and Oceania have seen dramatic increases and BMI and overweight with significant stagnation in height gains compared to the rest of the world [13].

In summary, the world population has seen a substantial decrease in child mortality and undernutrition and gains in height in just the last 200 years. The last 50 years have seen an acceleration in these improvements, with a dramatic increase in overweight and obesity prevalence, which will soon overtake undernutrition. Most children with wasting, stunting, overweight, obesity, and nutrient deficiencies live in lower-income countries or in disadvantaged communities within a country. And all forms of malnutrition can coexist at a country, community, and household level, even in the same child. Thus, the world bears today a double burden of undernutrition (caused by a lack of macro and/or micronutrients) and overnutrition (an excess in energy intake versus expended), which, as in past centuries, are reflective of social and economic disparities. These global disparities persist and, in some cases, may be worsening [14].

Changing Diets and Their Consequences

At the most basic level, nutritional status is reflected in the human body's somatic growth, function, and energy storage. This depends on the intake of energy and nutrients: our diets.

A myriad of factors will, directly and indirectly, influence such diets, and it is beyond the scope of this chapter to discuss the relative contribution of each of the multiple factors that influence individuals' diets (individual, social, economic, environmental, etc.). However, it is ultimately the diets of individuals and populations, in relation to their biological needs and energy expenditure over the life cycle, that underpin nutritional markers, such as anthropometry (wasting, stunting, overweight, obesity), that we see over time in individuals and populations.

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Diets Today and Their Consequences

Globally, diet patterns today are far from ideal. It is estimated that 48% of the global population eats too many or too few calories. And dietary intake of key foods (food groups) is far from the recommended targets. With significant regional variations, global consumption of fruits, vegetables, and legumes is less than 50% of the recommended intake, while excessive consumption of sugar and sweetened beverages is prevalent everywhere, and the global intake of red meat is about 200% of the recommended intake [15, 16].

The dietary patterns of children today reflect the global and regional social and economic variables, as well as the effect of prevalent food systems and food security: energy and protein insufficient diets in some populations, coexisting with dietary excesses, and an obesogenic environment in most of the world. More importantly, the diets of children today, starting with complementary feeding, reflect that of adults. This is particularly concerning, given that dietary patterns are set very early and persist for life. Recent studies suggest that the relative energy intake from each major food group becomes well established by 20 or 24 months of age [17, 18]. In most countries today, too many infants and young children consume diets with excess calories, starting with bottle feeding instead of breastfeeding, and very low intake of fruits and vegetables with high intakes of sugar, sweetened beverages, and saturated fat. Less than half of children globally are even close to the recommended intakes of fruit and vegetables, both in high- and low-income countries. Furthermore, in high-income countries, micronutrient intakes are marginal or adequate, while in LMICs, micronutrients, particularly iron, are significantly deficient [14, 16, 18].

The consequences of inadequate diets, particularly the excesses in energy intake in relation to energy expenditure, are reflected in the global burden of disease (GBD). By 2010, more than half of the top 20 leading factors associated with early death or disability were nutrition related (e.g., high intake of sodium and high blood pressure, diets low in fruits, high body mass index, high fasting glucose, low intake of nuts and seeds, iron deficiency, high cholesterol, low whole grains and vegetables, and suboptimal breastfeeding) [19]. Remarkably, all these leading dietary factors in GBD are already present in most toddlers by 2 years of age [16–18]. By 2019, all these same dietary factors in the GBD remained; however, the fastest growing and highest risk factors for death and disability are now high body mass index, high fasting plasma glucose, high cholesterol, and elevated blood pressure. At the same time, in many places, undernutrition remains unresolved. Among children (birth to 9 years), the three leading risk factors for death and disability were all related to malnutrition, and iron deficiency remains the leading risk factor for children 10–24 years [20]. The evolution in the GBD

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reflects the dramatic increase in overweight, obesity, and related noncommunicable diseases, and is evidence of the profound global dietary transition that has occurred in the last 50 years.

The Global Dietary Transition

As discussed above, using height as a proxy for nutrition, there was no apparent change in global height in the last 2,000 years. Only after the Industrial Revolution in the mid-1800s did human height begin to increase in all regions of the world. The most important factor explaining this temporal increase in height and the differences between world regions appears to be dietary, in particular the availability and intake of high-quality protein and specifically the ratio between intake of high-quality animal protein and low-quality cereal sources of proteins. There is increasing evidence of an association between childhood stunting and animal source food consumption. And animal protein intake is also correlated with a country's GDP per capita, health expenditure, and level of urbanization [8, 21].

Global height gains have been significant and consistent for the last 150 years, mirroring increased global energy and protein supply. The last 50 years saw a gradual and accelerated increase in BMI worldwide, first evident in high-income countries and now ubiquitous. Changes in BMI respond to energy intake in relation to expenditure; therefore, they can be roughly associated with long-term estimates of energy intake. Variations in energy intake can, in part, be gleaned from variations in energy supply (food available for consumption at the end of the supply chain), even if they do not indicate actual calories consumed. Global estimates show that the daily supply of calories per person accelerated significantly after 1960 in practically all countries. Estimates from the Food and Agriculture Organization (FAO) indicate that after a relatively flat global energy supply for many decades, in the 1960s, there was an inflection point, with a significant and steady increase that continues today. Between 1960 and 2018, the global average increase of energy supply was +740 calories per capita. This increase varied widely by country and region, e.g., from +512 in Africa to +763 cal per day in the Americas, and +1,112 in Asia [22]. This coincides with changes in mechanization and transportation, which decreased energy expenditure. However, offsetting such energy increases with additional exercise is not realistic. Therefore, even if decreased activity and exercise play a role, the main driver for the obesity epidemic today remains a temporal dietary transition in the world's population.

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Swinburn et al. [23] document that during the first half of the 20th century, increased mechanization and motorization were accompanied by a decreased food energy supply, indicative of some decrease in consumption: lower intake of calories followed by a corresponding decrease in energy expenditure. However, starting in the 1960s, various factors, primarily technological advances, intervened and drastically increased food availability. Thus, starting in high-income countries, the 1960s to 1970s marked a "flipping point" with increased food energy supply which pushed up energy intake and population weight.

Many factors increased food availability. As only one example, the change in global cereal production from 1961 until the present has increased by 280% (e.g., 150% increase in the United States, 500% increase in China), mostly from improvements in crop yield. This increase in agricultural yields, as an outcome of the technology-driven "green revolution," far outpaced the rate of population growth in the world [24]; and changes in technology, agriculture, industry, and commercialization reduced the time cost of food. At the same time, global per-capita income also grew. By some estimates, global GDP per capita in 1850 was $1,225 (international dollars). This grew to $4,386 in 1960; and to $15,212 in 2018. All world regions saw this accelerated economic growth; however, the fourfold difference between the poorest and wealthiest countries in 1850 grew to a 15-fold difference by 2018 [25].

In summary, over the last 5 to 6 decades, food systems (the complex networks that link agricultural and food production to consumption) underwent a dramatic change, primarily driven by technology. Food supply increased, time cost of food decreased, incomes increased, and food processing, storage, distribution, and preparation improved, also partially driven by technology. All these changes increased food availability and enabled this dietary transition. In addition, changes in mass media, including airwave and digital media, transportation, and regional and global commercialization, contributed to the growing demand for increasingly processed, less healthy food choices, and decreased exercise and energy expenditure. Globalization, as well as domestic "nutrition transitions" (responding to economic development, urbanization, and women's empowerment at country and regional levels), further facilitated food access and affordability, leading to dietary shifts from a primarily plant-based diet to a primarily more energy-dense, meat and processed food diet. With varying levels of contribution, all these factors led to an obesogenic environment, changes in dietary behaviors, and our current epidemic of obesity and noncommunicable diseases [23, 26, 27].

This dietary transition, driven by the transformation of food systems, began in more developed societies but is now globally ubiquitous, and is responsible for the global epidemic of obesity and its multiple health consequences. The

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transition began later in LMICs but is advancing at faster rates, worsening the double burden of malnutrition in many populations. The increase in rates of obesity now seems to be decreasing in high-income countries, while accelerating in LMICs [26, 27]. Furthermore, acceleration of the transition in low-income populations may disproportionally worsen long-term health outcomes. For example, a faster diet transition in populations with persistent stunting, as observed in school-age children in Africa, may lead to even greater adiposity, with little improvement in linear growth, and more significant health consequences in the long term [13].

The Benefits and Challenges of Today's Food Systems

The remarkable advances in food systems, tied to global economic growth, allowed for enough food to support the exponential growth of the world population, improving survival rates and decreasing global undernutrition. This progress, however, has come at a price. Today, food systems are a major, if not the most, direct contributor to the global transition to less healthy diets and its nutrition outcomes, which threaten the health of populations. And in the process, it has also widened disparities in food security, nutrition, and health [28].

Moreover, food systems also contribute to an even larger threat: the health of our planet. Today, about 50% of all habitable land and 70% of fresh water are used for agriculture, and agriculture is responsible for 78% of ocean water pollution (eutrophication). Of particular concern is the amount of land used for animal feed: 77% of all agricultural land is used for animal-based foods (meat and dairy), which provide only 18% global calorie supply and 37% of protein supply. Meanwhile, only 23% of the land is used for plant-based foods, which provide 82% of energy and 63% of protein [29, 30].

Of even greater concern is that around 26% of all greenhouse gases emitted today, contributing to climate change, come from food production. Agriculture is not only a major factor in deforestation, but greenhouse gases are produced at every step of the current modern food systems. Furthermore, what we produce and consume matters: of all food produced today, animal-based foods (e.g., beef, lamb, and dairy) produce 10–50 times more greenhouse gases than all fruit, vegetables, and cereals. In addition, 40% of all global food production is lost or wasted. One-half is lost at the farm and on route to market, and one-half is wasted at retail, food services, and households, further adding to greenhouse gas emissions [30–32]. Thus, the food systems that support today's current diet habits globally are also a major contributor to environmental threats and the health of the planet.

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The effects of climate change on human health and well-being cannot be understated. Climate change can dramatically affect food systems themselves and therefore threaten food security at local, regional, and global levels. It also increases populations' exposure to extreme events, with environmental changes that enable food-borne and infectious disease transmission, and alter population movements, livelihoods, and mental health. And these stresses on health and social systems disproportionally affect more vulnerable populations and amplify inequalities [33].

Toward Healthy, Sustainable Children's Diets

Today's nutrition, health, and environmental changes are linked in a complex interaction, recently termed "the global syndemic" of obesity, undernutrition, and climate change. Addressing this "syndemic" will require reorienting and collectively focusing our efforts on systems that simultaneously promote adequate nutrition, health, and environmental sustainability, while fostering economic prosperity in all sectors of society, including the agricultural sector [34].

Improving nutrition and health will require a dietary shift to healthier diets, to improve food and nutrient deficits (particularly fruits, vegetables, whole grains, and micronutrients) and to decrease excesses (sugar, refined cereals, meat and animal proteins, and sodium). Of relevance will be improving the diet of infants and young children, the future consumers of food systems outputs. Early diet is not only a major determinant of long-term health, but it sets a child on the path to healthy eating habits and behaviors for life. Thus, improving the education of parents and caregivers remains critical and necessary to achieve dietary change [35].

It is imperative that diets be not only healthy but sustainable. Food systems, which can help shape and reorient the current dietary transitions, need to be transformed to deliver on both counts. Some of the changes needed are synergistic: increasing plant foods and decreasing animal food consumption supports both health and sustainability – a win-win effort [36].

Global action and engagement of all sectors of society will be needed to reverse dietary, nutritional, and environmental trends. Almost 10 years ago, the FAO Report "Food Systems for Better Nutrition" called for a multisectoral approach that includes complementary food systems, public health, and education interventions. Several efforts have begun, increasingly bringing together all public and private stakeholders to advance these objectives [28, 37, 38]. In keeping with the world's SDGs, the recent UN Food Systems Summit put forth key action tracks, the first three of which included ensuring access to safe and nutritious

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food for all, shifting to healthy and sustainable diets, and optimizing food production, processing, and distribution – addressing planetary boundaries [39].

As a species, we have transformed the planet and used its resources successfully to improve the world population's nutrition, health, and well-being. However, the work remains unfinished, and this progress now threatens our future health and the health of our planet. Nonetheless, opportunities remain. Global food production is the single largest human pressure on Earth, so changing what we eat and how we produce it is also the single strongest lever to optimize human health and the environment [36].

Conflict of Interest Statement

J. Saavedra is the former Chief Medical Officer of Nestlé Nutrition and former Chairman of the Board of the Nestlé Nutrition Institute.

References

1 Roser M. The world is awful. The world is much better. The world can be much better; 2020. Available from: https://ourworldindata.org/much-better-awful-can-be-better.
2 Goldewijk K, Beusen A, Doelman J, Stehfest E. New anthropogenic land use estimates for the Holocene. Earth Syst Sci Data. 2016. DOI: 10.5194/essd-2016-58.
3 Roser M, Ritchie H, Ortiz-Ospina E, Rodés-Guirao L. World population growth; 2013. Available from: https://ourworldindata.org/world-population-growth.
4 Volk A, Atkinson JA. Infant and child death in the human environment of evolutionary adaptation. Evol Hum Behav. 2013;34(3):182–92.
5 Roser M, Ritchie H, Dadonaite B. Child and infant mortality; 2013. Available from: https://ourworldindata.org/child-mortality.
6 United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). Levels & trends in child mortality: report 2020. New York: United Nations Children's Fund; 2020.
7 Koepke N, Baten J. The biological standard of living in Europe during the last two millennia. Eur Rev Econ Hist. 2005;9(1):61–95.
8 Grasgruber P, Cacek J, Kalina T, Sebera M. The role of nutrition and genetics as key determinants of the positive height trend. Econ Hum Biol. 2014;15:81–100.
9 NCD Risk Factor Collaboration (NCD-RisC). A century of trends in adult human height. Elife. 2016 Jul 26;5:e13410.
10 Schönbeck Y, Talma H, van Dommelen P, Bakker B, Buitendijk SE, HiraSing RA, et al. The world's tallest nation has stopped growing taller: the height of Dutch children from 1955 to 2009. Pediatr Res. 2013;73(3):371–7.
11 UNICEF. The state of the world's children 2019. Children, food and nutrition: growing well in a changing world. New York: UNICEF; 2019.
12 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016:a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–42.
13 NCD Risk Factor Collaboration (NCD-RisC). Height and body-mass index trajectories of school-aged children and adolescents from 1985 to 2019 in 200 countries and territories: a pooled analysis of 2181 population-based studies with 65 million participants. Lancet. 2020;396(10261):1511–24.
14 Saavedra JM. The changing landscape of children's diet and nutrition: new threats, new opportunities. Ann Nutr Metab. 2022;78(Suppl. 2):40–50.
15 Global Nutrition Report. The state of global nutrition. Bristol: Development Initiatives; 2021. Available from: https://globalnutritionreport.org/reports/2021-global-nutrition-report/.
16 United Nations Children's Fund (UNICEF). Fed to fail? The crisis of children's diets in early life. 2021 Child Nutrition Report. New York: UNICEF; 2021.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 91–102 (DOI: 10.1159/000534960)

17 Reidy KC, Deming DM, Briefel RR, Fox MK, Saavedra JM, Eldridge AL. Early development of dietary patterns: transitions in the contribution of food groups to total energy—Feeding Infants and Toddlers Study, 2008. BMC Nutr. 2017 Dec;3(1):1–4.
18 Saavedra JM, Deming D, Dattilo A, Reidy K. Lessons from the feeding infants and toddlers study in North America: what children eat, and implications for obesity prevention. Ann Nutr Metab. 2013;62(Suppl. 3):27–36.
19 Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224–60.
20 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.
21 Headey D, Hirvonen K, Hoddinott J. Animal sourced foods and child stunting. Am J Agric Econ. 2018;100(5):1302–19.
22 Roser M, Ritchie H, Rosado P. Food supply; 2013. Available from: https://ourworldindata.org/food-supply.
23 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.
24 Ritchie H, Roser M, Rosado P. Crop yields; 2022. Available from: https://ourworldindata.org/crop-yields.
25 Roser M. Economic growth; 2013. Available from: https://ourworldindata.org/economic-growth.
26 Popkin BM, Ng SW. The nutrition transition to a stage of high obesity and noncommunicable disease prevalence dominated by ultra-processed foods is not inevitable. Obes Rev. 2022;23(1):e13366.
27 Fox A, Feng W, Asal V. What is driving global obesity trends? Globalization or "modernization"? Global Health. 2019;15(1):32.
28 Hemrich G. The role of food systems in shaping diets and addressing malnutrition: delivering on the sustainable development agenda. World Rev Nutr Diet. 2020;121:116–26.
29 Ritchie H, Rosado P, Roser M. Environmental impacts of food production; 2022. Available from: https://www.fao.org/faostat/en/#data; https://ourworldindata.org/environmental-impacts-of-food.
30 United States Environmental Protection Agency. Greenhouse gas emissions; 2023. Available from: https://www.epa.gov/ghgemissions/global-greenhouse-gas-emissions-data.
31 Hensel K. Facing the food waste crisis. Food Technology Magazine. 2022. Available from: https://www.ift.org/news-and-publications/food-technology-magazine/issues/2021/december/features/facing-the-food-waste-crisis.
32 Poore J, Nemecek T. Reducing food's environmental impacts through producers and consumers. Science. 2018;360(6392):987–92.
33 Romanello M, McGushin A, Di Napoli C, Drummond P, Hughes N, Jamart L, et al. The 2021 report of the Lancet Countdown on health and climate change: code red for a healthy future. Lancet. 2021;398(10311):1619–62.
34 Swinburn BA, Kraak VI, Allender S, Atkins VJ, Baker PI, Bogard JR, et al. The global syndemic of obesity, undernutrition, and climate change: the Lancet Commission report. Lancet. 2019;393(10173):791–846 [Erratum in: Lancet. 2019 Feb 23;393(10173):746].
35 Saavedra JM, Dattilo AM. Nutrition in the first 1000 days of life: society's greatest opportunity, Chapter 1. In: Saavedra JM, Dattilo AM, editors. Early nutrition and long-term health. 2nd ed. Sawston: Woodhead Publishing, Elsevier; 2022. p. 3–25.
36 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 Feb 2;393(10170):447–92 [Erratum in: Lancet. 2020 Oct 3;396(10256):e56].
37 FAO 2013 Food and Agriculture Organization of the United Nations. The State of Food and Agriculture 2013. Food systems for better nutrition. Rome: Food and Agriculture Organization of the United Nations; 2013.
38 FAO and WHO. Food and Agriculture Organization of the United Nations, World Health Organization. Sustainable healthy diets: guiding principles. Rome: World Health Organization; 2019.
39 Sustainable Development Goals. United Nations Food Systems Summit; 2021. Available from: https://www.un.org/sustainabledevelopment/blog/2020/09/leading-experts-chosen-to-drive-five-priority-areas-for-un-food-systems-summit/.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 91–102 (DOI: 10.1159/000534960)

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Human Milk Oligosaccharides: Impact on Infant Gut Microbiome and Health

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Abstract

Breastfeeding protects the infant against diseases, although the mechanisms are not fully understood. Besides macro- and micronutrients, breast milk contains a range of bioactive components such as immunoglobulins, hormones and growth factors, cytokines, and antimicrobial compounds. In addition, breast milk contains a variety of human milk oligosaccharides (HMOs), which are small indigestible oligosaccharides that together comprise the third most abundant solid fraction of breast milk. HMOs directly enhance the gastrointestinal barrier function, protect against invading viral or bacterial pathogens by coating them and acting as decoys for receptors located on the gut epithelium, and suppress inflammatory signaling in intestinal epithelial cells. They also provide indirect effects by stimulating the growth of beneficial bacteria in the gastrointestinal tract. HMOs are strong contributors to the establishment of a healthy gut microbiota in early life, as they promote a community rich in specialized *Bifidobacterium* species, capable of consuming HMOs and in turn producing immune-regulatory metabolites, which may protect the infant against infectious and immune-related diseases. The use of this knowledge to support breastfeeding, but also develop *Bifidobacterium*-based probiotics and/or HMO-based formula milk may hold great promise to prevent infectious, inflammatory, and immune-related diseases in infants that cannot be breastfed or are lacking *Bifidobacterium* species in the gastrointestinal tract.

Introduction

The beneficial effects of breastfeeding are well established and first and foremost include protection of the infant against infectious diseases and reduction of the mortality rate during infancy [1]. Further, although still controversial, breastfeeding may confer some protection against asthma and allergic diseases, inflammatory bowel diseases, and some autoimmune diseases [2–4]. Besides essential macro- and micronutrients, breast milk contains a plethora of bioactive compounds, including immunoglobulins, hormones and growth factors, cytokines, and various antimicrobial compounds, as reviewed in detail elsewhere [5], as well as human milk oligosaccharides (HMOs). The beneficial effects of breastfeeding are likely to be mediated by the combined effects of these aforementioned compounds. While it is out of scope to review individual and combined contributions of all of these complex components of breast milk to disease risks, this review focuses on the contribution of HMOs. Indeed, in recent years, considerable attention has been given to the HMOs, as they comprise the third most abundant solid fraction of human milk, after lactose and lipids, and because they exhibit both direct and indirect beneficial effects on infant gastrointestinal function and the immune system and may be key to prevent diseases [6]. Total HMO concentrations in breast milk range from 5 to 20 g/L, but concentrations can vary over the lactation period according to geographical population and human genetics [6, 7]. HMOs are composed of five mono-saccharide units: glucose (Glu), galactose (Gal), sialic acid (SiaAc), fucose (Fuc), and *N*-acetylglucosamine (GlcNAc), which in various combinations represent the more than 200 different oligosaccharide structures found in breast milk. Core structures are composed of a lactose (β1,4 linked Gal-Glu) unit, which may be extended with either lacto-*N*-biose (β1,3 linked Gal-GlcNAc, termed type 1) or *N*-acetyllactosamine units (β1,4 linked Gal-GlcNAc, termed type II) and/or decorated with either or both Fuc and SiaAc [6]. Although great interindividual variation in HMO composition exists, on average 2′FL, LNT, LNFP I and LNFP II, and DFLNT represent the most abundant structures across populations [7]. The strongest determining factor of HMO composition seems to be the FUT2 and FUT3 genotypes (also termed "Secretor" and "Lewis" genotypes, respectively). The FUT2 and FUT3 genes encode fucosyltransferases responsible for the decoration of the core HMO units with fucose residues either α-1,2-linked or α-1,3/4-linked. Therefore, individuals with defects in the FUT2 gene (termed "nonsecretors") present much lower abundances of α-1,2 fucosylated HMO in breast milk, especially 2′FL being close to undetectable in nonsecretors. Likewise, individuals with defects in FUT3 (termed "Lewis negative") have reduced levels of α-1,3/4 fucosylated HMOs such as LNFP II [8]. A key feature of HMOs is that they are

poorly digested in the upper gastrointestinal system of the infant. It has been estimated that less than 5% of all ingested HMOs are digested in the small intestine [9], and only a fraction is absorbed from the gut into systemic circulation [10]. In the gastrointestinal tract, the HMOs can interact directly and indirectly (through our gut microbiome) with our intestinal epithelium as well as gut-associated immune cells, which may serve as the basis for understanding their disease-preventive effects.

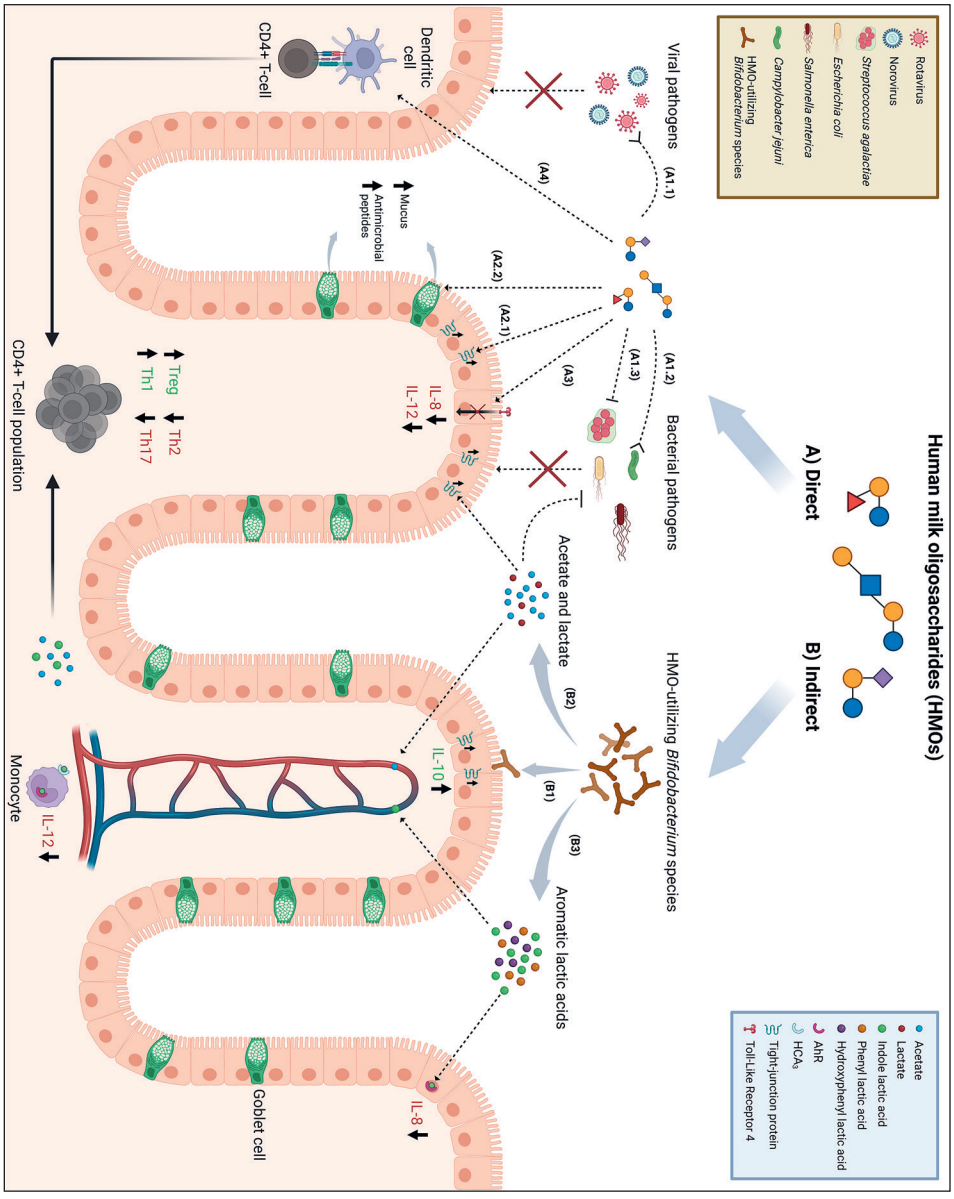
HMOs and Associations with Disease

By assessing maternal secretor status, quantifying the breast milk concentrations of specific or total HMOs, as well as performing intervention studies using formula supplemented with selected HMOs, several studies have investigated if HMOs are linked with parameters of infant health/disease risks.

Individual HMOs have been associated with infant growth and risk of obesity in numerous studies, but results do not appear consistent across cohorts [11]. The potential of HMOs to regulate neuro-development has also been explored in several observational studies, suggesting that concentrations of individual and/or total HMOs are positively associated with cognitive, language, and motor skill development assessed at 18–24 months of age [12]. Most evidence is found for the prevention of respiratory infectious diseases and gastrointestinal infectious diseases such as *Campylobacter*-associated diarrhea, *Escherichia coli* stable toxin-associated diarrhea, rotavirus infection, and well as general gastrointestinal tract symptoms such as diarrhea and vomiting [13]. A handful of studies have linked secretor status and breast milk abundance of specific HMOs to the prevention of necrotizing enterocolitis (NEC), a devastating inflammatory disease in preterm infants [14]. HMOs have also been suggested to protect against the development of inflammatory bowel diseases later in life [15], but the evidence is currently lacking. Almost nothing is known about the potential influence of HMOs on the risk of developing autoimmune diseases, such as type 1 diabetes and multiple sclerosis, which have been inversely linked with breastfeeding [3]. There is limited and conflicting evidence regarding the potential protective effects of HMOs against allergic diseases and asthma [16]. However, recent studies suggest that HMOs may significantly contribute to an infant's immune system development via their effect on the infant's gut microbiome [17, 18]. Focusing on infectious, inflammatory, and immune-related diseases, potential mechanisms of direct as well as indirect effects of HMOs are reviewed below and summarized in Figure 1.

Direct Effects of HMOs

A range of studies have demonstrated that HMOs can provide direct protection against viral and bacterial pathogens (Fig. 1, A1). One mechanism of this is by acting as decoy receptors for the receptors situated on the intestinal surface that pathogens normally use for adhesion and invasion. For example, the sialylated



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HMOs, 3′SL and 6′SL, directly inhibit the binding of rotavirus to host epithelial cells, and fucosylated HMOs, 2′FL and 3FL, block norovirus from interacting with histo-blood group antigens on the surface of epithelial cells [13]. However, this may be virus-strain dependent, as some HMOs, such as LNT, have been shown to increase the infectivity of a specific rotavirus strain [19]; in that case, HMOs were not acting as decoy receptors. Various HMOs, such as 2′FL, 3FL, and 6′SL, inhibit the adhesion of several bacterial pathogens such as *Campylobacter jejuni*, *E. coli* and *Salmonella enterica* to intestinal cell lines [13]. Animal studies, as well as *ex vivo* studies using cultured human intestinal mucosa, have shown that this, at least for *C. jejuni*, occurs by 2′FL mimicking histo-blood group antigens, covering the bacterial surface to prevent its adhesion to the intestinal epithelium [20]. Indeed, prevalence of *C. jejuni*-associated diarrhea is lower among breastfed infants whose mothers contained high levels of 2′FL in the breast milk [21]. Preincubation of Enteropathogenic *E. coli* (EPEC) cells with a pooled mixture of purified HMOs blocks the pathogen's adhesion to intestinal cells *in vitro* and pretreatment with the mixture protected against EPEC colonization in newborn mice [22]. A range of HMOs can also bind toxins produced by bacterial pathogens, such as *E. coli* and *Vibrio cholera*, and studies suggest that this protects against the toxic effects. However, the extent to which the mere binding of HMOs to toxins interferes with the toxic effects has been questioned [23]. Although direct growth inhibitory effects of HMOs on many common bacterial pathogens have not been found, inhibitory effects on growth and biofilm formation have been observed for group B Streptococci [24], such as *Streptococcus agalactiae*, a leading cause of neonatal infection and sepsis. Thus, HMOs provide protection against infectious pathogens by direct interactions at multiple levels.

Fig. 1. Direct and indirect effects of human milk oligosaccharides in the gastrointestinal tract. A1: Direct anti-infective effects of HMOs acting as decoy receptors for (A1.1) viral and (A1.2) bacterial pathogens or (A1.3) exhibiting anti-biofilm effects. A2: HMOs increase barrier function by (A2.1) stimulating tight-junction proteins, intestinal epithelial integrity, and (A2.2) promoting secretion of mucin and antimicrobial peptides from goblet cells. A3: Anti-inflammatory effects of HMOs on intestinal epithelial cells. A4: Immune-regulatory effects of HMOs mediated via dendritic cells resulting in altered CD4+ T-cell populations. B1: HMO-facilitated adhesion of *Bifidobacterium* species on intestinal epithelium, resulting in anti-inflammatory responses and increased intestinal integrity. B2: Production of acetate and lactate as main fermentation end-products of HMO metabolism, resulting in inhibition of bacterial pathogens, increased intestinal epithelial integrity, and immune-regulatory effects on T-cell populations after absorption from the gut. B3: Production of aromatic lactic acid as HMO-stimulated metabolic products of aromatic amino acid fermentation, resulting in anti-inflammatory effects on the intestinal epithelium and upon absorption from the intestine showing immune-regulatory effects on monocytes as well as CD4+ T-cell populations.

A range of *in vitro* studies have provided evidence that HMOs can also contribute to the barrier function of the gut epithelium in various ways (Fig. 1, A2). Multiple studies have demonstrated that HMOs affect the maturation of intestinal cell lines *in vitro* [25]. Stimulation of intestinal cell differentiation has been shown for mixtures as well as individual HMOs, although effects seem to be cell-line and HMO-type specific. Mixtures of HMOs, and especially 2′FL, increase intestinal cell integrity, after challenge with proinflammatory cytokines and 2′FL as well as 3FL stimulate the development of intestinal epithelial glycocalyx, a protective layer of glycoproteins on the surface of the gut epithelium [13, 25]. Selected HMOs, such as 3FL and LNT-2, promote mucin expression and secretion from goblet cell lines under inflammatory conditions [26]. Neonatal mice are protected against NEC, when treated with a mixture of HMOs compared with a treatment using infant formula, via improved mucus secretion and intestinal integrity [27]. Preterm infants born by nonsecretor mothers have a higher risk of NEC and sepsis-related death compared with infants born by secretor mothers, suggesting an important role of α-1,2 fucosylated HMOs, such as 2′FL [28]. However, the mechanisms are not clear and may in addition to effects on barrier function and direct interaction with the pathogens, also include suppression of inflammatory signals from the gut epithelium and associated immune cells. While a porcine model of NEC failed to demonstrate significant improvements of 2′FL supplementation [29], other rodent and porcine models of NEC have shown that 2′FL supplementation results in protection against NEC [30] and indicated that it occurs via inhibition of inflammation mediated by Toll-Like Receptor-4 (TLR-4) signaling [31]. Remarkably, a protective effect of another single HMO, DSLNT, against the development of NEC has been demonstrated in animal models and also indicated in several human studies [14]. The human studies, despite representing different populations from South Africa, America, and the United Kingdom, all found lower concentrations of DSLNT in breast milk of mothers whose preterm infants developed NEC [14]. As recently demonstrated in a rodent model of NEC, the mechanism may involve DSLNT-induced inhibition of the mast cell-mediated gut inflammation observed in NEC tissue [32]. Thus, in addition to enforcing gut epithelial integrity, HMOs may also contribute to mucosal homeostasis by affecting the intestinal epithelium's response to inflammatory conditions as well as immune cell responses. Indeed, various HMOs have been shown to exert direct anti-inflammatory effects on intestinal epithelial cells (Fig. 1, A3). For example, colostrum-derived HMOs attenuate inflammatory responses *ex vivo* in immature intestinal mucosal cells after stimulation with common microbial pathogen-associated molecules, termed Pathogen-Associated Molecular Patterns [33]. 2′FL reduces the proinflammatory response (as measured by the cytokine IL-8), induced by the TLR-4

ligand lipopolysaccharide in epithelial cell lines and inhibits invasion of these with pathogenic *E. coli* strains [34]. 3′SL has been shown to reduce the secretion of the proinflammatory cytokine IL-12 from Caco-2 cells (an intestinal cell line) via distinct pathways [35]. HMOs may also directly affect immune cell function (Fig. 1, A4). Several *in vitro* and *ex vivo* studies have demonstrated that HMOs have modulatory effects on macrophages and peripheral blood mononuclear cells [25]; however, the concentrations required in these studies to observe effects may not reflect the low amounts absorbed from the intestine. However, one study [36] used cord blood mononuclear cells and *ex vivo* tested different purified HMO fractions at concentrations similar to those detected in breastfed infants [10] and found significant effects on T-cell populations. Of note, the acidic HMO fractions stimulated INF-γ producing T-cells, which is suspected to drive the immune system away from allergy- (Th2) and autoimmune- (Th17) associated phenotypes. Furthermore, HMO mixtures *in vitro* directly modulate the maturation of gut sampling monocyte-derived dendritic cells and their interactions with the T-cells of the adaptive immune system via promotion of regulatory T-cells (T_{reg}), inducing tolerance [37]. In a randomized controlled trial, interventions with 2′FL supplemented formula milk in exclusively formula-fed infants lowered the infant plasma levels of inflammatory cytokines, compared with non-2′FL supplemented formula [38].

Thus, in addition to affecting innate immune responses of the intestinal epithelium, HMOs may directly interact with immune cells and affect immune development, but further research is required to establish to what extent this occurs via direct HMO-immune cell interactions given the very poor absorption of HMOs across the epithelial barrier. Perhaps effects on the immune system are more likely to result from the indirect effects of HMOs via the gut microbiome.

Indirect Effects of HMOs

A majority of ingested HMOs reach the colon intact and here they stimulate the growth of specific bacterial taxa in the infant gut (Fig. 1). Although studies have shown that HMOs can be consumed to some extent by *Bacteroides* species (and other gut bacteria), this appears to be unspecific and largely due to their ability to degrade host mucins, the glycosylated part of which is structurally similar to HMOs [39]. Highly specific HMO-degraders are found within the genus of *Bifidobacterium* and confined to specific infant-type species such as *Bifidobacterium longum* subsp. *infantis (B. infantis)*, *Bifidobacterium longum* subsp. *longum (B. longum)*, *Bifidobacterium bifidum* and *Bifidobacterium breve* [40]. These bifidobacteria encode a range of transporters and saccharolytic enzymes necessary

for the import and degradation of the HMOs [40]. This efficient HMO utilization has the consequence that the gut microbiota of breastfed infants is highly dominated by infant-type *Bifidobacterium* species often accounting for 80%–99% of the total microbiota [17]. *B. infantis* is a highly efficient and broad-range HMO utilizer [40], and some breastfed infants display almost sole colonization with this bacterial taxon [17]. Several studies imply that HMOs affect the adhesion of infant-type *Bifidobacterium* species to intestinal epithelial cells and affect their cytokine release and permeability (Fig. 1, B1). As compared with lactose, mixtures of HMOs increase adhesion of *B. infantis* to intestinal cells *in vitro* [41, 42]. When grown *in vitro* on a HMO mixture, compared with lactose, *B. infantis* and *B. bifidum* induce the expression of the anti-inflammatory cytokine IL-10, reduce the expression of proinflammatory chemokines, and alter the expression of tight-junction proteins in intestinal cell lines [41, 43]. In a rodent model of NEC, *B. infantis* supplementation improves the compromised barrier function and ameliorates inflammation [44]. Data from a human study suggest that higher concentrations of DSLNT in mothers' own milk couple with higher abundances of infant-type *Bifidobacterium* species in corresponding preterm infants' guts and together protect against the development of NEC [45]. When infant-type *Bifidobacterium* species grow on HMOs, they produce acetate, lactate, formate, and 1,2-propanediol as fermentation end-products, with the former two being the main products detected in feces [46]. Some of these metabolites may significantly contribute to the beneficial indirect effects of HMOs (Fig. 1, B2). Indeed, acetate and lactate reduce proinflammatory response in intestinal epithelial cells [47]. Further, acetate and lactate reduce the luminal pH, which may suppress the growth of opportunistic pathogens [25]. In addition, acetate produced by orally administered *B. longum* inhibits EPEC infection in a mouse model, by maintaining intestinal epithelial integrity [48]. Acetate can also promote the colonic pool of T_{reg} [49], which may protect against colonic inflammation.

Infant-type *Bifidobacterium* species also produce aromatic amino acid-derived metabolites when consuming HMOs [17]. In essence, they convert the aromatic amino acids, tryptophan, phenylalanine, and tyrosine, contained in breast milk into indole lactic acid (ILA), phenyl lactic acid, and hydroxyphenyl lactic acid (Fig. 1, B3). These metabolites interact with the aryl hydrocarbon receptor (AhR), expressed in most tissues including enterocytes and immune cells and the Human Carboxylic Acid 3 receptor (HCA3), expressed in some immune cells such as neutrophils, monocytes, and macrophages [17, 50]. One of these metabolites, ILA, shows anti-inflammatory and immuno-regulatory effects on intestinal cells and immune cells, at least partly mediated via receptors AhR and HCA3 [17, 51, 52]. For example, under inflammatory conditions, ILA decreases

intestinal epithelial production of the proinflammatory cytokine IL-8 in a manner that depends on the nuclear receptor AhR [51, 52]. This may limit the excessive inflammation occurring when the intestinal epithelium is challenged by microbial pathogens, as in the case of NEC. ILA may also have local and systemic immune effects upon absorption from the gut, as it decreases monocyte production of the proinflammatory cytokine IL-12 (AhR and HCA3 dependent) [17]. In addition, ILA has been shown to regulate T-cell activation, reducing the activity of the autoimmune-associated Th17-cells and allergy-associated Th2-cells [18]. An early-life intervention in breastfed infants with a HMO-degrading, ILA-producing *B. infantis* strain demonstrated reduction in markers of intestinal inflammation and modulated immune profiles away from the aforementioned allergy and autoimmune associated immune phenotypes. An effect that is at least partly dependent on ILA-mediated regulation of T-cell responses [18]. Interestingly, in populations with a low prevalence of atopic diseases (such as the old order Mennonites practicing a traditional farming lifestyle), *B. infantis* colonization is prevalent and abundant among breastfed infants. By contrast, in urban populations, with a high prevalence of atopic diseases, low prevalence and abundance of *B. infantis* is found among breastfed infants [53]. Furthermore, several interventions with HMO-consuming infant-type *Bifidobacterium* species in term and preterm breastfed infants show reduced colonization with opportunistic pathogens and reduced abundance of antimicrobial resistance genes in the gut [54].

In summary, HMOs stimulate the growth of beneficial bacteria in the infant gut and promote the production of beneficial metabolites, which is likely to explain some of the anti-infective, anti-inflammatory and immune-regulatory effects of HMOs. However, multiple studies have demonstrated the lack of or delayed colonization with infant-type *Bifidobacterium* species in preterm infants as well as infants born by caesarean section. In addition, *Bifidobacterium* colonization is drastically reduced by many types of antibiotics administered in early life. Furthermore, in some American and European populations, *B. infantis*, which is considered the most efficient HMO utilizer, is almost extinct from the infant gut microbiome, despite a relative high *current* breastfeeding prevalence. This has been suggested to be due to a *historic*, very low breastfeeding prevalence in these populations, leading to reduced *B. infantis* colonization, followed by compromised interindividual transmission and loss of *B. infantis* over generations [55]. Nonetheless, recent interventions with infant-type *Bifidobacterium* species in breastfed infants have shown that it is possible to promote the establishment of these important taxa in the gut of individuals with disrupted/compromised colonization [56–58], and such interventions can positively affect markers of intestinal inflammation and immune development [18]. For infants

that cannot be breastfed, supplementation of HMOs into formula milk may recapitulate some of the microbiota-mediated health benefits. At least, addition of 2′FL and LN*n*T to infant formula has been shown to promote a *Bifidobacterium*-rich gut microbiota, more similar to that of breastfed infants [59].

Conclusion

In summary, HMOs seem to confer direct and indirect protection against infectious diseases. There is also evidence to suggest that specific HMOs can protect preterm infants against developing NEC. The role of HMOs in immune-related diseases is currently not clear, but recent studies suggest that HMOs, likely via effects on the gut microbiome, could play an important role in immune system development. The beneficial effects of HMOs are first and foremost an additional argument to support breastfeeding. But, our increasing knowledge of these milk oligosaccharides and their direct and microbiome-dependent effects encourage the development of HMO-based formula milk and/or *Bifidobacterium*-based probiotics, which may contribute to prevention of infectious, inflammatory, and immune-related diseases in infants that cannot be breastfed or are lacking infant-type *Bifidobacterium* species in the gastrointestinal tract.

Conflict of Interest Statement

The author declares no conflict of interest.

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References

1 Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016 Jan;387(10017):475–90.

2 Oddy WH. Breastfeeding, childhood asthma, and allergic disease. Ann Nutr Metab. 2017 May;70(Suppl. 2):26–36.

3 Vieira Borba V, Sharif K, Shoenfeld Y. Breastfeeding and autoimmunity: programing health from the beginning. Am J Reprod Immunol. 2018 Jan;79(1):e12778.

4 Agrawal M, Sabino J, Frias-Gomes C, Hillenbrand CM, Soudant C, Axelrad JE, et al. Early life exposures and the risk of inflammatory bowel disease: systematic review and meta-analyses. EClinicalMedicine. 2021 Jun;36:100884.

5 Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: a review on its composition and bioactivity. Early Hum Dev. 2015 Nov;91(11):629–35.
6 Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology. 2012 Sep;22(9):1147–62.
7 McGuire MK, Meehan CL, McGuire MA, Williams JE, Foster J, Sellen DW, et al. What's normal? Oligosaccharide concentrations and profiles in milk produced by healthy women vary geographically. Am J Clin Nutr. 2017 May;105(5):1086–100.
8 Williams JE, McGuire MK, Meehan CL, McGuire MA, Brooker SL, Kamau-Mbuthia EW, et al. Key genetic variants associated with variation of milk oligosaccharides from diverse human populations. Genomics. 2021 Jul;113(4):1867–75.
9 Gnoth MJ, Kunz C, Kinne-Saffran E, Rudloff S. Human milk oligosaccharides are minimally digested in vitro. J Nutr. 2000 Dec;130(12):3014–20.
10 Goehring KC, Kennedy AD, Prieto PA, Buck RH. Direct evidence for the presence of human milk oligosaccharides in the circulation of breastfed infants. PLoS One. 2014 Jul;9(7):e101692.
11 Ma J, Palmer DJ, Geddes D, Lai CT, Stinson L. Human milk microbiome and microbiome-related products: potential modulators of infant growth. Nutrients. 2022 Dec;14(23):5148.
12 Berger PK, Ong ML, Bode L, Belfort MB. Human milk oligosaccharides and infant neurodevelopment: a narrative review. Nutrients. 2023 Jan;15(3):719.
13 Hill DR, Chow JM, Buck RH. Multifunctional benefits of prevalent HMOs: implications for infant health. Nutrients. 2021 Sep;13(10):3364.
14 Abbas S, Keir AK, Makrides M, Klein LD, Grzeskowiak LE, McPhee AJ, et al. Tailoring human milk oligosaccharides to prevent necrotising enterocolitis among preterm infants. Front Nutr. 2021 Jul;8:461.
15 Agrawal M, Allin KH, Petralia F, Colombel JF, Jess T. Multiomics to elucidate inflammatory bowel disease risk factors and pathways. Nat Rev Gastroenterol Hepatol. 2022 Mar;19(6):399–409.
16 Han S, Binia A, Godfrey KM, El-Heis S, Cutfield WS. Do human milk oligosaccharides protect against infant atopic disorders and food allergy? Nutrients. 2020 Oct;12(10):1–12.
17 Laursen MF, Sakanaka M, von Burg N, Mörbe U, Andersen D, Moll JM, et al. *Bifidobacterium* species associated with breastfeeding produce aromatic lactic acids in the infant gut. Nat Microbiol. 2021 Oct;6(11):1367–82.
18 Henrick BM, Rodriguez L, Lakshmikanth T, Pou C, Henckel E, Arzoomand A, et al. Bifidobacteria-mediated immune system imprinting early in life. Cell. 2021 Jul;184(15):3884–98.e11.
19 Ramani S, Stewart CJ, Laucirica DR, Ajami NJ, Robertson B, Autran CA, et al. Human milk oligosaccharides, milk microbiome and infant gut microbiome modulate neonatal rotavirus infection. Nat Commun. 2018 Nov;9(1):1–12.
20 Ruiz-Palacios GM, Cervantes LE, Ramos P, Chavez-Munguia B, Newburg DS. Campylobacter jejuni binds intestinal H(O) antigen (Fucα1, 2Galβ1, 4GlcNAc), and fucosyloligosaccharides of human milk inhibit its binding and infection. J Biol Chem. 2003 Apr;278(16):14112–20.
21 Morrow AL, Ruiz-Palacios GM, Altaye M, Jiang X, Lourdes Guerrero M, Meinzen-Derr JK, et al. Human milk oligosaccharides are associated with protection against diarrhea in breast-fed infants. J Pediatr. 2004 Sep;145(3):297–303.
22 Manthey CF, Autran CA, Eckmann L, Bode L. Human milk oligosaccharides protect against enteropathogenic *Escherichia coli* attachment in vitro and EPEC colonization in suckling mice. J Pediatr Gastroenterol Nutr. 2014 Feb;58(2):165–8.
23 El-Hawiet A, Kitova EN, Klassen JS. Recognition of human milk oligosaccharides by bacterial exotoxins. Glycobiology. 2015 Aug;25(8):845–54.
24 Ackerman DL, Doster RS, Weitkamp JH, Aronoff DM, Gaddy JA, Townsend SD. Human milk oligosaccharides exhibit antimicrobial and antibiofilm properties against *Group B Streptococcus*. ACS Infect Dis. 2017 Aug;3(8):595–605.
25 Walsh C, Lane JA, van Sinderen D, Hickey RM. Human milk oligosaccharides: shaping the infant gut microbiota and supporting health. J Funct Foods. 2020 Sep;72:104074.
26 Cheng L, Kong C, Walvoort MTC, Faas MM, de Vos P, Cheng L, et al. Human milk oligosaccharides differently modulate goblet cells under homeostatic, proinflammatory conditions and ER stress. Mol Nutr Food Res. 2020 Mar;64(5):e1900976.
27 Wu RY, Li B, Koike Y, Määttänen P, Miyake H, Cadete M, et al. Human milk oligosaccharides increase mucin expression in experimental necrotizing enterocolitis. Mol Nutr Food Res. 2019 Feb;63(3):1800658.
28 Morrow AL, Meinzen-Derr J, Huang P, Schibler KR, Cahill T, Keddache M, et al. Fucosyltransferase 2 non-secretor and low secretor status predicts severe outcomes in premature infants. J Pediatr. 2011 May;158(5):745–51.
29 Cilieborg MS, Bering SB, Østergaard MV, Jensen ML, Krych Ł, Newburg DS, et al. Minimal short-term effect of dietary 2′-fucosyllactose on bacterial colonisation, intestinal function and necrotising enterocolitis in preterm pigs. Br J Nutr. 2016 Sep;116(5):834–41.

30 Autran CA, Schoterman MHC, Jantscher-Krenn E, Kamerling JP, Bode L. Sialylated galacto-oligosaccharides and 2′-fucosyllactose reduce necrotising enterocolitis in neonatal rats. Br J Nutr. 2016 Jul;116(2):294–9.
31 Werts AD, Fulton WB, Ladd MR, Saad-Eldin A, Chen YX, Kovler ML, et al. A novel role for necroptosis in the pathogenesis of necrotizing enterocolitis. Cell Mol Gastroenterol Hepatol. 2020 Jan;9(3):403–23.
32 Zhang W, He-Yang J, Zhuang W, Liu J, Zhou X. Causative role of mast cell and mast cell-regulatory function of disialyllacto-*N*-tetraose in necrotizing enterocolitis. Int Immunopharmacol. 2021 Jul;96:107597.
33 He Y, Liu S, Leone S, Newburg DS. Human colostrum oligosaccharides modulate major immunologic pathways of immature human intestine. Mucosal Immunol. 2014 Nov;7(6):1326–39.
34 He YY, Liu SB, Kling DE, Leone S, Lawlor NT, Huang Y, et al. The human milk oligosaccharide 2′-fucosyllactose modulates CD14 expression in human enterocytes, thereby attenuating LPS-induced inflammation. Gut. 2016 Jan;65(1):33–46.
35 Zenhom M, Hyder A, de Vrese M, Heller KJ, Roeder T, Schrezenmeir J. Prebiotic oligosaccharides reduce proinflammatory cytokines in intestinal Caco-2 cells via activation of PPARγ and peptidoglycan recognition protein 3. J Nutr. 2011 May;141(5):971–7.
36 Eiwegger T, Stahl B, Schmitt J, Boehm G, Gerstmayr M, Pichler J, et al. Human milk-derived oligosaccharides and plant-derived oligosaccharides stimulate cytokine production of cord blood T-cells in vitro. Pediatr Res. 2004;56(4):536–40.
37 Xiao L, van De Worp WR, Stassen R, van Maastrigt C, Kettelarij N, Stahl B, et al. Human milk oligosaccharides promote immune tolerance via direct interactions with human dendritic cells. Eur J Immunol. 2019 Jul;49(7):1001–14.
38 Goehring KC, Marriage BJ, Oliver JS, Wilder JA, Barrett EG, Buck RH. Similar to those who are breastfed, infants fed a formula containing 2′-fucosyllactose have lower inflammatory cytokines in a randomized controlled trial. J Nutr. 2016 Dec;146(12):2559–66.
39 Masi AC, Stewart CJ. Untangling human milk oligosaccharides and infant gut microbiome. iScience. 2022 Jan;25(1):103542.
40 Sakanaka M, Gotoh A, Yoshida K, Odamaki T, Koguchi H, Xiao J, et al. Varied pathways of infant gut-associated *Bifidobacterium* to assimilate human milk oligosaccharides: prevalence of the gene set and its correlation with bifidobacteria-rich microbiota formation. Nutrients. 2019 Dec;12(1):71.
41 Wickramasinghe S, Pacheco AR, Lemay DG, Mills DA. Bifidobacteria grown on human milk oligosaccharides downregulate the expression of inflammation-related genes in Caco-2 cells. BMC Microbiol. 2015 Aug;15(1):1–12.
42 Kavanaugh DW, O'Callaghan J, Buttó LF, Slattery H, Lane J, Clyne M, et al. Exposure of *Bifidobacterium longum* subsp. *infantis* to milk oligosaccharides increases adhesion to epithelial cells and induces a substantial transcriptional response. PLoS One. 2013 Jun;8(6):e67224.
43 Chichlowski M, De Lartigue G, Bruce German J, Raybould HE, Mills DA. Bifidobacteria isolated from infants and cultured on human milk oligosaccharides affect intestinal epithelial function. J Pediatr Gastroenterol Nutr. 2012 Sep;55(3):321.
44 Underwood MA, German JB, Lebrilla CB, Mills DA. *Bifidobacterium longum* subspecies *infantis*: champion colonizer of the infant gut. Pediatr Res. 2014 Oct;77(1–2):229.
45 Masi AC, Embleton ND, Lamb CA, Young G, Granger CL, Najera J, et al. Human milk oligosaccharide DSLNT and gut microbiome in preterm infants predicts necrotising enterocolitis. Gut. 2021 Dec;70(12):2273–82.
46 Tsukuda N, Yahagi K, Hara T, Watanabe Y, Matsumoto H, Mori H, et al. Key bacterial taxa and metabolic pathways affecting gut short-chain fatty acid profiles in early life. ISME J. 2021 Sep;15(9):2574–90.
47 Iraporda C, Errea A, Romanin DE, Cayet D, Pereyra E, Pignataro O, et al. Lactate and short chain fatty acids produced by microbial fermentation downregulate proinflammatory responses in intestinal epithelial cells and myeloid cells. Immunobiology. 2015 Oct;220(10):1161–9.
48 Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. Nature. 2011;469(7331):543–7.
49 Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013 Aug;341(6145):569–73.
50 Peters A, Krumbholz P, Jäger E, Heintz-Buschart A, Çakir MV, Rothemund S, et al. Metabolites of lactic acid bacteria present in fermented foods are highly potent agonists of human hydroxycarboxylic acid receptor 3. PLoS Genet. 2019 May;15(5):e1008145.
51 Ehrlich AM, Pacheco AR, Henrick BM, Taft D, Xu G, Huda MN, et al. Indole-3-lactic acid associated with *Bifidobacterium*-dominated microbiota significantly decreases inflammation in intestinal epithelial cells. BMC Microbiol. 2020 Dec;20(1):357.

52 Meng D, Sommella E, Salviati E, Campiglia P, Ganguli K, Djebali K, et al. Indole-3-lactic acid, a metabolite of tryptophan, secreted by *Bifidobacterium longum* subspecies *infantis* is anti-inflammatory in the immature intestine. Pediatr Res. 2020 Aug;88(2):209–17.
53 Seppo AE, Bu K, Jumabaeva M, Thakar J, Choudhury RA, Yonemitsu C, et al. Infant gut microbiome is enriched with *Bifidobacterium longum* ssp. *infantis* in Old Order Mennonites with traditional farming lifestyle. Allergy Eur J Allergy Clin Immunol. 2021 Nov;76(11):3489–503.
54 Laursen MF. Gut microbiota development: influence of diet from infancy to toddlerhood. Ann Nutr Metab. 2021 Aug:1–14.
55 Taft DH, Lewis ZT, Nguyen N, Ho S, Masarweh C, Dunne-Castagna V, et al. *Bifidobacterium* species colonization in infancy: a global cross-sectional comparison by population history of breastfeeding. Nutrients. 2022 Mar;14(7):1423.
56 Frese SA, Hutton AA, Contreras LN, Shaw CA, Palumbo MC, Casaburi G, et al. Persistence of supplemented *Bifidobacterium longum* subsp. *infantis* EVC001 in breastfed infants. mSphere. 2017 Dec;2(6):e00501–17.
57 Alcon-Giner C, Dalby MJ, Caim S, Ketskemety J, Shaw A, Sim K, et al. Microbiota supplementation with *Bifidobacterium* and *Lactobacillus* modifies the preterm infant gut microbiota and metabolome: an observational study. Cell Rep Med. 2020 Aug;1(5):100077.
58 Nguyen M, Holdbrooks H, Mishra P, Abrantes MA, Eskew S, Garma M, et al. Impact of probiotic *B. infantis* EVC001 feeding in premature infants on the gut microbiome, nosocomially acquired antibiotic resistance, and enteric inflammation. Front Pediatr. 2021 Feb;9:618009.
59 Berger B, Porta N, Foata F, Grathwohl D, Delley M, Moine D, et al. Linking human milk oligosaccharides, infant fecal community types, and later risk to require antibiotics. MBio. 2020;11(2):e03196–19.

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Multiomics, Artificial Intelligence, and Prematurity

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Abstract

Novel technologies such as artificial intelligence and multiomics are being applied in the fields of medicine including perinatology and neonatology as research tools. They are also being used to augment our abilities to improve patient care. This review provides a brief background as to how these are being applied in perinatal and neonatal research and how they are and will be increasingly useful for patient care. To accomplish this, a brief historical background will be provided, and we will summarize some perinatal and neonatal problems such as preterm birth, intestinal injuries, retinopathy, and precision nutrition that may benefit from the application of these technologies.

Introduction

Novel emerging technologies are dramatically changing the landscape for care of the pregnant mother and newborn, just as they are in many other fields of medicine. This review provides a brief background on artificial intelligence (AI) and multiomics and how we can integrate these to improve care for mothers and neonates. These are broad areas thus for purpose of this review will need to be limited to a few examples.

Historical Perspective

Artificial Intelligence

If we split the eras of medicine into the past, present, and future, we see interesting trends. In the past, physicians relied on intuition-based medicine where they evaluated a patient based on physical signs and symptoms and their previous knowledge, made a diagnosis, and prescribed a treatment.

The current era continues to use intuition-based approaches but is expanding toward greater evidence-based approaches focused on what is best for a population average given a certain set of patient data. These can lead to guidelines for patient care that may not provide the best approaches for all individuals and may in fact be harmful for certain susceptible individuals.

In the future, knowing that the "one-size-fits-all" approach is not optimal, we will continue to rely on intuitive individual physician judgement and evidence-based approaches but will also utilize newly developed technologies that include AI and multiomics-derived causal mechanisms and tools such as prognostic and diagnostic biomarkers to enhance our ability to provide precision-based preventative and therapeutic strategies for individual patients.

AI has become a part of everyday life. Our cell phones, smartwatches, shopping, and transportation are just some examples of how many aspects of everyday life have changed in the past decade with AI. The same holds true for the medical sciences, where great advances are being made in patient diagnosis as well as prognosis [1]. Interpretation of clinical imaging data for dermatologic and retinal conditions and radiographs enhance the diagnostic capabilities of clinicians. AI predictive analytics provide automated grading of diabetic retinopathy and other eye conditions and are engendering advances for screening programs that will reduce barriers to access [2, 3]. AI has also been used in the prediction of contact tracing during an epidemic and may eventually mitigate exposure to infectious diseases [4]. New platforms such as GUID Partition Table are progressing whereby they can pass sophisticated professional examinations [5]. Various forms of AI are being utilized in perinatology and neonatology as listed in Table 1.

Multiomics

AI can be used for personalization of treatment options based on human genomic data. This can be extended to the evaluation of previous environmental exposures that are capable of modulating the expression of our inherent genomic template resulting in different phenotypes [6]. These interactions between our inherent genomic template and extrinsic environment can now be evaluated using integrated multiomics, which also rely on AI for the analysis of huge data sets [6].

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Table 1. The various categories of AI being applied to medicine, perinatology, and neonatology

Supervised learning	Algorithms that learn to predict outcomes associated with a given set of input features and known outcomes
Unsupervised learning	Without knowledge of an outcome or label, will define hidden structure from the data
Machine learning	An application of artificial intelligence that provides the ability to learn and improve from experience without being explicitly programmed
Deep learning	Artificial neural networks, with algorithms modeled to work like the human brain, earn from large amounts of data
Neural networks	Computer systems modeled on the human brain and nervous system. There are interconnected nodes with multiple layers that connect via weighted links. Learning is accomplished by adjusting the weights to perform the task at hand with maximum accuracy

In the fields of fetal–maternal medicine and neonatology, the research and clinical care of the future will extensively utilize these newly developed tools. The rest of this review will provide a brief overview with examples of their application.

Preterm Birth Prediction

Preterm birth is one of the leading causes of newborn deaths and long-term disabilities. It has emotional and challenging financial consequences for families and society. Early prediction of preterm birth could lead to closer monitoring and preventative strategies so that many of these premature births could be avoided.

Several studies have utilized AI techniques for the prediction of preterm birth. A systematic review that included 22 publications suggested that large datasets are needed for accurate prediction [7]. Several algorithms have been evaluated and their predictive accuracy has been determined using area under the curve measurements [8]. Types of data such as imaging versus clinical features provided different levels of accuracy depending on the algorithms used [9].

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Neonatal Intensive Care

Neonatal care is becoming increasingly complex with large amounts of rich, routinely recorded physiological, diagnostic, and outcome data. AI has the potential to harness this vast quantity of information and is becoming a powerful tool to support clinical decision-making, personalized care, precise prognostics, and enhanced patient safety. Current AI approaches in neonatal medicine include tools for disease prediction and risk stratification, neurological diagnostic support, and novel image recognition technologies. The following are examples where AI and multiomics may be applied in neonatal intensive care.

Clustering of Preterm Neonates Using Unsupervised AI

An example of how neonatal outcomes can be more precisely defined is by phenotypic differentiation using AI. A study by Matsushita et al. [10] was able to utilize unsupervised machine learning, which involves agnostic evaluation of numerous clinical and laboratory characteristics to cluster and classify different types of patients. In this study, six different clusters with clinical and laboratory characteristics were identified.

Of the six different clusters, there was a mature, mechanically ventilated with adequate ventilation, mechanically ventilated with poor ventilation, extremely immature, intensive resuscitation in the delivery room, and early septic group [10].

In an analogous manner, several poorly defined entities in neonatal intensive care which require further refinement can be addressed. These include late-onset sepsis, bronchopulmonary dysplasia, and necrotizing enterocolitis (NEC). Here we will focus on what has been termed "NEC" and how clustering may aid in better defining intestinal injuries that we are calling "NEC."

Poorly Defined Intestinal Injuries

We are beginning to recognize that NEC is not a distinct disease. We do not have an adequate definition for this diagnosis [11, 12]. Because of the lack of refinement of the different problems that have been termed NEC, the field has made little progress in terms of preventative or therapeutic strategies [13].

NEC is an ambiguous and poorly defined diagnosis. Examples include "stage 1, 2, and 3 NEC" [14]. This is highly confusing because as we care for more immature infants, most extremely low gestational age infants exhibit signs and symptoms that would fit "stage 1 NEC." Stage 1 involves feeding intolerance, abdominal distention, signs, and symptoms of overall clinical instability, which represent immaturity rather than a distinct disease entity. Stage 2 is based on radiographic criteria such as pneumatosis intestinalis and portal venous gas, which

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may be subtle or not even present even when the infant has intestinal necrosis. All too often, a reading of "bubbly lucencies" by the radiologist leads to prolonged periods of not feeding these babies using the intestinal tract, prolonged antibiotic use, and prolonged hospital stays. These bubbly lucencies all too often are simply stool in the intestinal lumen which may mimic pneumatosis intestinalis.

Several intestinal pathologies have been termed "NEC." Spontaneous intestinal perforations (SIPs), for example, are perforations in the distal small intestine involving minimal or no necrosis, hence should not be diagnosed as "NEC." However, many of these infants who have SIP end up being recorded in medical records as having "NEC." This is largely because no direct visualization is made when the widespread practice of placing a perineal drain secondary to a radiograph that shows pneumoperitoneum is provided. Without direct visualization of the intestine, it is difficult to discern whether this was actual necrosis of the intestine or SIP. This problem complicates the datasets upon which studies of NEC are based rendering them unreliable for accurate studies.

We recently employed supervised machine learning technologies using two commonly utilized techniques of Ridge Logistic Regression and Random Forest Regression placing several features into the models and determining whether these learning model algorithms could perform accurately. Both models performed accurately with high precision and accuracy [15]. This was done in one institution and whether this will apply to other institutions as well using these same features needs further evaluation.

Clustering of Intestinal Injuries in Neonates

There are several other forms of intestinal injury that are labeled as NEC that continue to contaminate our research bases. These include cardiac-induced mesenteric hypoperfusion syndrome, food protein–induced enterocolitis syndrome, infectious enteritis, general feeding intolerance, and immature gastrointestinal motility.

Currently studies are underway that will test the hypothesis that neonatal intestinal injuries commonly diagnosed as NEC are not a single disease process with a specific pathophysiology and anticipated clinical course, but they are rather a conglomeration of poorly understood acquired pathologies. It is likely that unsupervised machine learning techniques will reexamine and reclassify these acquired neonatal intestinal pathologies into unique clusters of injury in a manner analogous to the study by Matsushita et al. [10] described above. Once these clusters are better delineated, they can be characterized more specifically utilizing newly developed multiomic integration technologies.

There are numerous forms of omic technologies including genomics metagenomics for microbes, transcriptomics, metabolomics, epigenomics, ex-

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poseomics, etc. Many of the recent studies have been done using single omics. An example of application of one of these includes the use of microbiome evaluation in preterm neonates' feces who subsequently developed NEC versus control infants. In a study that evaluated sequence data from several different institutions, Pammi et al. [16] demonstrated differences in the intestinal microbial colonization prior to the development of NEC in these infants. However, such an evaluation shows only an association, providing sparse information in terms of causality or mechanisms.

To achieve a better understanding of causality and mechanisms, an integration of various omic technologies will yield better information than the association of a disease to a single omic evaluation. Such an analysis is being applied to inflammatory bowel disease where the interaction between these different omic is termed the "interactome," which is designed to build a comprehensive molecular map of the mechanistic interactions that lead to the pathogenesis of inflammatory bowel disease [17].

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a leading cause of decreased vision/blindness in children worldwide [18–20]. Currently, serial ophthalmologic examinations are done, and if severity progresses to advanced stages, laser therapy [21] and/or bevacizumab (an antivascular endothelial growth factor antibody) [22, 23] are used to prevent further progression to retinal detachment and blindness. These are both invasive procedures associated with significant complications and could be circumvented if progression of retinopathy could be prevented exceedingly early in the infant's postnatal life.

In the first weeks after birth, in many infants born at <30 weeks gestation, there is a lag period during which diagnosis of ROP is exceedingly difficult. This period is one that may be highly amenable to pharmacologic or nutritional interventions, but we currently do not have a scoring system that shortly after birth predicts which patients would be candidates for such early interventions.

Investigations are underway to develop a predictive tool using AI. In addition to better defining timing for providing preventative strategies, this also may decrease the need for invasive screening exams, which by itself, will be an especially important advance in this field.

Precision Nutrition

Precision nutrition challenges and opportunities have become increasingly apparent [24]. In a study of adult human postprandial responses to food and the potential for precision nutrition [25], a large interindividual variability was observed even in twins when provided with the same meals. Blood triglycerides,

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glucose, and insulin responses varied following identical meals. The gut microbiome in each person had a greater influence on these parameter variances than did meal macronutrients. Thus, factors beyond dietary intake need consideration when providing precision-based nutrition.

Preterm infants are a highly heterogeneous group, where 22-week gestation preterm nutritional requirements are quite different than those of a 32-week gestation preterm and pose significant challenges in providing precision nutrition. Infants born with intrauterine growth restriction, preeclampsia, maternal use of antibiotics, maternal obesity, and sex of the infant are all potentially important determinants of their individual nutritional needs and where certain nutrients may be potentially toxic if given in inappropriate quantities.

Thus, we are moving from the evidence-based Gaussian type of statistics that rely on providing what is thought to be best for the average of the population to individualized precision-based evaluations and therapies. Nutrition is currently being monitored with the use of growth curves and certain metabolic parameters such as blood urea nitrogen and total protein. However, when these show aberrations such as faltering on a growth curve, it may already be too late to prevent long-term adverse consequences. Proactive strategies based on accurate predictive analytics will provide major advances for these rapidly growing individuals who are highly sensitive during these windows of development where small perturbations may have lifelong consequences.

Recent studies have integrated longitudinal clinical and microbiome data to predict growth faltering in preterm infants and have been shown to provide a high level of accuracy with clinical measurements that have been augmented with the integration of microbiome data [26]. It is anticipated that in the future, similar studies utilizing larger datasets, different AI techniques, and multiomics will provide a better understanding of mechanisms and causality of not only growth failure but also more short-term adverse outcomes such as bronchopulmonary dysplasia ROP and late-onset sepsis. Utilizing the knowledge gained from these multiomic integrations, biomarkers can be found that provide predictive accuracy for the development of some of these problems and will aid in preventative as well as therapeutic strategies.

Conclusion

The rapidly emerging fields of AI 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

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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 AI. These will be applied in the future to better understand mechanisms and to provide personalized nutrition for both mothers and their infants.

The future in these areas is very exciting but we will need to closely collaborate in highly functioning teams that include clinicians, basic scientists, engineers, bioinformaticians mathematicians, and other highly skilled individuals.

Conflict of Interest Statement

The author is a member of the Global Scientific Council for the Nestlé Nutrition Institute, serves on the Scientific Advisory Boards for Astarte and Medela, and receives a research grant from Infant Bacterial Therapeutics. These have no bearing on the review.

References

1 Thomas LB, Mastorides SM, Viswanadhan NA, Jakey CE, Borkowski AA. Artificial intelligence: review of current and future applications in medicine. Fed Pract. 2021;38(11):527–38.
2 Gunasekeran DV, Zheng F, Lim GYS, Chong CCY, Zhang S, Ng WY, et al. Acceptance and Perception of Artificial Intelligence Usability in Eye Care (APPRAISE) for ophthalmologists: a multinational perspective. Front Med (Lausanne). 2022;9:875242.
3 Chia MA, Turner AW. Benefits of integrating telemedicine and artificial intelligence into outreach eye care: stepwise approach and future directions. Front Med (Lausanne). 2022;9:835804.
4 El-Sherif DM, Abouzid M. Analysis of mHealth research: mapping the relationship between mobile apps technology and healthcare during COVID-19 outbreak. Global Health. 2022;18(1):67.
5 Gilson A, Safranek CW, Huang T, Socrates V, Chi L, Taylor RA, et al. How does ChatGPT perform on the United States medical licensing examination? The implications of large language models for medical education and knowledge assessment. JMIR Med Educ. 2023;9:e45312.
6 Putignani L, Gasbarrini A, Dallapiccola B. Potential of multiomics technology in precision medicine. Curr Opin Gastroenterol. 2019;35(6):491–8.
7 Akazawa M, Hashimoto K. Prediction of preterm birth using artificial intelligence: a systematic review. J Obstet Gynaecol. 2022;42(6):1662–8.
8 Begum M, Redoy RM, Anty AD. Preterm baby birth prediction using machine learning techniques. In: 2021 International Conference on Information and Communication Technology for Sustainable Development (ICICT4SD). Dhaka: IEEE; 2021.
9 Lee K-S, Ahn KH. Application of artificial intelligence in early diagnosis of spontaneous preterm labor and birth. Diagnostics. 2020;10(9):733.
10 Matsushita FY, Krebs VLJ, de Carvalho WB. Identifying clinical phenotypes in extremely low birth weight infants – an unsupervised machine learning approach. Eur J Pediatr. 2022;181(3):1085–97.
11 Lueschow SR, Boly TJ, Jasper E, Patel RM, McElroy SJ. A critical evaluation of current definitions of necrotizing enterocolitis. Pediatr Res. 2022;91(3):590–7.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 116–124 (DOI: 10.1159/000534956)

12 Martin CR. Definitions of necrotizing enterocolitis: what are we defining and is machine learning the answer? Pediatr Res. 2022;91(3):488–9.
13 Neu J, Modi N, Caplan M. Necrotizing enterocolitis comes in different forms: historical perspectives and defining the disease. Semin Fetal Neonatal Med. 2018;23(6):370–3.
14 Bell MJ, Shackelford PG, Feigin RD, Ternberg JL, Brotherton T. Alterations in gastrointestinal microflora during antimicrobial therapy for necrotizing enterocolitis. Pediatrics. 1979;63(3):425–8.
15 Lure AC, Du X, Black EW, Irons R, Lemas DJ, Taylor JA, et al. Using machine learning analysis to assist in differentiating between necrotizing enterocolitis and spontaneous intestinal perforation: a novel predictive analytic tool. J Pediatr Surg. 2021;56(10):1703–10.
16 Pammi M, Cope J, Tarr PI, Warner BB, Morrow AL, Mai V, et al. Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis. Microbiome. 2017;5(1):31.
17 de Souza HSP, Fiocchi C, Iliopoulos D. The IBD interactome: an integrated view of aetiology, pathogenesis and therapy. Nat Rev Gastroenterol Hepatol. 2017;14(12):739–49.
18 Flynn JT, Bancalari E, Bachynski BN, Buckley EB, Bawol R, Goldberg R, et al. Retinopathy of prematurity. Diagnosis, severity, and natural history. Ophthalmology. 1987;94(6):620–9.
19 Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2013;74(Suppl 1):35–49.
20 Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163–96.
21 Del Portillo MC, Navarro PI, Duran D, Serrano JC. Effect of laser photocoagulation, antiangiogenic therapy or a combined treatment on refractive outcomes of newborns with ROP. Eur J Ophthalmol. 2022;32(6):3295–302.
22 Taher NO, Ghaddaf AA, Al-Ghamdi SA, Homsi JJ, Al-Harbi BJ, Alomari LK, et al. Intravitreal anti-vascular endothelial growth factor injection for retinopathy of prematurity: a systematic review and meta-analysis. Front Med (Lausanne). 2022;9:884608.
23 Chow SC, Lam PY, Lam WC, Fung NSK. The role of anti-vascular endothelial growth factor in treatment of retinopathy of prematurity – a current review. Eye (Lond). 2022;36(8):1532–45.
24 Kirk D, Catal C, Tekinerdogan B. Precision nutrition: a systematic literature review. Comput Biol Med. 2021;133:104365.
25 Berry SE, Valdes AM, Drew DA, Asnicar F, Mazidi M, Wolf J, et al. Human postprandial responses to food and potential for precision nutrition. Nat Med. 2020;26(6):964–73.
26 Lugo-Martinez J, Xu S, Levesque J, Gallagher D, Parker LA, Neu J, et al. Integrating longitudinal clinical and microbiome data to predict growth faltering in preterm infants. J Biomed Inform. 2022;128:104031.

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Nutrition and Early Life Immune Health

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Abstract

The primary role of the immune system is to provide protection against pathogens, but it is also important in achieving tolerance to harmless environmental exposures. There are a number of mechanisms by which diet and nutrition can influence the immune system: providing the necessary energy to support immune cells to function; as substrates for the synthesis of proteins, cells and other structures involved in the immune response; as essential components or cofactors of enzymes involved in the immune response; as precursors for immune signaling molecules; and via the microbiome. Some aspects of the immune system are poorly developed at birth indicating the importance of passive immunity from the mother (e.g., via breast milk) and immune maturation occurs over the first months to years of life. This maturation occurs alongside gut maturation and acquisition of a mature microbiome and is driven in part by factors derived from breast milk and, later on, from the diet but also by exposure to antigens of different kinds including from microbes. Consequently, immune function in early life is highly variable, and is under the influence of both genetic and environmental factors including mode of birth; exposure to immune active components within human breast milk, to antibiotics, and microbes; and the timing of solid food introduction. Observational and interventional studies have been undertaken to assess the immunomodulatory effect of a number of dietary components in early life, including omega-3 fatty acids, prebiotics, and probiotics. Some of these studies confirm significant effects of supplementation during pregnancy and/or early life in reducing the risk of both atopic and infectious disease, but the findings are not consistent across all studies and the extent and duration of the effects seen vary depending upon the duration and dose of supplementation and the

established disease risk of the population. Ongoing research will require an integrated and collaborative scientific approach in order to capture all potential interactions between the maternal and infant diet, infant microbiome and the immune system in early life, and how these relate to disease risk.

Introduction

The human immune system includes organs such as the thymus, specialized tissues such as lymph nodes and the gut-associated immune tissue, a wide variety of cell types such as T cells, B cells, monocytes and neutrophils, and signaling molecules including amino acid derivatives such as histamine, proteins such as cytokines, for example, the interleukins, and fatty acid derived mediators such as prostaglandins. The many cell types have specialized roles, but interact with one another. These interactions can be direct cell-to-cell or can be through chemical mediators released from one cell type that act on another. As a result of these interactions, cellular activity changes so that there is increased or decreased functionality in response to different signals over time. When functioning optimally, the immune system serves to protect the host from adverse external challenges such as bacteria, fungi, viruses, and parasites; the immune system also can provide a degree of protection from internal challenges, with some capacity to recognize and target cancerous cell growth within both the innate and acquired arms of the immune system, and it has a role in clearing damaged cells and cellular debris. To maintain its protective role, there are a number of key functional features of the immune system. One arm of innate (sometimes called natural) immunity is the physical barriers which prevent pathogens from entering the body or from surviving within it. These barriers to entry include the skin, linings of mucus membranes (e.g., respiratory, gastrointestinal, and genitourinary tracts), the acid environment of the stomach, and bactericidal proteins within secretions such as lysozyme. Should a pathogen gain entry into the body, a second line of immune defense requires the recognition of that pathogen and identification of whether it is harmful or harmless. The process of recognition may be generic and innate; for example, a number of immune cells express pattern recognition receptors which can identify general structural characteristics of pathogens such as the presence of lipopolysaccharide. At other times, the recognition may be specific (i.e., for a single antigen) and acquired. This will result in the activation of antigen-specific T cells and the production of antibodies (antigen-specific immunoglobulins) by activated B cells. If recognized as harmful, the immune system functions to eliminate the pathogen. For extracellular

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pathogens, this can involve direct destruction through innate cellular processes such as phagocytosis and oxidative burst. For intracellular pathogens, such as viruses and some bacteria, the killing of infected host cells by specialized immune cells such as natural killer cells or cytotoxic T cells is required. Finally, the immune system can retain a component of memory once an infection has been dealt with. This is because memory T and B cells are generated during an immune response and these can be very long-lived. The purpose of immune memory is to provide a faster and stronger immune response should there be reinfection. The generation of immune memory is the basis of vaccination, which, in some cases, can provide lifetime protection.

In health, the human immune system operates within a careful balance to distinguish between "things that belong" and "things that don't belong," maintaining strong, protective responses when exposed to invasive pathogens, but being tolerant of self-antigens and harmless environmental exposures such as food components and nonpathogenic microbes. If this balance is not maintained, it can result in increased susceptibility to infections, inflammatory diseases such as ulcerative colitis, autoimmune diseases such as rheumatoid arthritis, or atopic diseases such as food allergies. There are a number of factors which can influence the immune system, including genetic background and epigenetic changes caused by varying environmental factors [1]. The latter links the environment with immune development and immune function. Mode of birth is a significant predictor of allergy, with infants born by caesarian section having a significantly increased risk of later allergic disease [2]. Environmental and lifestyle factors such as pet ownership, antibiotic use in early life, and the timing and type of food introduced during weaning have also been identified to have a role in determining the risk of development of allergic disease [3]. That environmental exposures have the potential to modify the risk of allergic disease or to enable tolerance in those with previously diagnosed allergies is evidenced by epigenetic differences (i.e., in DNA methylation) in cytokine genes among those children who outgrow their food allergy, compared to those who do not, with a profile moving toward that observed in healthy controls [4].

Immune cells and immune structures develop during fetal life, but the principal mode of immune defense for the fetus is through passive immunity, mainly the passage of maternal antibodies across the placenta [5]. During pregnancy, the infant's immune environment is one of tolerance, with stem cell expansion and differentiation, limited T cell function and antibody production, and upregulated regulatory T cell activity (Fig. 1). Immediately after birth, passive immunity provided by breast milk is very important to protect the neonate from infections. During early life, the infant transitions from dependence on passive immunity toward the development of independent, mature immune function

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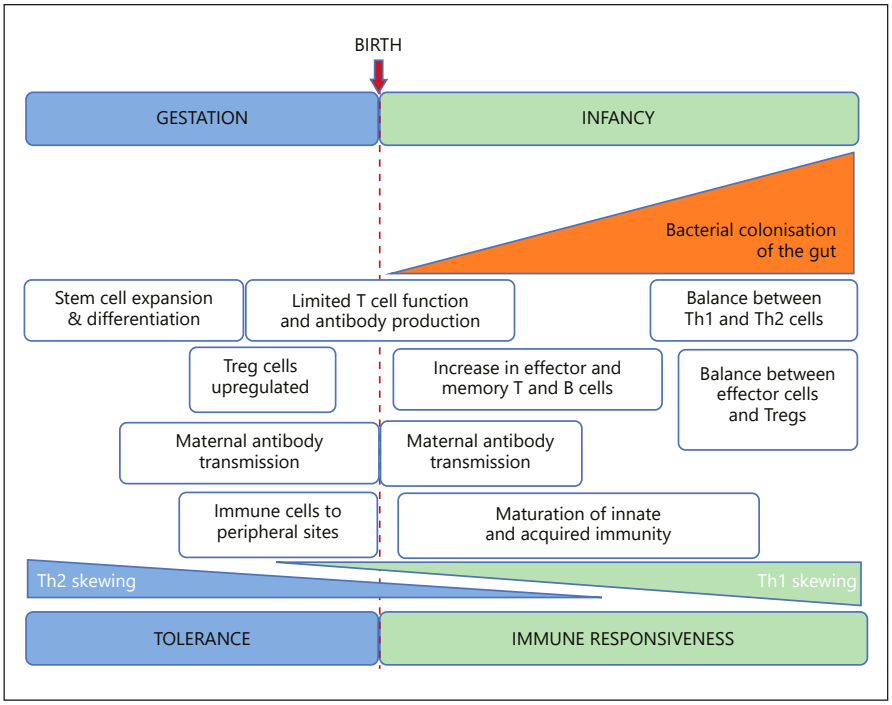

Fig. 1. Schematic depiction of the early development of the human immune system. Th, helper T cell; Treg, regulatory T cell. Reproduced with permission from Miles [6].

(Fig. 1). The infant must rapidly transition to an environment of immune responsiveness due to potential exposure to pathogens, and during this time, bacterial colonization of the gut is also established and there is an increase in the number of effector and memory T and B cells, and the infant moves toward maturation of both innate and acquired immune function (Fig. 1) [6]. While some characteristic patterns are identified which influence the trajectory of immune function in infancy such as the association of preterm birth with inflammation, there is a great deal of variability in immune cell populations between individuals during the early period of life [7].

The Microbiome and Early Immune Development

One important contributor to infant immune development is the maternal skin, gut, and vaginal microbiome, which may in itself explain some of the effects observed for mode of birth on the later risk of allergic and infectious disease. The human gastrointestinal tract is home to a significant and diverse collection of

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microbes, including bacteria, fungi, and viruses, collectively known as the gut microbiome. It is estimated that a human adult has around 200 g of bacteria within their gut, with the majority being within the large intestine [8]. The gut wall is home to a significant number of immune cells (estimated to be 70% of the body's immune cell complement), which both sense and interact with the gut microbiome. The sensing and interaction involve different mechanisms. Specialized regions of the gut wall called Peyer's patches, which are structured assemblies of different immune cells, can sample the gut contents via M cells, respond to changes in the microbiome via dendritic cells, and secrete immunoglobulins such as IgA into the gut lumen from B cells, enabling the coating of bacteria to prevent adherence [9]. This intimate and two-way interaction between the gut contents and the host immune system has led to scientific research on the potential for whole diets, foods, specific nutrients, and functional foods to benefit both gut and systemic immune health in early life acting through modulation of the gut microbiome.

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [10]. The effectiveness of microbes acting as probiotics can vary according to both the species and/or strain of microorganism and the characteristics of the target population [11]. Prebiotics are defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" [12]. Prebiotics are often oligosaccharides although other types of food components can also have prebiotic action [12]. Essentially, prebiotics act by promoting the growth of beneficial microbes that are already present. A synbiotic is the combination of one or more probiotics and one or more prebiotics; the two components may be synergistic, whereby the prebiotic is specifically selected to support the growth of the probiotic strain, or complementary, where both probiotic and prebiotic have distinct health benefits but without necessarily interacting [13]. There are additional emerging strategies mimicking the effects of a beneficial microbiome, including postbiotics from sources such as fermented foods, which are defined as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" [14].

There are a number of mechanisms by which modifying the gut microbiome, through diet or increased consumption of probiotics or prebiotics, may influence host immune defense in early life either through improved barrier function or through improved innate and acquired immunity (Fig. 2). Perhaps the most well-understood mechanism is the direct effect of dietary exposures on specific bacterial species and/or strains which can colonize the gut. The presence of bacterial populations such as bifidobacteria or lactobacilli has been associated with health benefits, while others may confer risk such as the link identified between

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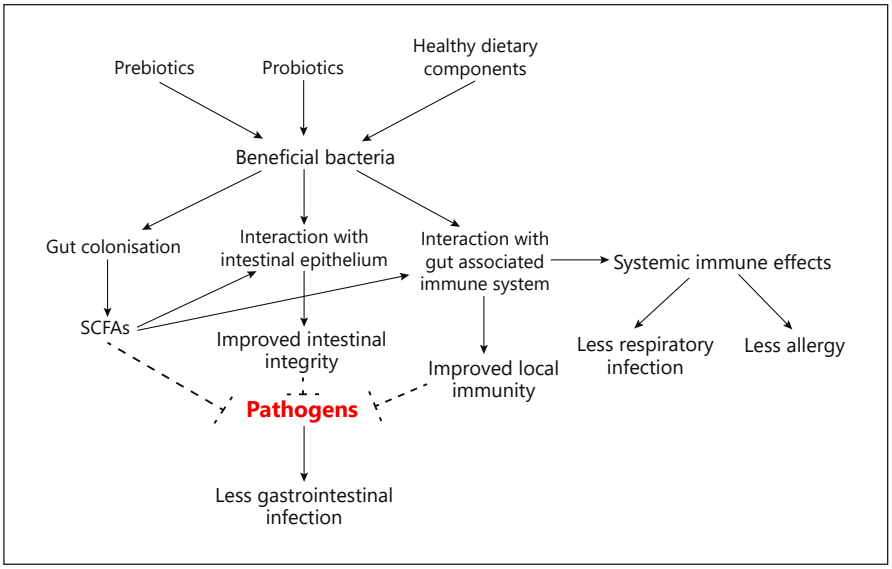

Fig. 2. The relationship between beneficial dietary components, the microbiome, host immunity, and disease risk.

sulfate-reducing bacteria and ulcerative colitis in adults [15]. Health-promoting bacteria may directly compete with pathogens. In addition, the SCFAs they produce may have adverse effects on pathogens but also promote intestinal integrity (especially butyrate) and have effects on immune cells within the gut-associated immune system, in particular by providing anti-inflammatory and tolerogenic signals [16–20]. Through these local effects of the more healthy gut microbiome that is fostered by probiotics and prebiotics, there can be a reduction in the risk of gastrointestinal infections in infants and children. Effects on the gut-associated immune system can have systemic actions because immune cells circulate from the gut wall to other sites within the body, including the lungs. This may explain why probiotics have been shown in some studies to lower the risk of respiratory tract infections in infants and children, as supported by systematic reviews and meta-analyses [21–23]. Although most of the focus to date has been on the gut microbiome, effects also extend beyond this, with recent research highlighting that within the maternal vaginal microbiome, specific microbial species and their metabolic processes are linked to infant allergic outcomes [24].

In addition to the role of human breast milk in providing nutrition for the infant, there are a number of important immune-active components found within human breast milk [25, 26]. These include components which provide

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passive immunity, such as maternal antibodies, complement proteins and antimicrobial enzymes, and those which promote maturation of the infant gut microbiome and gut-associated immune system such as cytokines, growth factors, human milk oligosaccharides (HMOs) and the breast milk microbiome [27]. These immune components within breast milk vary a great deal between individuals and populations in terms of both absolute quantities and component heterogeneity [28, 29]. HMOs may have prebiotic effects, act to mature the infant immune system, and/or have direct effects upon infant immune cells, made possible by the increased permeability of the infant gut epithelium [30–32].

As well as a role in determining the risk of infectious disease in infancy, the gut microbiome is also related to the risk of allergic disease. Interest in the potential to reduce the risk of allergic disease in infants using probiotic interventions arose from studies which identified that children who developed allergic disease in the first year of life tended to have lower fecal bifidobacteria and lactobacilli contents than those who did not go on to develop allergic disease [33–36]. These observational findings are supported by some randomized controlled trials which identified that probiotic interventions provided during pregnancy and/or lactation could reduce the risk of allergic disease in infants, with one meta-analysis reporting the strongest effects in studies which used a mixture of probiotic strains, and where eczema was assessed before 2 years of age [37]. However, data from such trials are inconsistent [38]. The World Allergy Association (WAO) guidelines for allergic disease prevention state:

> "Currently available evidence does not indicate that probiotic supplementation reduces the risk of developing allergy in children. However, considering all critical outcomes in this context, the WAO guideline panel determined that there is a likely net benefit from using probiotics resulting primarily from the prevention of eczema. The WAO guideline panel suggests (a) using probiotics in pregnant women at high risk for having an allergic child; (b) using probiotics in women who breastfeed infants at high risk of developing allergy; and (c) using probiotics in infants at high risk of developing allergy. All recommendations are conditional and supported by very low-quality evidence" (Fiocchi [39]).

Given the likely role of prebiotics in supporting the development of both the gut microbiome and the infant immune system, infant formula-containing prebiotics has been studied for its potential to modify the risk of infections and allergies. A formula containing prebiotic fructo- and galacto-oligosaccharides was found to promote a fecal metabolite profile closer to that of breastfed infants than standard formula-fed infants, with a lower fecal pH compared to the standard formula, reflecting an increased acetate content and reduced propionate content [40]. Infant formula containing these prebiotics also increased fecal secretory IgA when compared to the standard infant formula [41]. Infants pro-

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vided with a formula containing neutral oligosaccharides and pectin-derived acidic oligosaccharides were found to have a reduced risk of eczema in the first year of life [42, 43], and while some studies found that this effect was maintained for up to 5 years [44, 45], other studies found that the effect was no longer visible when infants were reassessed at age 5 years, perhaps reflecting the other contributions of environmental factors which arise throughout childhood [46]. The WAO guidelines for allergic disease prevention state:

> "the WAO guideline panel suggests using prebiotic supplementation in not exclusively breastfed infants and not using prebiotic supplementation in exclusively breastfed infants. Both recommendations are conditional and based on very low certainty of the evidence. We found no experimental or observational study of prebiotic supplementation in pregnant women or breastfeeding mothers. Thus, the WAO guideline panel chose not to provide a recommendation about prebiotic supplementation in pregnancy or during breastfeeding, at this time" (Moro [47]).

In one study, prebiotic containing infant formula was found to significantly reduce the number of upper respiratory tract and gastrointestinal tract infections within the first 6 months of life [48].

Omega-3 Polyunsaturated Fatty Acids and Immune Function in Early Life

Omega-3 (n-3) polyunsaturated fatty acids have been extensively studied in relation to their anti-inflammatory effects and with a view to their potential role in preventing allergic disease in early life [6]. n-3 fatty acids are available within the diet from both plant and marine sources. The n-3 fatty acid α-linolenic acid (ALA) is found within plant sources such as walnuts, flaxseeds, flaxseed oil, and green leafy vegetables, while oily fish are a rich dietary source of the longer-chain n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There is a metabolic pathway which allows the synthesis of EPA and DHA from ALA, although the activity of this conversion is considered to be low in humans. The same series of enzymes is also involved in the metabolism of n-6 fatty acids, in which linoleic acid (LA) is converted into arachidonic acid (AA). This shared enzymic pathway means that the dietary balance between n-3 and n-6 fatty acids (or at least between ALA and LA) will determine the abundance of longer-chain fatty acid products that are generated; prior to birth, differential placental transfer of fatty acids plays a role in supply of the different fatty acids to the fetus [5]. These fatty acid metabolic pathways are important as AA, EPA, and DHA can be precursors to key immune signaling molecules including prostaglandins, leukotrienes, resolvins, protectins, and maresins, which have key roles in regulating immunity and controlling inflammation. The anti-inflammatory effects of n-3

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fatty acid intake have been traditionally understood to arise from the basis that signaling molecules derived from EPA are less proinflammatory than those derived from AA. However, there are also potential contributing factors to the effects of n-3 fatty acids upon the membrane fluidity of immune cells, interactions of n-3 fatty acids with secondary messenger cascades and transcription factors, and the generation of immunomodulatory and inflammation-resolving mediators like resolvins, protectins, and maresins [6].

A number of observational studies identified links between the intake of different fatty acids and the risk of allergic disease, with populations consuming high intakes of n-3 fatty acids observed to have low incidence of asthma, n-6 intakes in childhood found to be a positive predictor of asthma, and regular consumption of fresh oily fish (a rich source of EPA and DHA) identified as protective against the risk of current asthma in childhood [49–52].

Several randomized controlled trials of n-3 fatty acid supplementation in women during pregnancy and/or lactation reported that high-dose supplements can reduce the risk of sensitization of the infant to common food allergens such as egg, and reduce the risk of severe eczema, food allergy, or wheezing/asthma in infants and children [53–55]. A meta-analysis of some of these trials published in 2016 [56] identified that n-3 fatty acid supplements in pregnancy decreased the risk of atopic eczema (eczema with positive skin prick test) in the first 12 months of life, positive skin prick test to any allergen in the first 12 months of life, positive skin prick test to hens' egg in the first 12 months of life, and positive skin prick test to any food extract in the first 12 months of life. A more recent meta-analysis, published in 2019 and using data from 10 randomized controlled trials [57] reported that maternal n-3 fatty acids decreased risk of sensitization to egg and sensitization to peanut, but did not identify significant effects on risk of eczema or asthma/wheezing. An even more recent meta-analysis, published in 2022 [58], reported that perinatal supplementation with n-3 fatty acids can reduce the incidence of asthma/wheezing and allergic asthma in in European children and that higher doses are more effective.

In preterm infants, formula containing both AA and DHA led to immune effects significantly different from those seen in preterm infants provided with control formula, and consistent with those observed in preterm infants provided with human milk [59]. For term infants, use of infant formula which included both AA and DHA was found to promote an immune profile similar to breastfed infants [60], to reduce the risk of allergic disease in infancy [61, 62] and to reduce the risk of common respiratory illnesses [63]. Some supplementation studies in infants have shown that EPA + DHA results in a more mature immune system [64] and a lower risk of allergic disease [65].

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Conclusion

The immune system develops early in life, with breastfeeding, introduction of foods, and microbe exposure all being important influences. More optimal immune development results in a greater ability to combat pathogens and a lower risk of allergic diseases. The gut microbiome is an important determinant of immune development and in early life the gut microbiome and the immune system seem to "comature." There are multiple mechanisms by which the gut microbiome can interact with the immune system, and the pattern of environmental exposures an infant has before, during, and after birth is likely to significantly influence the development of both the gut microbiome and the immune system, potentially setting the trajectory for immune health and disease throughout the life course. Maternal diet during pregnancy and lactation and infant diet after birth seem to be important in immune development; breast milk particularly contains many immune active and immune maturing factors as well as prebiotics and microbes to promote infant gut colonization. There is some evidence for the effects of early exposure to probiotics, prebiotics, and n-3 fatty acids on infant risk of allergic, and in some cases, infectious disease, but the longevity of these effects and the populations most likely to benefit from such interventions remain unclear. Given the multifactorial influences on immune function in early life, an integrated and collaborative scientific approach is required to study the potential interactions between the gut microbiome and the immune system and to enable the identification of biomarkers or characteristics which may predict those most likely to benefit from specific dietary components that may be introduced as supplements or in fortified life-stage-specific foods.

Conflict of Interest Statement

Consultancies/advisory roles of Philip C. Calder: BASF AS, DSM, Danone/Nutricia, Cargill, Nutrileads, Bayer Consumer Care, Haleon Wellness (formerly GSK Consumer Healthcare), Barilla, Fresenius Kabi. Philip C. Calder has received speaking honoraria from DSM, Danone/Nutricia, Fresenius Kabi, Bayer Consumer Care, GSK Consumer Healthcare, Biogredia, Pepsico, Procter & Gamble, and Abbott. Caroline E. Childs has received speaking honoraria from Nutrilicious, Nutricia Ltd, Clasado Biosciences, Nestlé UK Ltd., Yakult, and Friesland Campina.

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Author Contributions

Caroline E. Childs: Writing – Original draft, review, and editing; Philip C. Calder: Writing – Review and editing.

References

1 Childs CE, Munblit D, Ulfman L, Gomez-Gallego C, Lehtoranta L, Recker T, et al. Potential biomarkers, risk factors and their associations with IgE-mediated food allergy in early life: a narrative review. Adv Nutr. 2021;13(2):633–51.
2 Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. Clin Exp Allergy. 2008;38(4):634–42.
3 Kim H, Sitarik AR, Woodcroft K, Johnson CC, Zoratti E. Birth mode, breastfeeding, pet exposure, and antibiotic use: associations with the gut microbiome and sensitization in children. Curr Allergy Asthma Rep. 2019;19(4):22.
4 Berni Canani R, Paparo L, Nocerino R, Cosenza L, Pezzella V, Di Costanzo M, et al. Differences in DNA methylation profile of Th1 and Th2 cytokine genes are associated with tolerance acquisition in children with IgE-mediated cow's milk allergy. Clin Epigenetics. 2015;7(1):38.
5 Lewis RM, Childs CE, Calder PC. New perspectives on placental fatty acid transfer. Prostaglandins Leukot Essent Fatty Acids. 2018;138:24–9.
6 Miles EA, Childs CE, Calder PC. Long-chain polyunsaturated fatty acids (LCPUFAs) and the developing immune system: a narrative review. Nutrients. 2021;13(1):247.
7 Olin A, Henckel E, Chen Y, Lakshmikanth T, Pou C, Mikes J, et al. Stereotypic immune system development in newborn children. Cell. 2018;174(5):1277–92.e14.
8 Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533.
9 Macdonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. Science. 2005;307(5717):1920–5.
10 Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11(8):506–14.
11 You J, Yaqoob P. Evidence of immunomodulatory effects of a novel probiotic, *Bifidobacterium longum* bv. *infantis* CCUG 52486. FEMS Immunol Med Microbiol. 2012;66(3):353–62.
12 Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14(8):491–502.
13 Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. Nat Rev Gastroenterol Hepatol. 2020;17(11):687–701.
14 Salminen S, Collado MC, Endo A, Hill C, Lebeer S, Quigley EMM, et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nat Rev Gastroenterol Hepatol. 2021;18(9):649–67.
15 Rowan FE, Docherty NG, Coffey JC, O'Connell PR. Sulphate-reducing bacteria and hydrogen sulphide in the aetiology of ulcerative colitis. Br J Surg. 2009;96(2):151–8.
16 Li M, van Esch B, Wagenaar GTM, Garssen J, Folkerts G, Henricks PAJ. Pro- and anti-inflammatory effects of short chain fatty acids on immune and endothelial cells. Eur J Pharmacol. 2018;831:52–9.
17 Jeurink PV, van Esch BC, Rijnierse A, Garssen J, Knippels LM. Mechanisms underlying immune effects of dietary oligosaccharides. Am J Clin Nutr. 2013;98(2):572S-7S.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 125–138 (DOI: 10.1159/000534961)

18 Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. Adv Immunol. 2014;121:91–119.
19 Del Fabbro S, Calder P, Childs C. Microbiota-independent immunological effects of non-digestible oligosaccharides in the context of inflammatory bowel diseases. Proc Nutr Soc. 2020;79(4):468–78.
20 Wang Y, Gao X, Zhang X, Xiao Y, Huang J, Yu D, et al. Gut microbiota dysbiosis is associated with altered bile acid metabolism in infantile cholestasis. mSystems. 2019;4(6):e00463–19.
21 Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, et al. Probiotics for prevention and treatment of respiratory tract infections in children: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2016;95(31):e4509.
22 Liu S, Hu P, Du X, Zhou T, Pei X. Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. Indian Pediatr. 2013;50(4):377–81.
23 Laursen RP, Hojsak I. Probiotics for respiratory tract infections in children attending day care centers – a systematic review. Eur J Pediatr. 2018;177(7):979–94.
24 McCauley KE, Rackaityte E, LaMere B, Fadrosh DW, Fujimura KE, Panzer AR, et al. Heritable vaginal bacteria influence immune tolerance and relate to early-life markers of allergic sensitization in infancy. Cell Rep Med. 2022;3(8):100713.
25 Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: a review on its composition and bioactivity. Early Hum Dev. 2015;91(11):629–35.
26 Ogra PL. Immunology of human milk and lactation: historical overview. Nestle Nutr Inst Workshop Ser. 2020;94:11–26.
27 Demmelmair H, Jiménez E, Collado MC, Salminen S, McGuire MK. Maternal and perinatal factors associated with the human milk microbiome. Curr Dev Nutr. 2020;4(4):nzaa027.
28 Donovan SM, Comstock SS. Human milk oligosaccharides influence neonatal mucosal and systemic immunity. Ann Nutr Metab. 2016;69(Suppl 2):42–51.
29 Ruiz L, Espinosa-Martos I, García-Carral C, Manzano S, McGuire MK, Meehan CL, et al. What's normal? Immune profiling of human milk from healthy women living in different geographical and socioeconomic settings. Front Immunol. 2017;8:696.
30 He Y, Liu S, Leone S, Newburg DS. Human colostrum oligosaccharides modulate major immunologic pathways of immature human intestine. Mucosal Immunol. 2014;7(6):1326–39.
31 Plaza-Diaz J, Fontana L, Gil A. Human milk oligosaccharides and immune system development. Nutrients. 2018;10(8):1038.
32 Singh RP, Niharika J, Kondepudi KK, Bishnoi M, Tingirikari JMR. Recent understanding of human milk oligosaccharides in establishing infant gut microbiome and roles in immune system. Food Res Int. 2022;151:110884.
33 Bjorksten B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy. 1999;29(3):342–6.
34 Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol. 2001;108(4):516–20.
35 Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol. 2001;107(1):129–34.
36 Ouwehand AC, Isolauri E, He F, Hashimoto H, Benno Y, Salminen S. Differences in *Bifidobacterium* flora composition in allergic and healthy infants. J Allergy Clin Immunol. 2001;108(1):144–5.
37 Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A, et al. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy. 2015;70(11):1356–71.
38 Colquitt AS, Miles EA, Calder PC. Do probiotics in pregnancy reduce allergies and asthma in infancy and childhood? A systematic review. Nutrients. 2022;14(9):1852.
39 Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, Agarwal A, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): probiotics. World Allergy Organ J. 2015;8(1):4.
40 Knol J, Boehm G, Lidestri M, Negretti F, Jelinek J, Agosti M, et al. Increase of faecal bifidobacteria due to dietary oligosaccharides induces a reduction of clinically relevant pathogen germs in the faeces of formula-fed preterm infants. Acta Paediatr Suppl. 2005;94(449):31–3.
41 Scholtens PA, Alliet P, Raes M, Alles MS, Kroes H, Boehm G, et al. Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. J Nutr. 2008;138(6):1141–7.
42 Grüber C, van Stuijvenberg M, Mosca F, Moro G, Chirico G, Braegger CP, et al. Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. J Allergy Clin Immunol. 2010;126(4):791–7.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 125–138 (DOI: 10.1159/000534961)

43 Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child. 2006;91(10):814–9.
44 Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr. 2008;138(6):1091–5.
45 Arslanoglu S, Moro GE, Boehm G, Wienz F, Stahl B, Bertino E. Early neutral prebiotic oligosaccharide supplementation reduces the incidence of some allergic manifestations in the first 5 years of life. J Biol Regul Homeost Agents. 2012;26(3 Suppl):49–59.
46 Grüber C, van Stuivenberg M, Mosca F, Moro G, Chirico G, Braegger CP, et al. Immunoactive prebiotics transiently prevent occurrence of early atopic dermatitis among low-atopy-risk infants. J Allergy Clin Immunol. 2015;136(6):1696–8.e1.
47 Cuello-Garcia CA, Fiocchi A, Pawankar R, Yepes-Nunez JJ, Morgano GP, Zhang Y, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): prebiotics. World Allergy Organ J. 2016;9:10.
48 Arslanoglu S, Moro GE, Boehm G. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. J Nutr. 2007;137(11):2420–4.
49 Haby MM, Peat JK, Marks GB, Woolcock AJ, Leeder SR. Asthma in preschool children: prevalence and risk factors. Thorax. 2001;56(8):589–95.
50 Hodge L, Salome CM, Peat JK, Haby MM, Xuan W, Woolcock AJ. Consumption of oily fish and childhood asthma risk. Med J Aust. 1996;164(3):137–40.
51 Horrobin DF. Low prevalences of coronary heart disease (CHD), psoriasis, asthma and rheumatoid arthritis in Eskimos: are they caused by high dietary intake of eicosapentaenoic acid (EPA), a genetic variation of essential fatty acid (EFA) metabolism or a combination of both? Med Hypotheses. 1987;22(4):421–8.
52 Lee-Sarwar K, Kelly RS, Lasky-Su J, Kachroo P, Zeiger RS, O'Connor GT, et al. Dietary and plasma polyunsaturated fatty acids are inversely associated with asthma and atopy in early childhood. J Allergy Clin Immunol Pract. 2019;7(2):529–38.e8.
53 Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadottir E, Schoos AM, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. N Engl J Med. 2016;375(26):2530–9.
54 Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol. 2003;112(6):1178–84.
55 Furuhjelm C, Warstedt K, Larsson J, Fredriksson M, Bottcher MF, Falth-Magnusson K, et al. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr. 2009;98(9):1461–7.
56 Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. Am J Clin Nutr. 2016;103(1):128–43.
57 Vahdaninia M, Mackenzie H, Dean T, Helps S. Omega-3 LCPUFA supplementation during pregnancy and risk of allergic outcomes or sensitization in offspring: a systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2019;122(3):302–13.e2.
58 Jia Y, Huang Y, Wang H, Jiang H. A dose-response meta-analysis of the association between the maternal omega-3 long-chain polyunsaturated fatty acids supplement and risk of asthma/wheeze in offspring. BMC Pediatr. 2022;22(1):422.
59 Field CJ, Thomson CA, Van Aerde JE, Parrott A, Euler A, Lien E, et al. Lower proportion of CD45R0+ cells and deficient interleukin-10 production by formula-fed infants, compared with human-fed, is corrected with supplementation of long-chain polyunsaturated fatty acids. J Pediatr Gastroenterol Nutr. 2000;31(3):291–9.
60 Field CJ, Van Aerde JE, Robinson LE, Clandinin MT. Effect of providing a formula supplemented with long-chain polyunsaturated fatty acids on immunity in full-term neonates. Br J Nutr. 2008;99(1):91–9.
61 Foiles AM, Kerling EH, Wick JA, Scalabrin DM, Colombo J, Carlson SE. Formula with long-chain polyunsaturated fatty acids reduces incidence of allergy in early childhood. Pediatr Allergy Immunol. 2016;27(2):156–61.
62 Birch EE, Khoury JC, Berseth CL, Castaneda YS, Couch JM, Bean J, et al. The impact of early nutrition on incidence of allergic manifestations and common respiratory illnesses in children. J Pediatr. 2010;156(6):902–6.e1.
63 Pastor N, Soler B, Mitmesser SH, Ferguson P, Lifschitz C. Infants fed docosahexaenoic acid- and arachidonic acid-supplemented formula have decreased incidence of bronchiolitis/bronchitis the first year of life. Clin Pediatr (Phila). 2006;45(9):850–5.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 125–138 (DOI: 10.1159/000534961)

64 Damsgaard CT, Lauritzen L, Kjaer TM, Holm PM, Fruekilde MB, Michaelsen KF, et al. Fish oil supplementation modulates immune function in healthy infants. J Nutr. 2007;137(4):1031–6.

65 D'Vaz N, Meldrum SJ, Dunstan JA, Lee-Pullen TF, Metcalfe J, Holt BJ, et al. Fish oil supplementation in early infancy modulates developing infant immune responses. Clin Exp Allergy. 2012;42(8):1206–16.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 125–138 (DOI: 10.1159/000534961)

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The Benefits and Challenges of Digital Health

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Abstract

Since the internet globalization started in the 1990s, the society has experienced a fast-growing pace of change. Many cultural and social habits were modified, and new experiences of communication and networking became the "new normal," like using smartphones and application software to interact, from e-mail to the current instant messengers and recently the social media. To potentialize the benefits and reduce the challenges of digital health, the combination of digital tools (like artificial intelligence) with better nutrition, healthcare strategies for children, and integrated health population data management to enhance the delivery of healthcare for individuals will be a must. The challenge of Digital Health in the 21st Century will not be primarily technological, but above all human!

Introduction

In the early 19th century, the telegraph was invented by Samuel Morse, the creator of Morse code. His invention opened a new era of interaction between people, when they could overcome barriers of long distances and managing to communicate. Around 1860, the Italian Antonio Meucci invented a new device that he called the "talking telegraph" – it was the birth of the telephone! Again, people would have greater freedom to communicate more clearly and quickly.

But in their early days there was a practical problem with these inventions. People had to move to where this new form of communication was physically present. Who does not remember in Western movies people going to the train station where there was a telegraph operator who transcribed messages in Morse code, or even telephone booths (which still exist!) with those countless cables to be able to connect people?

The telegraph and the telephone, as well as many other innovations we know, often show that the initial emphasis is on the created system, on the technological structure, and much less on the user who must adjust to it. It was not until the late 20th century that personal mobile telephone communication began to become a reality. The focus was migrating from the system to the user. Who today still imagines going to a telephone booth? Smartphones have become an extension of our own expression of personal communication.

The Digital Era Fast-Changing Pace

Well, in terms of health, we can say that something similar is also changing. We all have the natural reaction that if we get sick "we have to go" to a clinic or hospital to find out what is wrong with us because there are professionals and the structure to take care of us, right? In more serious cases, the health professional, usually the doctor or paramedic, "must come" to see the patient. The healthcare system of patient care has been centered on physical locations that require us to travel. And all of this requires *time*! Time to go or come, time to wait for care that seems not to arrive, time to wait for the diagnosis, time that can often represent the patient's chance of survival or death.

Since the internet globalization started in the 1990s, society has experienced a fast-growing pace of change. Many cultural and social habits were modified, and new experiences of communication and networking became the "new normal," like using smartphones and application software to interact (from e-mail to the current instant messengers and recently the social media).

If we look at all the areas impacted by digital transformation, health is a very important one and, in some ways, still resistant to change. We had a three-way process in the digital transformation journey, starting with digitization, then digitalization, and now the digital transformation stage (shown in Fig. 1).

But what is Digital Health? Digital Health is the coming together of the digital and genetic revolutions with health, with the aim of reducing inefficiencies in the delivery of health care, improving access, reducing costs, increasing quality, and making medicine more personalized and accurate. Digital Health depends in many ways on a large quantity of data generated by patients, healthcare

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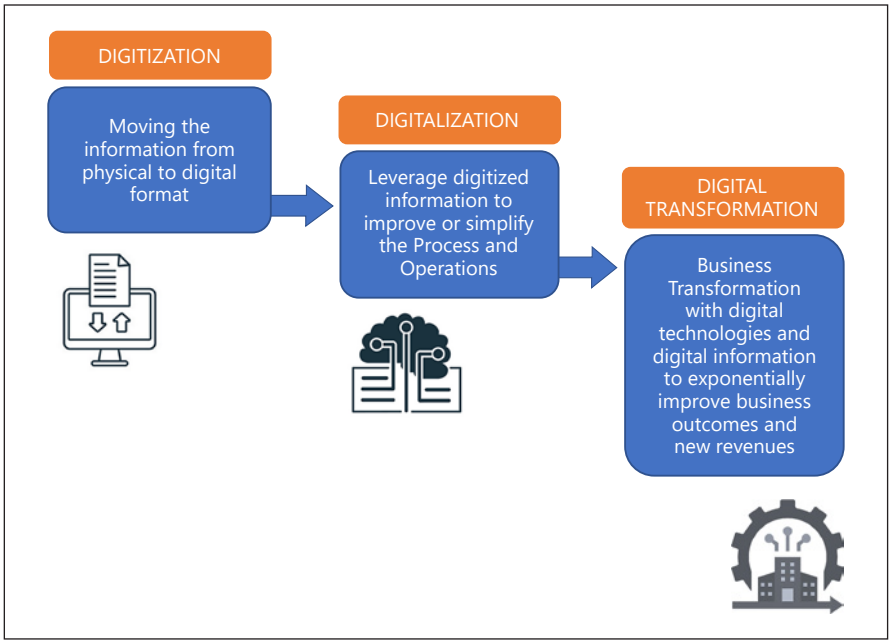

Fig. 1. Digital transformation journey – three stages.

professionals, companies, and government entities associated with health services.

To be able to handle such increasing and exponential big data content generation, artificial intelligence (AI) tools and applied AI solutions will play a major role. They are already in use and contributing to processing massive data information.

The FDA (U.S. Food and Drug Administration) also adds that

> from mobile medical apps and software that support the clinical decisions doctors make every day to artificial intelligence and machine learning, digital technology has been driving a revolution in health care. Digital health tools have the vast potential to improve our ability to accurately diagnose and treat disease and to enhance the delivery of health care for the individual (shown in Fig. 2). Patients and consumers can use digital health technologies to better manage and track their health and wellness-related activities (U.S. Food and Drug Administration [1]).

The market for new devices and solutions for remote diagnosis is growing fast, becoming today a new area of Medicine and Health that brings a revolution in the very way of understanding the patient through the data that can be collected from him and, therefore, that counts a much more reliable history of your health and habits.

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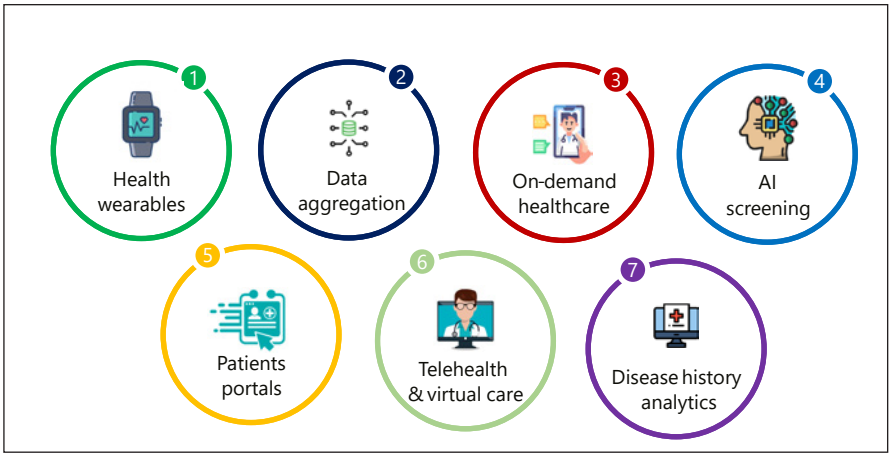

Fig. 2. Digital health tools.

As many expert market reports [2] on new products for Digital Health show, the mass adoption of mobile health devices and the introduction of technologically advanced product designs are anticipated to stimulate demand [3]. Wearable medical things, which include sensors and mobile communication devices, are expected to continue to drive industry growth in the future.

Some points can be highlighted:

1. Consumer wearables can provide patients with personalized health data that can aid in self-diagnosis and behavior change interventions.
2. There are several concerns about the safety, reliability, and security of using consumer wearables in healthcare.
3. Practitioners and researchers should consider how these technological advances might affect health care in the 21st century. Of course, there are all the ethical, social, professional, and economic dilemmas involved.

The Pandemic Effect

Another recent tipping point in the digital health transformation was reached in early 2020, with the advent of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic. Although the coronavirus disease 2019 pandemic cannot be credited for the radical change in healthcare that has been experienced over the last 2 years, there is no doubt that the digital transformation of healthcare has accelerated worldwide because of this pandemic [4–6].

As a brief from the European parliament stated,

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coronavirus has accelerated the rise of digital health, a broad concept that includes solutions for telemedicine and teleconsultation, remote monitoring, connected devices, digital health platforms and health apps. The concept also covers the related health data analysis and application in systems based on big data, for instance, for epidemiological research and AI-enabled diagnosis support (Negreiro [7]).

Digital technologies are becoming essential in the fight against any pandemic and large disease-based population. Patients with existing critical illnesses (specially the noncommunicable diseases, NCDs), reluctant to go to hospital because of the risk of contracting viruses, have been able to get online consultations from home and have in some cases been monitored remotely.

Nevertheless, there are many challenges to overcome as advances in the digitalization of healthcare come with drawbacks. We highlight a widening "digital divide" in society that risks leaving behind the elderly and socially disadvantaged groups, who are less able to master (called the digital illiteracy population) or afford the access to technology. In addition, liability, reimbursement, and cybersecurity issues are among the other key challenges that need to be considered, as cyber-attacks on hospitals are on the rise and privacy laws (like the *General Data Protection Regulation* (EU GDPR) in Europe and *Lei Geral de Proteção de Dados Pessoais* (General Personal Data Protection Law, LGPD) in Brazil) are ineffective.

Challenges and Opportunities in Digital Health for the 21st Century

In 2017, at the World Economic Forum event, a statement was made that "NCDs were becoming the greatest challenge to global health. NCDs represent more than half the global burden of disease" [8]. In many ways, chronic diseases are preventable if managed with preventive strategies and better population health initiatives. The growing challenge is that such NCDs are happening in the early stages of life, impacting already millions of children. By definition, NCDs impact the health of children (directly and indirectly) just as much as they do the health of adults. Cancer, diabetes (both type 1 and type 2 diabetes), chronic respiratory diseases (such as asthma), congenital and acquired heart disease, and many endemic NCDs all affect children [9].

Strategies for reducing dietary risk factors for obesity are most successful when begun early and when healthy foods are available and affordable to all [10].

Improved lifestyle and quality of children's health are likely to reduce the burden of adult diseases and enhance longevity because seeds of most adult diseases are sown in childhood. Identification and decoding of the human genome are expected to revolutionize the practice of pediatrics [11].

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But Digital Health will require a great convergence of reliable data information that can only be achieved with the support of healthcare digitalization and AI solutions. AI and digitalization have introduced transformative advancements in healthcare, but they also come with certain challenges and threats. One of the key challenges is the potential for biased decision-making. AI systems are trained on existing data, which can reflect societal biases, leading to unfair treatment or outcomes for certain populations. Ensuring that AI algorithms are fair, transparent, and unbiased is crucial to maintaining trust and avoiding discrimination in healthcare. Additionally, ethical considerations have emerged regarding the use of AI in healthcare decision-making. Questions around accountability, responsibility, and transparency arise when relying on AI systems to make critical decisions that affect patient health and well-being.

So, new synergies between Digital Health, food, nutrition, and pediatrics to the younger generations will be an excellent field of research and application of the newer tools we are developing, considering AI, data analytics, genetic treatment personalization, and precision medicine.

Health innovation is no longer a matter of opportunity; it is a matter of survival! There is a revolution underway in health, a rebalancing of forces among its actors, and at this moment the patient is becoming one of the main actors. The most relevant medical costs are largely related to location, time, and people. Smart grids will allow place, time, and people to become more distributed. Technology will change how and where medical intelligence will exist. It will be distributed in the cloud, within connected communities and in our hands in ecosystems linked to smartphones and sensors (IoMT or Internet of Medical Things). AI applied to different health problems will become as natural and relevant as we use today the common digital maps on our phones and cars to guide us.

Conclusion

Food is indeed the breakthrough drug of the 21st Century! Almost 2,500 years ago, Hippocrates said, "Let thy food be thy medicine and thy medicine be thy food" [11].

So, to potentialize the benefits and reduce the challenges of digital health, the combination of digital tools with better nutrition, healthcare strategies for children, and integrated health data management to enhance the delivery of healthcare for individuals will be key to changing the current trend we see. It is important to carefully navigate these challenges and address the associated concerns to fully leverage the potential benefits of AI and digitalization in healthcare while ensuring the well-being and safety of patients and healthcare professionals.

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The future of healthcare is in digitally reimagined experiences for patients and caregivers alike. Digital health offers increased choice and convenience for patients and improved outcomes for caregivers while reducing costs and workloads.

The challenge of Digital Health in the 21st Century will not be primarily technological, but above all human!

Conflict of Interest Statement

G. Rabello has received honoraria as speaker from Baxter, Abbott, CSL Vifor, Nestlé, and Laboratorios Cristalia. The writing of this article was supported by the Nestlé Nutrition Institute.

References

1 U.S. Food & Drug Administration. What is digital health?; 2020. Available from: https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health.
2 Polaris Market Research. Healthcare analytics market share, size, trends, industry analysis report, 2021–2028;2020. Available from: https://www.polarismarketresearch.com/industry-analysis/wearable-medical-devices-market.
3 Bayoumy K, Gaber M, Elshafeey A, Mhaimeed O, Dineen EH, Marvel FA, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. Nat Rev Cardiol. 2021 Aug;18(8):581–99.
4 Petracca F, Ciani O, Cucciniello M, Tarricone R. Harnessing digital health technologies during and after the COVID-19 pandemic: context matters. J Med Internet Res. 2020;22(12):e21815.
5 Keesara S, Jonas A, Schulman K. Covid-19 and health care's digital revolution. N Engl J Med. 2020 Jun 4;382(23):e82.
6 Rabello GM, Pêgo-Fernandes PM, Jatene FB. Are we preparing for the digital healthcare era? Sao Paulo Med J. 2022 Mar-Apr;140(2):161–2.
7 Negreiro M. The rise of digital health technologies during the pandemic. European Parliamentary Research Service. PE 690.548-April 2021. Available from: https://www.europarl.europa.eu/thinktank/en/document/EPRS_BRI(2021)690548.
8 World Economic Forum. This is the biggest challenge to our health; 2017. Available from: https://www.weforum.org/agenda/2017/12/healthcare-future-multiple-chronic-disease-ncd/?DAG=3&gclid=CjwKCAiA8OmdBhAgEiwAShr400_OIAE0WU-5FYzMQMChN39WccFdmiroaFEg-4NQ6R51wwOYnuxPhOBoChvwQAvD_BwE.
9 Bhutta ZA, Hauerslev M, Farmer M, Lewis-Watts L. COVID-19, children and non-communicable diseases: translating evidence into action. Arch Dis Child. 2021 Feb;106(2):141–2.
10 Salam RA, Padhani ZA, Das JK, Shaikh AY, Hoodbhoy Z, Jeelani SM, et al. Effects of lifestyle modification interventions to prevent and manage child and adolescent obesity: a systematic review and meta-analysis. Nutrients. 2020 Jul 24;12(8):2208.
11 Singh M. Pediatrics in 21st century and beyond. Indian J Pediatr. 2016;83:1420–5.

Szajewska H, Kolaček S (eds): The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions. 99th Nestlé Nutrition Institute Workshop, February 2023. Nestlé Nutr Inst Workshop Ser. Basel, Karger, 2024, vol 99, pp 139–145 (DOI: 10.1159/000534958)

Subject Index

Nestlé Nutrition Institute Workshop Series

Vol. 98 Global Trends in Nutrition and Health through the Life Course

Editor: Sumantra Ray
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Vol. 99 The Changing Landscape of Pediatric Nutrition: Latest Trends and Future Directions

Editors: Hania Szajewska, Sanja Kolaček

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ISBN 978–3–318–07335–5

This groundbreaking book encapsulates fresh insights from the 99th Nestlé Nutrition Institute Workshop in Riyadh, Saudi Arabia, in February 2023, where experts discussed the changes in the nutrition landscape brought about by the challenging times of the pandemia and globalization, including the future trajectories of child nutrition.

This book delves into the profound impact of early nutrition on lifelong health and explores the intricate mechanisms of nutrition programming and the important role of human milk. It addresses the critical interplay between nutrition and epigenetic modifications, how this shapes gene expression and long-term health outcomes and emphasizes the importance of the microbiome and its modulators such as HMOs and how they support the development of the immune system in early life.

Amidst the still unfolding longer-term impacts of the COVID-19 pandemic, the authors examine the bidirectional relationship between the virus and nutrition, highlighting strategies to mitigate disease severity through optimal nutrition interventions. Additionally, the book tackles the rising prevalence of food allergies, and discusses how the shift in guidelines on food allergy prevention supports the early introduction of allergens rather than avoidance as well as dietary patterns and current diets' roles in reducing the risk of certain non-communicable diseases.

The book heralds a new era in pediatric nutrition – one that embraces personalized nutrition interventions, the transformative potential of digital health, and the principles of sustainable nutrition to ensure health-promoting dietary practices. It also explores the burgeoning role of artificial intelligence in identifying new biomarkers and developing predictive models for pediatric health.

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