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

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Contents

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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Environmental cues during early developmental plasticity, particularly the "First 1000 Days of Life," induce lasting programming effects on later health, performance, and disease risks. Understanding underlying mechanisms is crucial to fully utilizing the preventive potential of programming effects, and to develop targeted and effective interventions. Proposed mechanisms include effects on growth, body structure and composition, epigenome, metabolome, hormones, and microbiome (Fig. 1).

Growth and development are key characteristics of childhood. Rapid weight gain during the first 2 years is associated with increased obesity and associated disorders at later ages [1]. Breastfed infants tend to have a lower body weight and body fat mass at age one year than those bottle-fed, and less overweight and obesity later. However, residual confounding is likely, with the association of socioeconomic status with both breastfeeding rates and duration, and with health-related behaviors, health, and obesity. Nonetheless, infant feeding and related weight gain modulate subsequent obesity risk, likely through substrate supply. We need a better understanding on how infant feeding affects growth and body composition, which substrates are major modulators, and which infants or subgroups are most susceptible to feeding effects on later obesity and related NCDs.

Epigenetic modifications may be the missing link between nutritional and metabolic exposures and subsequent alterations in gene expression inducing 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, such as DNA methylation (DNAm). Animal studies and human observational studies associated DNAm with body size, fatness, and disease risk [2]. Uncertainties remain regarding fluidity or persistence of DNAm over

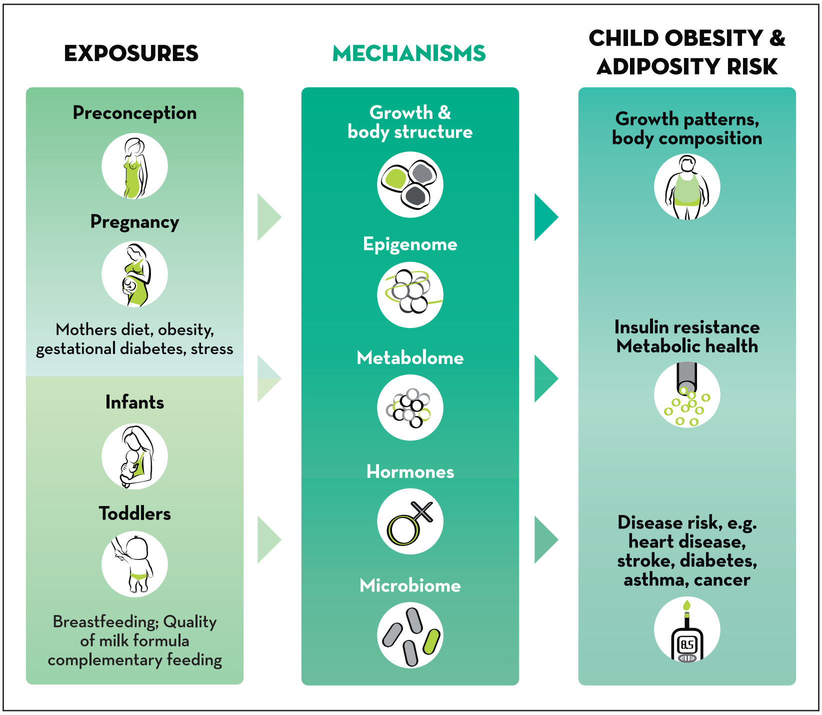

Fig. 1. Proposed mechanisms of early metabolic programming of later health and disease risk, linking nutritional exposures before and during pregnancy, and during early childhood, with later health outcomes. Adapted with permission from Child and Family Health Academy at Stiftung Kindergesundheit - Child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

time, functions and pathways altered by diet-imprinted genes, and causal roles of epigenetic effects on clinical endpoints.

Early nutrition affects metabolites in body fluids and tissues which modulate growth, tissue function, and health. Metabolomic profiling provides insights into the modulation of growth and body composition by amino acids and lipids. Findings support the Early Protein Hypothesis suggesting that high protein supply in infancy increases plasma and tissue amino acid concentrations, which stimulate secretion of the growth factors insulin-like growth factor-1 (IGF-1) and insulin, resulting in enhanced weight gain, body fat deposition, and obesity. In a large multicenter Childhood Obesity Project Trial funded by the European Commission, we found infant protein intake to markedly affect BMI (Fig. 2), obesity and body fatness until school age and early adolescence [3, 4]. Altered amino acid metabolism may trigger a large effect

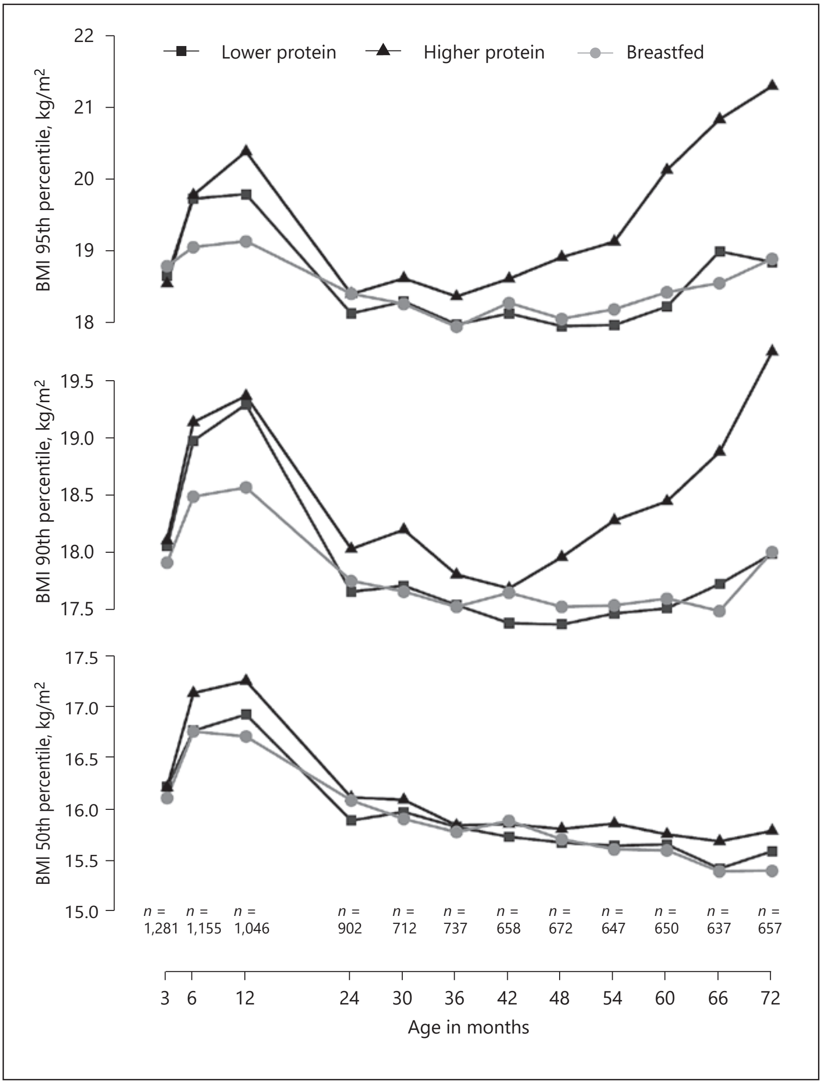

Fig. 2. Effect of infant feeding on BMI evolution from infancy to early school age. Higher protein supply with infant formula, compared to lower protein intakes, has a relatively modest effect on the mean BMI (mean BMI difference at the 50th percentile 0.29 kg/m^2), whereas there is a very large effect 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 [4].

on obesity. The relative roles of protein quantity and quality and the most sensitive time windows for interventions need further exploration. In this trial, protein stimulated insulin and IGF-1 secretion, the key mediators of infant growth that also activate the mammalian Target of Rapamycin. IGF-1 was the strongest predictor of BMI at age 1 year, and diet predicted IGF-1 much stronger than the genotype.

In a randomized crossover study in adults, higher protein supply markedly elevated plasma BCAA for at least 5 h, along with altered insulin, glucose, urea, and triglycerides [5]. Better understanding of individual differences could pave the way to more targeted and efficient precision prevention.

Exploring mechanisms of early nutrition programming is pivotal to establishing improved health promotion, with precision interventions in susceptible subgroups that can achieve greater efficacy, efficiency, and cost-benefit ratios. We need close collaboration of clinicians, basic scientists, and bioinformatics specialists to link clinical characterization with state-of-the-art biomarkers and large dataset evaluation utilizing machine learning and artificial intelligence methodologies. This should provide fundamental information on growth regulation, benefitting scientific understanding, opportunities for future research, promotion of public health, nutrition recommendations, and the development of improved food products.

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

Sanja Kolaček

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a cause of the human coronavirus disease 2019 (COVID-19) in December 2019, causing a pandemic that was officially announced on March 11, 2020. Soon after, 186 of 193 world countries adopted a lock-down policy, despite which, at the time of finalizing this manuscript (March 2023), there were almost 770 million confirmed cases reported by the World Health Organization, with a mortality rate of around 1%. Approximately 5% of the affected cases occurred below the age of 19 years, with most of them having mild disease and mortality below that reported for adults. Yet, the COVID-19 pandemic could negatively affect children in a wide array of indirect modes, primarily through implications on their nutritional status.

On one end of the spectrum, undernutrition and nutritional deficiencies are expected to increase due to an increase in poverty, unemployment, and food insecurity, which have been detected in less developed countries [1]. A recently published study from Nepal compared nutrition status before and during the pandemic, and obtained particularly grave results with respect to significant deterioration in the prevalence of stunting, underweight, and symptoms of micronutrient deficiencies such as Bitot's spots, depigmentation, dry cornea, and bleeding gums [2]. In addition, SARS-CoV-2 directly affects the gut resulting in a decreased intake and increased nutritional requirements, further increasing the risk of undernutrition. Finally, several studies have already revealed data on the increased risk of acquiring SARS-CoV-2 and developing a more severe presentation of COVID-19 in malnourished children.

In more affluent societies, during the COVID-19 pandemic and the lockdown, social distancing, a decrease in physical activities, an increase in screening time, and negative changes in eating habits and food intake have been detected in many studies comparing periods before and during the COVID-19 pandemic. Eight of ten studies included in the recently published systematic review reported that changed patterns of food

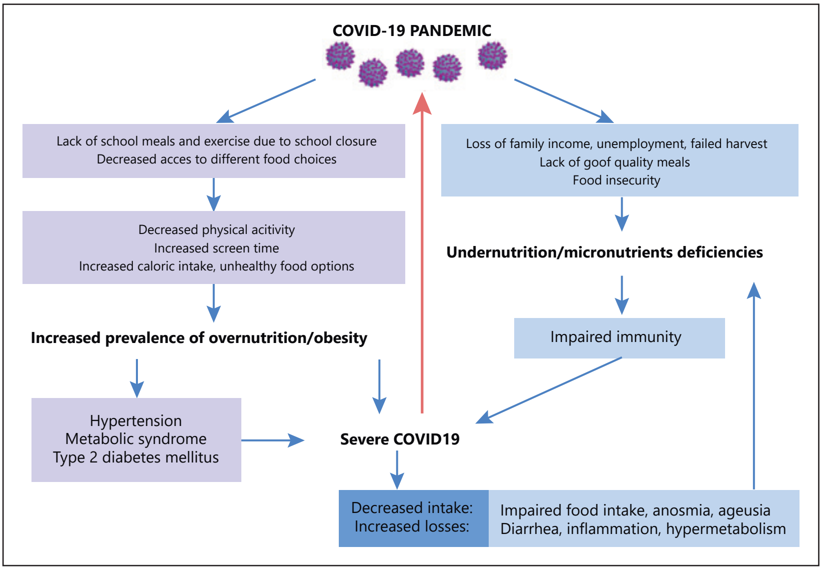

Fig. 1. A bidirectional relationship between the COVID-19 pandemic and nutrition status in children.

intake, increased screening time, and decreased physical activity resulted in a significant increase in body weight and/or body fat [3]. Furthermore, complications, such as increased blood pressure, insulin resistance, and newly diagnosed diabetes mellitus type 2, were already detected in children during the pandemic [4]. Similarly to undernourished children, recently published data do relate obesity to the worse clinical outcome of COVID-19 in children, closing the bidirectional vicious circle of causes and consequences (Fig. 1).

With respect to treatment, the European Society for Clinical Nutrition and Metabolism guidelines for the nutritional management of individuals with SARS-CoV-2 infection recommend stepwise nutritional interventions depending on the severity of the disease, spanning from dietetic advice with or without oral nutritional supplements, enteral nutrition in patients with still insufficient oral intake, up to parenteral nutrition reserved for patients with severely impaired intestinal function [5]. This is not different from the "pyramid of nutrition interventions" recommended to pediatric patients in general, which can be applied also to children infected with the SARS-CoV-2 virus. In addition, public health measures such as age-appropriate physical activity, restriction of screening time, and a balanced diet should be applied to all children. The prudent attitude regarding supplementation with micronutrients is to continue with the public health measures to prevent micronutrient deficiencies and to diagnose and treat them early, particularly in malnourished children. In nondeficient children, there is no evidence that the supplementation can improve the clinical outcome of COVID-19.

In conclusion, the COVID-19 pandemic fosters the development of undernutrition and obesity in children, and both, obesity and undernutrition through different pathogenic mechanisms, increase the risk of more severe clinical presentation of COVID-19, closing a vicious circle of causes and consequences (Fig. 1).

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

Aristea Binia

Human milk is the optimal food for infants. Exclusive breastfeeding is recommended for the first 6 months of life and breastfeeding continuation is recommended until the first 2 years of life. Health benefits for both child and mother have been reported with optimal growth, protection against infections, and reduction of risk for chronic metabolic diseases and cancer, respectively [1]. Numerous studies have been published reporting compositional data of human milk with an emphasis on macronutrients but also vitamins and minerals. Most of these studies focused on understanding the differences in lactation. Temporal changes during the day (circadian, ultradian, or diurnal) or during a single feeding (foremilk vs. hindmilk) are less studied. Overall, these differences in human milk are not well understood although it is believed that they reflect maternal health and nutritional status, and they are adapted to the needs of the growing child. Indeed, the mother, milk, and infant triad forms a dynamic relationship well adapted to preserve the health benefits for both mother and infant. In reality, a limited number of studies have considered to study or model associations along the tripartite relationship while producing results that are sometimes challenging to interpret [2].

Beyond the maternal and infant factors interplay with composition, human milk is also a dynamic biofluid with potentially multiple molecules, groups of bioactives, or molecules organized into complex structures delivered by the mammary gland to efficiently be delivered to the infant. Current literature offers us consistent reports on single components' composition. Deeper characterization of less abundant molecules combined and tested for correlations with more common and better-described nutrients or bioactives would be the next step to complement compositional data. Studying the effects of a group of molecules via either supervised and hypothesis-led but also unsupervised data approaches, would follow to move away from single molecules and understand the association or effects of milk profiles on infant physiology.

The first scientific reports using either maternal and/or infant metadata show that milk composition can be influenced or presumably adapted to a specific health or dietary exposure [3]. The presence of maternal and infant infections appears to alter the number of immune cells and the concentration of bioactive proteins in milk. Maternal dietary intake and food abundance impact the concentrations of certain macronutrients and micronutrients. Maternal BMI and metabolic status have also been reported to affect milk composition at least for fat and hormonal concentration. Little is understood about how these factors are associated or causing a change in human milk composition and even less is known about the physiological importance for the infant and potentially maternal health.

All these results highlight potentially only pieces of the puzzle composing the interplay of the mother, milk, and infant triad. Meta-analyses or data mining approaches to combine all the available data to synthesize this tripartite association would be limited by apparent heterogeneity among studies. A better approach would be to form research questions, leveraging on the concurrent advances in analytical methodologies and available robust data, including standardized and well-phenotyped outcomes from both mother and child and environmental factors to produce conclusive evidence. Follow-up clinical intervention studies can provide answers for applied clinical and nutritional recommendations for both lactating mother and growing child.

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Can Food Allergies in Children Be Prevented?

Hania Szajewska

Common allergenic foods include cow milk, eggs, wheat, soy, peanuts, tree nuts, and seafood. Assessing the exact prevalence of food allergies is challenging and varies with the diagnostic method and studied population. Self-reported rates are usually higher than those confirmed by rigorous methods. Higher rates of food allergies are typically found in high-income countries, but rising rates are also being observed in low- to middle-income countries, particularly in urban areas.

Factors that contribute to food allergy development include genetics, but this alone does not explain the increasing trend of food allergies. Therefore, several theories have been proposed to explain the rise, including the hygiene hypothesis (reduced exposure to microbes in early life leading to impaired immunoregulation), the biodiversity hypothesis (biodiversity loss causing immune dysfunction), the vitamin D hypothesis (vitamin D affecting immunologic tolerance), the short-chain fatty acid hypothesis (bacterial metabolites contributing to food allergy protection), and the dual-allergen exposure hypothesis (route of exposure to allergens affecting the development of tolerance). Mechanisms may vary in different populations.

Food allergies can significantly impact individuals and their families, making prevention crucial. A recent systematic review analyzed 28 food allergy prevention documents published up until 2019 [1]. Older guidelines recommended avoiding common allergens during pregnancy and breastfeeding, and the delayed introduction of allergenic foods after the age of 1–3 years, while more recent guidelines recommended early introduction of allergenic foods, such as peanuts and eggs. Table 1 summarizes the guidelines published from 2020 to 2022.

Current recommendations on early peanut introduction 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). It remains unclear whether these findings can be extrapolated to other populations and nonrisk groups. However, recent data support the conclusion that early peanut introduction is a safe and effective way to prevent peanut allergies and should not be limited to high-risk infants [2].

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

	ASCIA 2020 [7]	AAAAI/ACAAI/CSACI 2021 [8]	EAACI 2021 [9]	CSACI/CPS 2022 [10]
Maternal diet (pregnancy/lactation)	No			
Breastfeeding	Yes (even if it does not reduce the risk of FA)			
Hydrolyzed formula	No	No	No *for* or *against*	No
CMF	If BF is not possible, a standard CMF can be given	No clear statement	1st wk of life: no ≥2nd wk of life: no *for* or *against*	If introduced, regular ingestion (10 mL daily)
Peanuts	Around 6 mo, but not before 4 mo	Around 6 mo, but not before 4 mo	In populations with a high prevalence of peanut allergy, from 4 to 6 mo	• High-risk: at about 6 mo (not before 4 mo) • Low-risk: at around 6 mo of age • Regular ongoing ingestion
Eggs	As above, cooked (not raw) egg	Around 6 mo of life, but not before 4 mo	Well-cooked hen's egg (not raw or uncooked pasteurized egg), from 4 to 6 mo	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; 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.

Data on guideline adoption are limited, with significant uptake by parents introducing peanuts early in some settings (Australia) [3], but not others (United States) [4] (Table 2). Further data on guideline uptake for peanuts and other allergens in different populations and settings are needed to improve outcomes. Limited evidence exists on the impact of these new guidelines on peanut allergy prevalence. However, in settings with high guideline uptake, such as Australia [3], recent evidence suggests that earlier introduction of peanuts may not lower the risk of peanut allergy at the population level [5]. Further research is needed to clarify this finding and identify additional factors necessary to minimize food allergy risk. However, given the potential for benefit and low risk of harm, the results of this study should not discourage clinicians from following current consensus guidance that recommends early peanut introduction for infants.

In contrast to peanut allergy, cow milk protein allergy (CMPA) usually resolves with age. The early (in the first days or weeks of life) introduction of cow's milk protein (cow milk-based formula, CMF) in infants

Table 2. Adoption of updated allergy prevention guidelines by caregivers

	Introduction into infant's diet	Age 7 mo	Age 12 mo
US (2022) [5] *N* = 3,062	Egg	16%	59%
	Peanut	17%	66%
Australia (2020) [4] *N* = 1,940	Egg	No data	96%
	Peanut	No data	86%

as a means of preventing CMPA is a topic of ongoing discussion. However, clear evidence supporting this approach is currently lacking, and recommendations are inconsistent. Any new data on the subject may have limited conclusions due to a lack of randomization and/or confirmed CMPA diagnoses using strict criteria. Further research is needed to determine the most effective approach, despite the trend toward early introduction of CMF to prevent CMPA.

Many questions about specific food allergens remain unanswered. Further research should focus on a wider range of populations in terms of allergy risk and/or ethnicity. The optimal (minimal) amount/dosage and the importance of regular versus irregular ingestion of potential food allergens need to be clarified. In addition to peanut, egg and cow's milk proteins, which have been studied but more data are still needed, other food allergens need to be evaluated.

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Diet and Microbiome: The Link to Allergy

Gary Wong, Yuhan Xing

Over the past three 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 disorder are the result 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]. The prevalence of allergic disorders has increased significantly over the past century in parallel with industrialization and urbanization. Recent hospital data from Australia and Hong Kong 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. Therefore, it is of paramount importance to understand the cause of allergies to develop primary preventive strategies (Fig. 1). 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. Such interaction would lead to tolerance rather than an excessive uncontrolled immune response to innocuous environmental allergens such as house dust mites, pollens, or different food proteins. The understanding of the underlying mechanisms of such interactions will lead to the development of effective primary preventive strategies against the development of allergies.

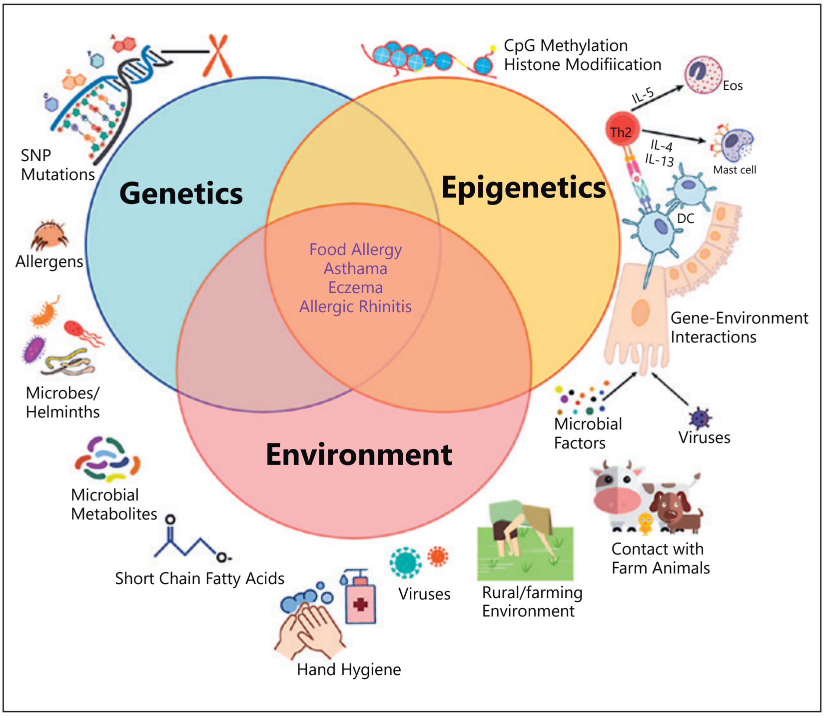

Fig. 1. Interactions between genetics, environmental factors, microbiome, and the manifestations of allergies.

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

Jorg Hager, Roko Plestina, Giles Major

Definitions of personalized medicine converge on the principle of greater characterization of an individual or group for better disease prevention and health management. This definition reflects the evolution of medical testing from diagnosis (assignment to a disease category) to risk assessment and prediction of response to various therapies (prognosis). Levels of personalization vary from "targeting" or "stratification," by geography or age, to "precision" design of individualized treatment.

Application of these principles to nutrition requires a relevant value proposition: that data provided can be interpreted to make recommendations that will improve health if followed. An effective offer should optimize the balance between the burden of data provision and the benefit of its interpretation. Frequent monitoring of nutrient levels is invasive so prediction approaches can add value.

Identification of monogenic disorders such as phenylketonuria provides an extreme example of a predicted response to nutrient intake. Advances in genome sequencing allow the formation of polygenic risk scores (PRS) to guide intake. Vitamin B12 levels vary widely; analysis of data from the National Health and Nutrition Examination Survey showed that more than one in four adults had suboptimal blood concentrations despite intake in line with recommendations. Effects of individual single-nucleotide polymorphisms within a PRS for B12 are additive, making the approach semiquantitative [1]. A similar approach can be applied to vitamin D levels, in combination with skin pigmentation density, to stratify supplementation recommendations.

Beyond genomics, there is increasing interest in gut metagenomics – analysis of the genetic material contained by the microbiome, the microbial ecosystem resident in the intestine. Several groups have reported that microbiome analysis can contribute to improved prediction of glycemic response to various foods [2]. It is less clear if microbiome differences cause variation or if they simply reflect carbohydrate malabsorption. Ongoing trials will determine whether the application of updated prediction models can inform and modulate behavior sufficiently to improve health outcomes.

The capability of the microbiome to digest glycans – oligosaccharides and fibers – is determined by the presence of carbohydrate-active enzymes (CAZymes). Individual CAZymes are specific to certain glycan bonds. Variation in CAZyme profiles can be a target for personalization through matching dietary choices with digestion profiles in order to optimize the product of bioactive metabolites such as short-chain fatty acids.

CAZyme profiles develop from infancy, through childhood, to adulthood [3]. This functional development is one axis of a general maturation of the microbiome in the first 3 years of life. Consolidation of multiple microbiome features into one "maturity" parameter can support understanding of associations with health: under-maturation is associated with slower growth, while early over-maturation has been associated with later increased incidence of immune-mediated disorders. While measurement of microbiome trajectory may not yet be sufficiently precise to guide individuals' nutrition, early observations that human milk oligosaccharides (HMOs) may direct microbiome maturation of formula-fed infants toward that of breastfed infants raise the possibility of adapting childhood glycan exposure to stages of CAZyme development.

Microbiome responses to dietary development were recently highlighted by Vatanen et al., in the identification of a distinct Bifidobacterial clade that thrives during weaning [4]. This clade's rare ability to digest both HMOs and plant fibers highlights the potential to target dietary and probiotic support across early life.

Effective personalization must present recommendations in a comprehensible, accessible format. Digital tools should link "back-end" database interpretation to "front-end" platforms that allow users to express their personal needs. The Crohn's & Colitis Foundation has recently launched an application to design recipes according to both dietary needs and individual taste. Informed choice must remain at the heart of personalized nutrition to ensure acceptance of the data provision required.

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Diet-Microbiome Interactions in Pediatric Gastrointestinal Disease

Konstantinos Gerasimidis, Bryn Short

The human gut is home to a complex microbiome which plays an important role in the maintenance of health and disease onset [1]. In certain diseases, the composition of the microbiome shifts from the "normal" profile, that we see in healthy people, to a state commonly referred to us as microbial dysbiosis. Dysbiosis has been implicated in the etiology of non-communicable diseases, including gastrointestinal diseases in children [2]. Diet is a major modifier of gut microbiome composition and function. In the causal pathway between microbiome causing disease, diet can have several roles (Fig. 1). Diet can simply confound the association between microbiome and the development of gastrointestinal disease; microbiome may modify the effect diet has on disease development and even more importantly, microbiome may comprise a target for dietary manipulation in order to improve disease outcomes or to enhance response to concomitant drug therapy. There are four gastrointestinal conditions, namely inflammatory bowel disease, celiac disease, intestinal failure, and necrotizing enterocolitis where the interactions between gut microbiome with diet have been studied the most in the past decade [2–6]. In each of these four conditions, the gut

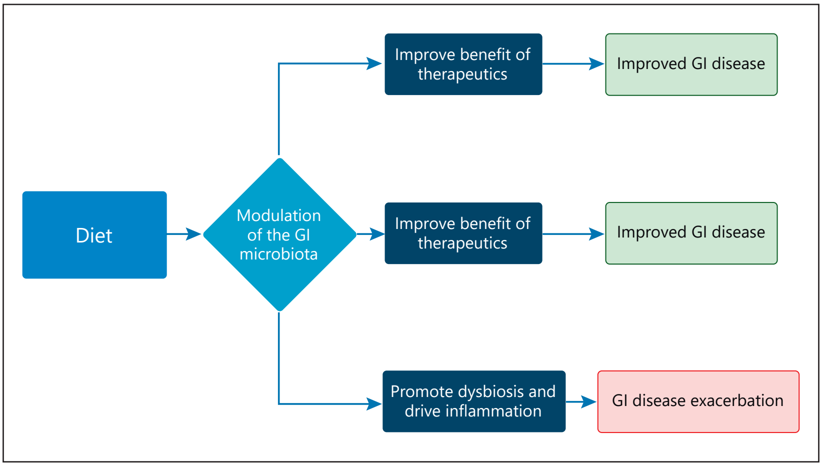

Fig. 1. Schematic displaying the complex interplay between diet and the human microbiome in the onset and management of gastrointestinal disease.

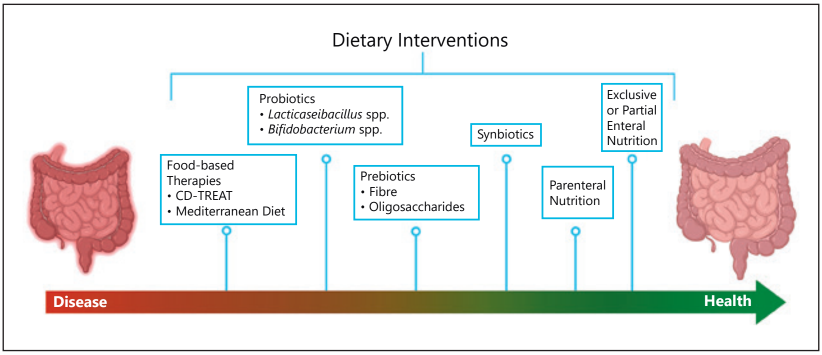

Fig. 2. Microbiota modifying dietary interventions with relevance to the management of gastrointestinal diseases and their potential effect on the gut microbiota.

microbiome is significantly altered with patients with celiac disease presenting the least, and patients with intestinal failure the most dysbiotic microbiome composition and function. Nonetheless, it is not yet clear whether the shifts observed are primarily involved in the etiology of these conditions or whether there are secondary effects of disease onset. There are various microbiome-modifying dietary treatments and supplements (Fig. 2) that can influence the microbiome composition and/or function and by extension the disease outcomes in those with gastrointestinal diseases. 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.

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

Wejdan Alabdulkarim

Today's consumers are better informed about the impact of food choices on their health, resulting in a growing desire to eat healthier. The media and social platforms have played a significant role in increasing awareness of diet, from nutrition courses in schools to media, and social platforms promoting healthy eating. There are various reasons for this, but the advent of the Internet is a big one. Marquis and Dubeau conducted a study examining the capacity of the Internet to address nutrition-related issues. The authors retained a survey from the Dietitians of Canada Website, collecting 870 questionnaires indicating the frequency with which participants obtained healthy eating information and how confident they were in the sources. In the past several decades, North Americans have become increasingly interested in purchasing diet and nutrition-based books and locating information online [1]. The Internet can offer users a good way to access content for free through blogs, YouTube, magazines, websites, and academic literature.

Dietary Patterns

Food preferences and eating routines are examples of behavior. Even though the language used in the field of nutrition has not been standardized, dietary patterns may refer to a pattern of eating behaviors. Indeed, eating habits have been connected to consequences for the environment, culture, and society as well as health. Dietary patterns that include foods and drinks associated with better health and a decreased risk of acquiring chronic illnesses are often referred to as having a high-quality diet.

Examples of Healthy Dietary Patterns

According to the World Health Organization (WHO), a nutritious diet aids in preventing noncommunicable diseases, such as diabetes, heart disease, stroke, and cancer, as well as malnutrition in all its manifestations.

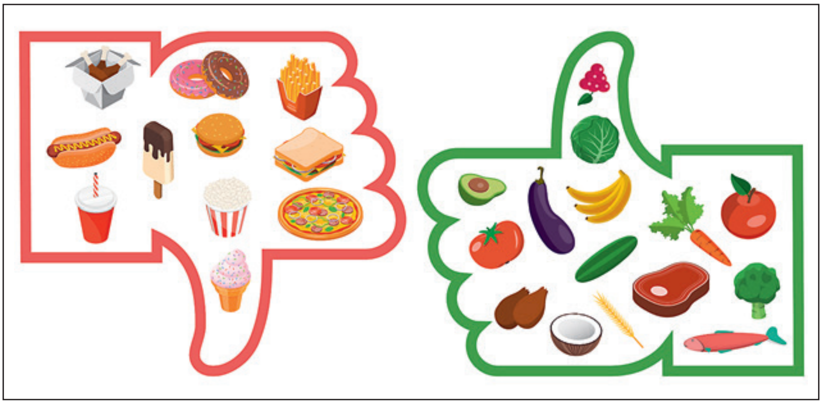

Fig. 1. Healthy versus unhealthy food choices.

Avoiding weight gain means fat should not go over 30% of one's total intake of energy, while one should consume under 10% of saturated fats. People should generally intake less than 1% of trans fats, with an emphasis on going toward unsaturated fats, rather than trans fats. Consumers should also be wary of consuming trans fats that are industrially (commercially) produced. Consumers should limit their free sugar intake to under 10% of total intake to be healthy, and further reduce to 5% of total intake. Healthy diets also include legumes, vegetables, and fruit, including whole grains, nuts, brown rice, wheat, beans, and lentils. People should consume a minimum of 400 g of vegetables and fruit per day [2].

Examples of Unhealthy Dietary Patterns

Rakhra et al. discuss the Western diet, which would be a typical contemporary example of a bad diet. According to the WHO, 650 million persons were classified as obese in 2016, while 1.9 billion adults were overweight. In 1999, over 20 years ago, the prevalence of obesity was already 30%. The Western diet is one of the major contributors to this epidemic. Much of this can be attributed to the consumption of high-fat and high-sugar foods. A daily calorie intake of 1,200–1,500 for women and 1,500–1,800 for males may result in healthy weight reduction. The updated USDA and U.S. Departments of Health and Human Services health plan encourage a diet that is nutrient-rich, while promoting the elimination of sugars, sodium, trans, and saturated fats. An unhealthy diet is when saturated fats comprise more than 10% of one's diet. Men should eat no more than nine teaspoons of sugar per day, while women should limit their intake to no more than six teaspoons [3]. Thus, an unhealthy diet would be one characterized by high sugar and fat consumption and not eating enough vegetables and fruit. A concrete example of someone consuming an unhealthy diet would be eating frozen dinners everyday instead of cooking fresh food, ordering takeout frequently that has high amounts of trans fat or eating processed food.

Figure 1 illustrates some healthy versus unhealthy food choices.

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Children's Diets and Their Sustainability in a Changing World

Jose M. Saavedra

Over the last 200 years, the world population has seen gradual decreases in child mortality and undernutrition, as well as gains in height reflective of increasing food availability and nutrition.

In the last 50 years, this progress dramatically accelerated, leading to major reductions in child mortality, hunger, wasting, and stunting, despite the exponential growth of the world population. However, the last 50 years also saw a gradual and accelerated increase in BMI worldwide, first evident in high-income countries and now a globally ubiquitous problem [1, 2].

Estimates show that after a relatively flat global food energy supply for many decades, in the 1960s, there was an inflection point, giving way to a significant and steady increase in food supply that continues today. In the last 5 decades, overall food production increased, outpacing population growth. Between 1960 and today, global cereal production grew by more than 250%, global average daily energy supply increased by more than 700 calories per capita, and global GDP per capita more than tripled. Food systems further developed ways to increase agricultural yield, storage, and processing of foods. And changes in transportation, commerce, and globalization, primarily driven by technological advances, drastically increased food availability. The time cost of food decreased such that – starting in high-income countries – the 1960s marked a "flipping point." Food energy supply, energy intake, and population weight all increased. Food systems also fostered the consumption of energy-dense and animal protein sources, to the detriment of other foods, especially fruits and vegetables. Thus, starting in the 1960s, the world is undergoing a global dietary transition that drives the epidemic of overweight and obesity, even while undernutrition persists. Almost 50% of the world's population eats too many or too few calories [1–3].

This dietary transition is also unequal, having started later but at an accelerated pace in lower-income countries. Today's dietary excesses (energy, sugar, sodium, animal proteins) with deficits (fruits, vegetables, micronutrients) are specially marked and impactful in lower-income countries. Therefore today, most children with wasting, stunting, and micronutrient deficiencies, as well as overweight and obesity, live in lower-income countries or in disadvantaged communities within a country. All forms of malnutrition can coexist at a country, community, and household level, even in the same child.

Obesity prevalence will very soon overtake undernutrition as the most common form of malnutrition, with serious long-term consequences. The fastest-growing conditions related to global death and disability are high body mass index, high fasting plasma glucose, high cholesterol, and elevated blood pressure, driving the epidemic of noncommunicable diseases. Of greater concern, most of the diet-related deficits and excesses leading to death and disability are already present in the diets of infants and young children [1, 2].

Progress has come at a price. The food systems that have allowed increasing survival and overcoming undernutrition have fueled a dietary transition that now hinders human health. Moreover, food systems also contribute to an even larger threat: the health of our planet. Food production accounts for about 70% of freshwater utilization, 80% of ocean water pollution, and 26% of all greenhouse gasses that drive climate change. Animal food sources disproportionally utilize land and resources and produce up to 50 times more greenhouse gasses than plant-based foods.

Thus, food systems will need to change to decrease and protect resources. And diets will need to improve in quality, including a shift to more plant-based and less animal food sources, making them both healthy and environmentally sound. Correcting course will require reorienting and collectively focusing our efforts on social, economic, technological, and educational changes that simultaneously promote adequate nutrition, human health, and the health of the planet [3–5].

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Human Milk Oligosaccharides: Impact on Infant Gut Microbiome and Health

Martin Frederik Laursen

Breastfeeding provides the infant with protection against infectious diseases and it is inversely related to various immune-related diseases, obesity and type 2 diabetes [1]. However, the mechanisms behind these links 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 that may contribute to these protective effects. In addition, despite being nonnutritive, the third most abundant solid fraction of breast milk is comprised of a variety of human milk oligosaccharides (HMOs), which are small indigestible oligosaccharides. HMOs may directly enhance the gastrointestinal barrier function by inducing mucin and antimicrobial peptide secretion by goblet cells. They may provide direct protection against invading viral or bacterial pathogens by coating them and acting as decoys for glycopeptides located on the gut epithelium. HMOs may also directly suppress inflammatory signaling in epithelial and immune cells and affect innate and adaptive immunity [2]. Besides these direct effects, HMOs also stimulate the growth of beneficial bacteria in the gastrointestinal tract by promoting the establishment of a gut microbial community rich in specialized *Bifidobacterium* species, capable of efficiently consuming HMOs and, in turn, produce immune-regulatory metabolites [3, 4]. These species include the major colonizers of the infant gut *Bifidobacterium longum* subsp. *longum, Bifidobacterium longum* subsp. *infantis*, *Bifidobacterium breve* and *Bifidobacterium bifidum*, which produce metabolites such as acetate and lactate from HMO catabolism. However, these taxa are concurrently able to convert the aromatic amino acids, tryptophan, phenylalanine and tyrosine contained in breast milk, into the aromatic lactic acids, indole lactic acid (ILA), phenyl lactic acid, and hydroxyphenyl lactic acid. Primary degradants from HMO metabolism, in particular acetate, can support barrier function and inhibit enteropathogenic infection [5]. The aromatic lactic acids, in particular ILA, decrease inflammatory response in both epithelial cells and innate immune cells, and downregulate T-cell activity in allergy and autoimmune-associated Th2 and Th17 subsets [3, 4]. Thus, HMO-promoted *Bifidobacterium*-produced molecules such as acetate and ILA may contribute to the protection of the infant against infectious and various immune-related diseases. Importantly, early life perturbations of the gut microbiome, such as birth by caesarean section, preterm birth, and antibiotics, have strong negative effects on the *Bifidobacterium* species producing these key metabolites and can potentially mitigate the beneficial effects of breastfeeding. The use of this knowledge to support breastfeeding, but also develop *Bifidobacterium*-based probiotics and/or HMO-based formula milk holds 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.

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Multiomics, Artificial Intelligence, and Prematurity

Josef Neu

Novel 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.

Previous environmental exposures can modulate the expression of our inherent genomic template resulting in different phenotypes. 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. We will use preterm birth prediction, improved characterization of neonatal intestinal injuries that are currently being placed under the umbrella diagnosis of necrotizing enterocolitis (NEC), prediction of retinopathy of prematurity (ROP) and precision nutrition as examples.

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. Progress is being made in this area using various AI algorithms [1].

To achieve a better understanding of causality and mechanisms, an integration of various omic technologies will likely yield better information than the association of a disease to a single omic evaluation. Such an analysis is being applied to inflammatory bowel disease (IBD) where the interaction between these different omic is termed the “interactome” to build a comprehensive molecular map of the mechanistic interactions that lead to the pathogenesis of IBD [2].

It is likely that unsupervised machine learning techniques will be highly useful to reexamine and reclassify acquired neonatal intestinal pathologies that we are currently calling “NEC” into unique clusters of injury in a manner analogous to the study by Matsushita et al. [3] described above. Once these clusters are delineated, they can individually be better characterized on a molecular level using integration of multiomic techniques. These can then be utilized for predictive and diagnostic biomarker discovery, which in turn can lead to prevention and treatment.

Investigations are underway to develop a predictive tool for ROP using AI [4]. 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 a very important advance in this field.

Another area where AI and multiomics are likely to be highly beneficial and preterm infants involves precision nutrition [5]. Current guideline-based strategies are based on statistics focusing on the mean of the population, but preterm infants are a highly heterogenous group that require precision-based approaches for both safety and subsequent health.

In summary, 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 infants with specialized needs and who may be on a path toward either early or late onset pathologies. With such recognition, clinicians can intervene early to prevent these problems from occurring. Similarly, we are beginning to make significant strides in precision nutrition. The future is very exciting, but we will need to collaborate in teams that include clinicians, basic scientists, engineers, bioinformaticians mathematicians, and other highly skilled individuals.

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Nutrition and Early Life Immune Health

Caroline E. Childs, Philip C. Calder

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. Modifying the gut microbiome, through diet or increased consumption of probiotics or prebiotics, may also influence host immune defense in early life either through improved barrier function or through improved innate and acquired immunity.

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, from the diet, and by exposure to antigens of different kinds including from microbes. 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 pattern of environmental exposures an infant has before, during, and after birth is likely to significantly influence the development of the gut microbiome and the immune system, potentially setting the trajectory for immune health and disease throughout the life course. Breast milk particularly contains many immune active and immune maturing factors as well as prebiotics and microbes to promote infant gut colonization. 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 [1]. Recent research also highlights that within the maternal vaginal microbiome, specific microbial species and their metabolic processes are linked to infant allergic outcomes [2].

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. Randomized controlled trials have identified that probiotic interventions provided during pregnancy and/or lactation could reduce the risk of allergic disease in infants, with the strongest effects observed in studies which used a mixture of probiotic strains, and where eczema was assessed before 2 years of age [3]. 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 [4]. Meta-analysis of trials investigating the effects of n-3 fatty acids on the risk of asthma and wheezing highlights the factors that influence outcomes observed, with significant effects more likely to be observed in studies providing high-dose n-3 supplementation throughout pregnancy and lactation within European populations [5]. 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.

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The Benefits and Challenges of Digital Health

Guilherme Rabello

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 one very important 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 on a large quantity of data, and 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.

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 & Drug Administration [1])

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 [2, 3].

In 2017, at the World Economic Forum event, a statement was made "that noncommunicable diseases (NCDs) were becoming the greatest challenge to global health. NCDs represent more than half the global burden of disease." 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.

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 is expected to revolutionize the practice of pediatrics [4, 5].

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" [5].

So, to potentialize the benefits and reduce the challenges of digital health, the combination of digital tools (like AI and digitalization) with better nutrition, healthcare strategies for children, and integrated health data management to enhance the delivery of healthcare for the individuals will be key to changing the current trend we see.

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.

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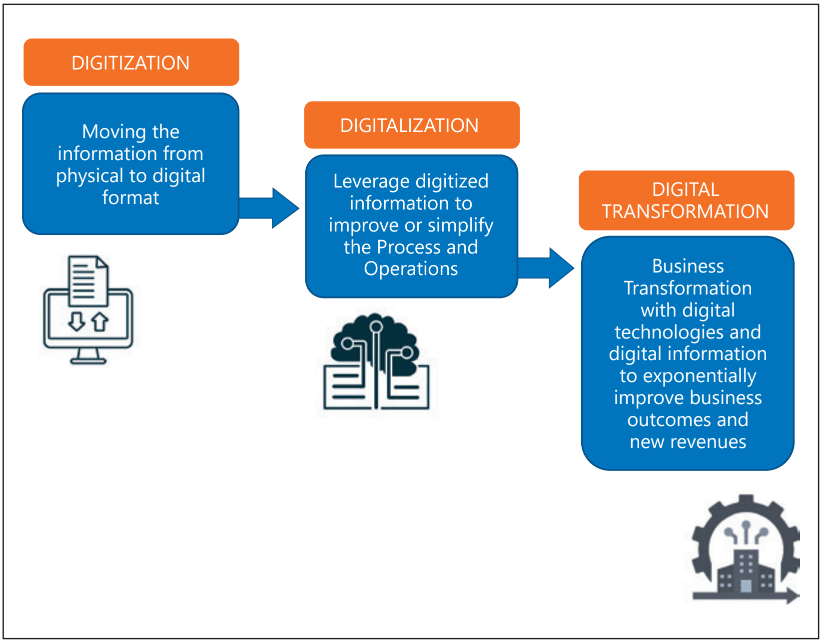

Fig. 1. Digital transformation journey – three stages.

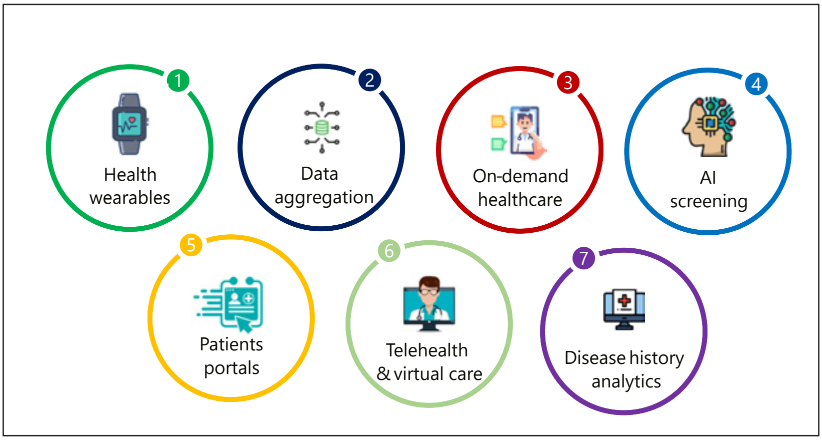

Fig. 2. Digital health tools.

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