Global Landscape of Malnutrition in Infants and Young Children

Lynnette M. Neufeld, Ty Beal, Leila M. Larson, and Françoise D. Cattaneo

Malnutrition during the first years of life has immediate adverse health consequences and impairs long-term health and capacities [1]. Children born small and those who become undernourished in early life are at higher risk of dying and are more susceptible to illness. Poor linear growth – stunting is associated with several physical and cognitive consequences and affects over 150 million children worldwide, one-third of whom live in India. Over 50 million children are wasted, half of whom live in South Asia, yet 5.4 million of the world’s 38.3 million overweight or obese children also live in South Asia. There is growing evidence that overweight in early life may be associated with the risk of noncommunicable diseases later in life.

The global prevalence of stunting fell from 32.6% in 2000 to 22.2% in 2017, with substantial variability in that reduction by region over the same period (Asia: 38.1–23.2%; Africa: 38.3–30.3%; Latin America: 15.9–9.6%) and dramatic progress in a few countries, for example, Nepal (57.1–36.0%) and Lesotho (52.7–33.4%) [2]. The prevalence of overweight in children varies substantially by region, as do the trends in prevalence from 2000 to 2017, which increased globally. The greatest rate of increase was Eastern Europe and Central Asia (8.2–14.8%) and only West and Central Africa saw a decline from 4.3 to 3.0%. If current trends continue, 70 million children will be overweight or obese by 2025. While these global, regional, and national statistics are critical for tracking progress and to inform policy and program priorities, specific actions to address them should be informed by more disaggregated data to understand which populations are most affected and the causes. For example, in India, the prevalence of stunting when disaggregated by district ranges from 12.4 to 65.1% [3]. Analyses from India, Indonesia, and Vietnam suggest that the determinants of stunting vary by geography within countries.

This variability should not be surprising given that all forms of undernutrition in early life have a complex etiology including factors at the individual, household, and societal levels. A conceptual framework of
stunting that builds on those developed previously by UNICEF and more recent evidence on determinants of healthy growth is shown in Figure 1. Returning to the India example, factors that explain the diversity in prevalence include geography (higher in the north and center), household-level factors (assets, household size), maternal factors (care during pregnancy, body mass index, age at marriage, education), as well as child factors (adequacy of the diet) [3]. All factors explained 71% of the variance in stunting prevalence, meaning that 29% remains unexplained by the included factors. Exploring additional determinants such as those
articulated in Figure 1 could provide further insights into stunting causation and its diversity within and among countries.

For decades the prevalence of anemia has been used as the sole indicator of micronutrient malnutrition in global tracking. Yet anemia, like stunting, has a complex etiology and numerous nonnutritional causes. Unfortunately, other indicators of micronutrient status are rarely collected at the national level. There is an urgent need for rigorous data collection that is nationally and subnationally representative, regularly collected, and standardized across countries so that policy and programs can be tailored to effectively improve all forms of malnutrition.

References

The first two years of life are a critical period to promote proper nutrition and dietary behaviors for optimal growth and development. Yet, almost 700 million children worldwide are suffering from malnutrition [1]. While undernutrition remains a significant problem, there continues to be an increase in the number of children who are becoming overweight as we undergo the nutrition transition. This transition is causing a shift in both dietary intake and physical activity that can impact childhood growth and development. Thus, there is a need to identify recommendations and interventions that will adequately prevent both the under- and overnourishment of children starting in infancy.

Exclusive breastfeeding is recommended until 6 months with the addition of safe, nutritionally adequate complementary foods. Caregiver adherence to international guidelines for feeding infants and toddlers varies depending on the setting, access to information and quality foods, and cultural beliefs [2]. The World Health Organization (WHO) infant and young child feeding (IYCF) indicators allow for the tracking and progress of these IYCF practices both within and across countries. Table 1 employs these indicators to assess the changes India has seen in their breastfeeding and complementary feeding patterns.

In the last 10 years, India has seen significant changes in their breastfeeding and complementary feeding patterns. These changes are evident in Table 1, which compares data from NFHS-4 from 2015 to 2016 to data from NFHS-3 from 2005 to 2006 [3, 4]. Breastfeeding initiation has increased by almost 20%, increasing the risk of longer exclusive breastfeeding duration and decreasing the odds of infant mortality. Additionally, exclusive breastfeeding improved by almost 10%. Children aged 6–8 months receiving solid or semisolid food and breast milk decreased by 10% [3, 4]. This suggests the need for more effective complementary feeding programs and policies along with breast milk promotion.

Caregiver feeding style also plays an important role in what foods and drinks are offered and whether young children accept those foods.
Feeding guidelines often include what is called “responsive feeding,” which is the importance of caregiver attention to child cues of hunger and satiety. A lack of responsive feeding has been shown to be associated with overnutrition, reduced odds of breastfeeding, and a higher risk of inappropriate feeding [5]. So, responsive feeding should be stressed within both guidelines and interventions as a method of encouraging proper child development.

While there are data on food consumption and dietary diversity in early childhood, the global literature on early childhood beverage consumption is limited. With the increased consumption and availability of sugar sweetened beverages, future research should aim to track both global food and beverage consumption among children under 2 years old and its impact on growth and development.

Overall, international feeding recommendations need to be followed to encourage proper growth and development in early childhood. While the types of food and beverages children consume remain important, there is a growing recognition for the importance of the way children are fed. Continuous research of both responsive feeding and diet will be a powerful tool to improve early childhood growth and development.

### Table 1. Child feeding practices and nutritional status of children in India comparing NFHS-4 and NFHS-3

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Children under age 3 years breastfed within 1 hour of birth (%)</td>
<td>41.6</td>
<td>23.4</td>
</tr>
<tr>
<td>Children under age 6 months exclusively breastfed (%)</td>
<td>54.9</td>
<td>46.4</td>
</tr>
<tr>
<td>Children aged 6–8 months receiving solid or semisolid food and breast milk (%)</td>
<td>42.7</td>
<td>52.6</td>
</tr>
<tr>
<td>Breastfeeding children aged 6–23 months receiving an adequate diet (%)</td>
<td>18.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Non-breastfeeding children aged 6–23 months receiving an adequate diet (%)</td>
<td>14.3</td>
<td>N/A</td>
</tr>
<tr>
<td>Total children aged 6–23 months receiving an adequate diet (%)</td>
<td>9.6</td>
<td>N/A</td>
</tr>
</tbody>
</table>
References

Improving Children’s Diet: Approach and Progress

Usha Ramakrishnan and Amy Webb-Girard

Worldwide, fewer than one-third of children aged 6–24 months receive adequate dietary diversity and only about half receive a sufficient number of meals each day. Such suboptimal complementary feeding practices put millions of infants at risk for stunting and developmental delays. Food insecurity and/or limited access to high-quality foods continue during the preschool age years with implications for poor development and increased risk of facing the dual or even triple burden of malnutrition associated with protein-energy malnutrition, micronutrient deficiencies, as well as overweight or obesity.

Strategies to improve the adequacy of dietary intakes in young children have focused on improving both dietary quality and quantity of food consumed. While access to quality food that will meet the nutrient needs of young children remains a problem in many resource-poor settings, the importance of initiation and maintenance of sustained behavior change has been recognized as foundational to improving child feeding practices especially during the first 2 years of life. A wide range of interventions that aim to improve dietary intakes of young children have been evaluated in large-scale effectiveness trials with varying success and challenges. This presentation highlights key findings from these various studies with a focus on the ones conducted in Sub-Saharan Africa and South and South-East Asia. The interventions include one or more of the following: (a) provision of targeted food-based supplements, (b) food-aid packages, (c) counseling and behavior change interventions, (d) conditional cash transfers, (e) nutrition-sensitive intervention such as home gardening and promotion of orange flesh sweet potato, and (f) micronutrient supplements and fortification (staple foods and point of use). Among the 64 interventions that used behavior change techniques (BCTs), interpersonal communication (IPC), either individually or in groups, was the most commonly used platform. The number of techniques used by any one intervention also ranged from 2 to 13, with a median of 6. All interventions provided instruction on how to perform the behavior, and
other commonly applied BCTs included use of a credible source \((n = 46)\); demonstration of the behavior \((n = 35)\); and information about health consequences \((n = 30)\). Forty-three interventions also reported strategies to shift the physical or social environment. We identified five large multi-country studies that included Alive & Thrive (Bangladesh, Ethiopia, India, Vietnam); Windows of Opportunity (CARE, multi-country); Nutrition at the Center (CARE, multi-country); Enhanced Homestead Food Production (Helen Keller International- HKI, multi-country); Sho- urado II (CARE, Bangladesh); ENGINE (Save the Children, Ethiopia); MICAH (World Vision, multi-country); and RAIN (Concern Worldwide, Zambia). Detailed reports of country-specific activities were found only for Alive & Thrive (A&T) and a limited number of HKI’s HFP programs that focused on young children. Of note, the A&T Project in Bangladesh combined intensified IPC with mass media and community mobilization and reported significant improvements in a variety of child diet indicators including proportion of young children (6–24 months) consuming a minimally adequate diet and minimum diet diversity. This at-scale project reached over 8 million mothers and was implemented by a strong community-based nongovernmental organization. Some key factors that contributed to the success of this program included the formation of alliances with key stakeholders, availability of funds and technical support from multiple donors, well-defined interventions and indicators, and streamlined processes and tools to aid implementation. A key finding of this systematic review is the lack of detail related to intervention design and implementation including cost and feasibility, all of which have important implications for the adoption, replication, and scale up of effective strategies. Another concern is the limited data on strategies targeted toward improving the diet of preschool age children (3–5 years).
The Importance of Food Composition Data for Estimating Micronutrient Intake: What Do We Know Now and into the Future?

Fernanda Grande

Reducing all forms of malnutrition represents a great challenge in many countries and recognizing population intake deficiencies is the first step to solve this problem. In this context, food composition tables or databases (FCT/FCDB) are an essential tool for dietary assessments as they provide the information required to convert food consumption data into energy and nutrient intakes [1–3].

FCT/FCDB centralize data on the nutrient content of foods of a certain country or region that are the basis for many activities involving nutrition and health, food security, and agriculture [2, 3]. The main factors that affect the quality of FCT/FCDB are coverage of foods and components, details included in the food description, component identification (including denominators, units, and definitions), appropriateness of the analytical procedures, and how well the foods analyzed represent the food supply (sampling). In addition, they also need to be regularly updated to reflect changes in the food supply and nutrition science [1].

FCT/FCDB should be elaborated at country level since the composition of foods differs from country to country due to geographical location, fortification programs, and dietary habits (types of foods and processing methods applied) [1]. Therefore, adapting an FCT/FCDB from another country can be a challenging and time-consuming work due to these differences in the food items.

Around three-quarters of all countries already have published at least one FCT/FCDB [4], even though many are outdated and vary considerably in terms of data quality, documentation, food and nutrient coverage, analytical methods used, and accessibility [1]. Moreover, a great number of those FCT/FCDB contain very few up-to-date analytical data obtained for food composition purposes, resulting in many data being estimated or copied from other publicly available FCT/FCDB [5].
Low-quality FCT/FCDB may introduce errors in the intake assessment resulting in under- or overestimated intake for a certain micronutrient. For example, total vitamin A may be calculated either as Retinol Equivalents (RE) or as Retinol Activity Equivalent (RAE), and they result in different values for the same vitamin A content in plant foods. Thus, using RE or RAE in estimating nutrient-deficient population would generate 2 significantly different figures. Similar problems may occur for other components, for example, niacin, folate, carbohydrate, or dietary fiber.

Furthermore, many other natural factors that can affect the composition of foods are often not reflected in FCT/FCDB including biodiversity, maturation degree, soil, and harvest season. The variation in the nutrient content for distinct varieties or cultivars of the same species can represent the difference between nutrient deficiency and nutrient adequacy in populations and individuals. For instance, vitamin A content of sweet potato may vary from trace amounts to 3,637 µg of RE per 100 g of edible

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**Table 1. Limitations and considerations for using food composition tables or databases [3]**

<table>
<thead>
<tr>
<th>Variability in the composition of foods</th>
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<tbody>
<tr>
<td>• Inherent (variety/cultivar/breed, maturity/age, color)</td>
</tr>
<tr>
<td>• Environmental (soil, water, weather, sunlight, fertilizer, feed)</td>
</tr>
<tr>
<td>• Transport and storage (time, temperature, light)</td>
</tr>
<tr>
<td>• Removal/addition of components (e.g., fat removal or nutrient fortification)</td>
</tr>
<tr>
<td>• Processing/preparation</td>
</tr>
<tr>
<td>• Product or recipe formulation</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Limited coverage of food items and components</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Food items or components of interest are not included, especially processed foods</td>
</tr>
<tr>
<td>• Missing values (results in underestimates of nutrient intakes)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Inappropriate database or food composition values</th>
</tr>
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<tbody>
<tr>
<td>• Lack of analytical data obtained for food composition purposes</td>
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<tr>
<td>• Out-of-date data</td>
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<table>
<thead>
<tr>
<th>Errors arising in database use</th>
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<tbody>
<tr>
<td>• Incorrect food matching</td>
</tr>
<tr>
<td>• Mistakes in nutrient definitions, units, and conversions</td>
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<tr>
<td>• Wrong procedures for recipe calculations</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incompatibility of databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Different analytical methods, definitions, and modes of expression</td>
</tr>
<tr>
<td>(“problematic components” include energy, protein, fat, carbohydrate, dietary fiber, vitamins A, D, E, K, C, folate, and niacin)</td>
</tr>
</tbody>
</table>

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portion, which corresponds to 6 times the recommended daily intake for this nutrient. Flesh color gives evidence of the vitamin A content since yellow- and orange-fleshed sweet potatoes contain higher amounts of vitamin A. Hence, these foods should be reported individually in FCT/FCDB with their unique nutrient profile instead of a singular food entry with an average value. Table 1 summarizes limitations and considerations for using FCT/FCDB.

In this context, FAO/International Network of Food Data Systems (INFOODS) coordinate food composition activities aiming to improve data quality and availability globally. INFOODS’ activities include capacity development and publication of both guidelines and regional and international FCT/FCDB that are available on their website free of charge [4].

In spite of food composition receiving more attention in recent years, many countries still need to generate and disseminate up-to-date and high-quality FCT/FCDB. Poor food composition data may lead to wrong conclusions resulting in the development of misleading policy and programs in nutrition to improve nutritional status, especially for micronutrients, of individuals and population [5].

References
Balancing Safety and Potential for Impact in Micronutrient Interventions

Andrew J. Baldi, Leila M. Larson, and Sant-Rayn Pasricha

Almost 300 million children under 5 years are anaemic worldwide [1]. Iron deficiency has traditionally been considered to account for half of these cases. International policy makers recommend universal distribution of iron-based interventions – either iron supplements or iron-containing multiple micronutrient powders to alleviate the burden of anaemia in young children. More recent analyses indicate that the burden of anaemia attributable to iron deficiency is less than originally anticipated.

When considering whether to implement universal iron interventions, it is essential to benefit putative benefits from these advantages with possible risks. Efficacy trials indicate that MNPs reduce the prevalence of anaemia by an average of 34%. Recent effectiveness studies have indicated that the impact of MNPs on anaemia may be even smaller. The key reason for deploying iron interventions in young children to reduce anaemia is to improve child development, well-being and growth. However, few randomised controlled trials of iron interventions have carefully measured these outcomes. Presently, there is inadequate evidence to support the hypothesis that universal iron interventions (either as iron supplements or multiple micronutrient powders) provide benefits on functional child health such as child development [2], growth, or well-being.

Conversely, several important randomised controlled trials have found that when universal iron interventions are given to all children in a population, they might increase the risk of infection, particularly malaria and diarrhoea. Populations with highest burdens of anaemia are the same that harbour high rates of these infections. Concerningly, in malaria endemic regions, iron interventions (either as supplements or micronutrient powders) increased serious adverse events [3]. Iron may exacerbate risk of malaria by producing a reticulocytosis; these young red cells are more susceptible to parasite invasion [4]. The mechanism by which iron increases risk of diarrhoea may be via reprofiling the intestinal microbiome in favour of pathogenic species [5].
Other possible risks of iron interventions have not yet been extensively described. Iron overdose induces marked gastrointestinal and systemic toxicity, and even small doses of iron can be lethal to small children. Universal iron distribution programmes to infants or adults results in large numbers of doses of iron in households across a population and is largely unsupervised. The incidence of iron toxicity in these populations is presently undocumented but should be considered when monitoring programmes. Finally, in some populations, carriage states or subclinical inherited red cell disorders may increase iron absorption from the diet or from supplements. Long-term provision of iron interventions (including fortification) may, in some cases, raise the risk of iron loading.

Identifying whether universal iron interventions provide a net benefit or harm to populations is challenging (Figure 1). Utilising a burden of disease approach, iron deficiency anaemia exerts far fewer disability-adjusted life years worldwide than either malaria or diarrhoea; thus, modest relative reductions in the burden of iron deficiency that come at a cost of small increases in relative burden of malaria or diarrhoea would likely produce a net harm to health. Crucially, the quality of evidence for both iron supplements and MNPs remains very low, with few high-quality trials having been performed, which address crucial outcomes. This situation should improve with 2 large trials in progress in Bangladesh and Malawi that will specifically define the evidence for functional benefits from universal iron interventions (MNPs and iron supplements), enabling these interventions to be compared to each other as well as to placebo for key outcomes including child development, well-being, growth, and haemoglobin and iron status. Until then, implementation of universal iron intervention programmes should be undertaken with caution.

![Fig. 1. Considerations when evaluating the net health impact of universal iron interventions.](image-url)
References

Human Milk as the First Source of Nutrients

Lindsay H. Allen and Daniela Hampel

The nutrient requirements of young infants are higher per unit body weight than at any other time of life. Those who are exclusively breastfed (EBF) consume on average about 750 mL/day between 1 and 6 months. There are substantial differences in daily milk intake among infants; on average the range is about 570–900 mL, but in reality it is even wider than this. It is assumed that milk intake is predominantly influenced by infant demand. But whether those who habitually consume less milk also have proportionately lower intakes of all nutrients has not been systematically studied – perhaps nutrients are more concentrated in milk of mothers who produce smaller volumes.

In general, the amount of nutrients in the milk of a well-nourished woman is sufficient to support optimal growth and development of her infant. There are, however, some nutrients that may not be sufficient especially toward the end of the first 6 months. These include iron and zinc, the concentrations of which fall during the postpartum period such that they do not meet the requirements of the infant. Requirements for iron and zinc are estimated by the factorial approach that provides a basis for concluding that their intake becomes inadequate. Also the prevalence of low hemoglobin in infants increases with time postpartum. Other nutrients that may be inadequate in milk of well-nourished women include vitamin B12, a conclusion based on falling serum B12 and increasing serum methylmalonic acid concentrations by the middle of the first year of life, and vitamin D.

It is actually difficult to make conclusions about the nutritional adequacy of human milk because there are few normative data on the nutritional status of infants during the first year of life. Cut-points for adequacy and deficiency are usually nonexistent, so adult values are used. Even cut-points for hemoglobin are controversial. An additional problem is the very limited amount of information on the concentrations of nutrients, due to limitations in the number of participants, analytical uncertainties and constraints, and the variable nutritional status of the mothers.
Typically, the nutritional status of infants is not studied until after age 6 months and there are few supplementation trials at younger ages (IRIS was an exception). The few data that exist indicate that there may already be a high prevalence of deficiencies by age 6 months in poorer populations. This is usually ascribed to lack of true EBF or illness and infections. Unfortunately, there are almost no studies of the benefits of maternal supplementation on infant function (mention B12, other B vitamins, iodine, etc.).

The assumption that human milk no longer provides sufficient amounts of all nutrients after age 6 months drives the recommendation that complementary foods are required after this age (include studies of this). A recent study in a rural poor population in The Gambia revealed, however, that following WHO’s recommendation of exclusive breastfeeding to age 6 months versus nonexclusive breastfeeding did not affect growth between birth and 2 years.

In recent years, we have developed efficient methods for measuring multiple nutrients in milk. This has enabled us to illuminate the large differences in milk micronutrient concentrations across populations and to study the effects of maternal supplementation in pregnancy and/or lactation on secretion of the micronutrients in milk and the effect on infant’s status. Maternal deficiency or low intake has a major impact on milk concentrations of all the B vitamins except folate; on vitamin A and B-carotene; iodine and selenium; and, to a lesser extent, vitamin D. Vitamin A, vitamin B12, and iodine will be discussed in most detail. The effects of maternal supplementation during lactation vary among nutrients, with milk riboflavin increasing the most rapidly and in the largest amount, B12 increasing only slowly, and folate not at all. Since there is an acute increase in some milk micronutrients within hours, the timing of collection of milk samples in supplementation studies is difficult; collection prior to consuming a daily supplement will underestimate the daily amount secreted in milk, while collection within a few hours after a supplement is consumed will overestimate daily secretion.

The ongoing Mothers, Infants and Lactation Quality (MILQ) study proposes to answer some of the uncertainties raised above. Participants are 250 mother–infant dyads in 4 countries who are EBF for at least 3.5 months and still consuming some milk through 8.5 months. The mothers are healthy, and well-nourished, but do not take supplements (except for iron and folic acid) during pregnancy or lactation, and do not have high intakes of fortified foods. The range of nutrient concentrations in the milk of these women will provide “Reference Values” against which other studies and surveys can evaluate the quality of milk in their population and possibly target nutrients with especially low values for treatment with supplements or fortification. The MILQ study will also collect
longitudinal samples of mother’s and infant’s blood so that Reference Values for nutrients can be established during this period. The values for milk concentrations of nutrients will also be useful for improving nutrient intake recommendations for infants, young children, and lactating women.

The lecture will end with a summary of the many information gaps concerning nutrients in human milk.
Role of Cow’s Milk in Growth of Children

Benedikte Grenov, Anni Larnkjær, Christian Mølgaard, and Kim F. Michaelsen

Cow’s milk has a stimulating effect on growth in young children. This has been shown for linear growth [1, 2], and it might also have an effect on accretion of lean body mass. The strongest evidence comes from intervention studies in low-income countries. The effect seems to be through a stimulation of IGF-I and insulin. There are several components of cow’s milk that are suggested to have a stimulating effect on growth [3]. The high-protein-quality score with a high content of especially the essential amino acids is likely to play a key role. Furthermore, the high content of lactose may act as prebiotics having an effect on the gut microbiota and a positive effect on mineral absorption [4]. In addition, cow’s milk has a high content of calcium and minerals important for growth such as potassium, phosphorus, magnesium, and zinc. The effect of milk on linear growth is further supported by a study of male adult stature in 105 countries where intake of dairy protein was the most significant nutritional correlate of stature [5]. Some studies have also shown that children with milk allergy are shorter, and when they terminate avoidance of cow’s milk, they have a catch-up [6].

A high intake of cow’s milk and dairy products has potential negative effects in young children. It results in a high protein intake, which can increase the risk of overweight and obesity. This is especially a problem in high- and middle-income countries. Furthermore, a high dairy intake can limit the diversity of the diet. This can lead to iron deficiency, also because iron content is very low in cow’s milk, and cow’s milk has a negative effect on iron absorption. In low- and middle-income countries, there is also a risk that a high intake of cow’s milk might replace breast milk, which also during the second year of life has important effects in reducing infections. It has been suggested that the daily intake of cow’s milk and dairy products should not be above what equals 500 ml of cow’s milk.

The effect on linear growth is important in populations where stunting is prevalent, but in populations with no stunting, this might not have
important beneficial health effects. It has been suggested that the higher levels of IGF-I and insulin could increase the risk of some noncommunicable diseases later in life, but the evidence is not convincing.

In products for treatment and prevention of undernutrition, most products include dairy protein because of the well-documented effects on growth and recovery [3, 7]. In addition to the effects on growth mentioned above, products with dairy protein will typically contain less antinutrients from plant protein, which could also have a positive effect on growth. However, as dairy is an expensive ingredient, there have been efforts to identify the lowest content that can support catch-up growth. Furthermore, there are newer studies that have examined the effect of a mixture of plant proteins with a high protein quality or plant proteins with added crystalline amino acids.

In conclusion, cow’s milk and dairy products are from the age of 1 year an important part of a healthy diet providing important nutrients and supporting growth. A high intake has potential negative effects, especially an increased risk of later obesity, and should be avoided. In foods for treatment and prevention of undernutrition, dairy protein plays an important role, but the amount needed and the effects of alternative protein sources are discussed.

References

Life Course Evolution of Vitamin B12 Deficiency in Indians, Lessons for Other Populations

Chittaranjan S. Yajnik

Vitamin B12 deficiency is common in vegetarian and economically deprived populations of the world. India provides a striking example. Unlike in the Western populations, this is not due to defects in the intrinsic factor-mediated gastrointestinal absorption but due to smaller intake of the vitamin in the diet. In nature, B12 is produced only by prokaryotes (microbes) and animals who eat microbes bring it in the food cycle. Smaller intake of animal origin foods is, therefore, a major cause of B12 deficiency. This may be driven by religious and cultural beliefs or poverty. Therefore, vegans and vegetarians and members of certain religions (Jain and Hindus) are at higher risk.

Pune Maternal Nutrition Study is a prospective preconceptional cohort in villages around Pune, India. It was set up to study maternal nutritional influences on fetal growth and future risk of noncommunicable disorders. The children born in the study (and their parents) are regularly followed up and are now in early 20s. Serial measurements of physical characteristics, circulating nutrients, and biochemical-endocrine markers have allowed to construct a life-course model of various conditions. B12 deficiency is common in this population; it progressively increased from 15% at 6 years of age to 58% at 18 years at which time it was higher than that in the parents.

Our analysis shows that ~10 to 12% of the deficiency is contributed by genetic factors that are not very different to those in the western populations. In addition, lower maternal transfer to the baby, prolonged breast feeding, lower milk intake in childhood, rapid childhood and adolescent growth, family environment (a surrogate for dietary practices and other lifestyle), and lower leucocyte count (a surrogate for hygiene and infections) contribute to B12 deficiency.

A picture emerges where nutrient deficiencies evolve during the life course with biological factors in the center, surrounded by family and
community influences that in turn are affected by national, international, and political factors. Immediate solutions to the problem include supplements and food fortification, but novel solutions are awaited to tackle the multifactorial and complex etiology.
In addition to regions where vegetarian and vegan diets have a long cultural- and religion-based tradition, these diets have recently become more and more prevalent in Europe and other western countries. Furthermore, it is estimated that the prevalence of vegan-nourished adolescents and adults in Western Europe countries ranges from around 0.2 to 3% [1]. Reliable population-based numbers on vegan-fed infants and young children are as yet not available.

In young children and adolescents, not only their weight and growth but also their psychomotor development is strongly influenced by the form and quality of their nutrition. In adult cohorts, a plant-based diet shows an advantage in the prevention of chronic diseases such as obesity, type 2 diabetes, cardiovascular diseases, and certain cancers. As yet, there is no clear evidence that a vegan diet started early in childhood brings a lasting health benefit [2]. However, health reasons are seldom the primary motivation for a vegan diet, whereas ethical-moral or sustainability considerations figure more prominently. This is important to realize as differing assumptions and concerns between the pediatrician and the involved family can lead to barriers in finding a common ground for communication and therefore for long-term follow-up.

Plant-based nutrition is characterized by rich coverage of β-carotene, vitamin C, folate, and magnesium as well as of fiber and phytochemicals. Several of the expected health effects are attributed to the latter. On the other hand, a diet that completely dispenses with products of animal origin can be potentially critical in terms of protein quality and inadequate energy, long-chain fatty acids, iron, zinc, vitamin D, iodine, calcium, and especially vitamin B12. Deficiencies in these nutrients can lead to severe and sometimes irreversible developmental disorders. Awareness of these potentially critical nutrients allows parents who plan a vegan diet for themselves and their children to choose a considered selection of adequate food products. However, even with a well-balanced and optimized variety of vegan food sources, it remains mandatory to supplement vitamin B12 and vitamin D as a minimum [3].
There are significant differences between the recommendations of the various nutrition and health associations worldwide, which, in turn, are probably due to the paucity and heterogeneity of available studies. The American Academy of Nutrition considers a well-balanced and well-planned vegan diet to be a healthy option in each stage of life [4]. However, European professional societies such as the Swiss Federal Commission for Nutrition, the German Society for Nutrition and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) do not recommend a vegan diet during childhood [1, 5, 6]. If such a diet is chosen for ethical, ecological, or health reasons, a well-planned, diversified diet, with additional supplementation of vitamin B12, D, iodine, and potentially other micronutrients, is crucial to ensure a healthy and nutritious intake during childhood. The younger the child, the more critically

Table 1. Practical points to accompany children fed a vegan diet (adapted to [7])

<table>
<thead>
<tr>
<th>In general:</th>
<th>Toddlers and children</th>
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<tbody>
<tr>
<td>• Vegan diet accompanied by qualified dietician and pediatrician</td>
<td>• Monitor energy intake (percentiles)</td>
</tr>
<tr>
<td>• Exploring motivation, discussing sources of information</td>
<td>• Limit raw food in toddlers (lower digestibility and caloric density)</td>
</tr>
<tr>
<td>• Collect a nutritional history, analyze a 3-day food diary, and regularly check critical nutrients (laboratory controls)</td>
<td>• Check calcium intake (e.g., Ca-rich mineral water)</td>
</tr>
<tr>
<td>• Discuss supplements</td>
<td>• Evaluate iodine supply (salt)</td>
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<td></td>
<td>• Discuss Vitamin B12 supplement</td>
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<td>• Check iron and Vitamin D levels, possibly supplement</td>
</tr>
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<td></td>
<td>• Cave danger of aspiration (e.g., grinding nuts)</td>
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</table>

Infants:
*Breast fed: if the mother is on a vegan/vegetarian diet, a nutritional evaluation is recommended (with analyses of critical micronutrients and potentially supplement them)*

*Formula-fed: adapted soy infant formula*

*Complementary food:*
- Breast milk (BM) or infant formula until 12 months
- Pulses (puréed)/tofu is possible from 6 months onward
- Calorie-dense solid food with oil supplemented (ALA-rich linseed, walnut, or rapeseed)
- Consider iron supplement (mainly in BM-fed infants after 6 months)
- Vitamin K and D prophylaxis as all infants
- Supplement Vitamin B12 (after starting with complementary food)

Toddlers and children:
- Monitor energy intake (percentiles)
- Limit raw food in toddlers (lower digestibility and caloric density)
- Check calcium intake (e.g., Ca-rich mineral water)
- Evaluate iodine supply (salt)
- Discuss Vitamin B12 supplement
- Check iron and Vitamin D levels, possibly supplement
- Cave danger of aspiration (e.g., grinding nuts)

Adolescents: Additionally explore any eating disorder.
we need to be aware of the potential dangers of a restrictive diet to the
growing individual and therefore primarily advocate a diet that does not
need to be supplemented [1]. At any age, a vegan diet requires profound
nutritional knowledge from the parents and regular laboratory testing
for the child. Qualified nutritional counseling and continuous pediatric
medical support are indicated when feeding a child a vegan diet. A sum-
mary of aspects that need to be considered in the different age groups is
shown in Table 1.

References

4. Melina V, Craig W, Levin S: Position of the academy of nutrition and dietetics: vegetar
Role of Optimized Plant Protein Combinations as a Low-Cost Alternative to Dairy Ingredients in Foods for the Prevention and Treatment of MAM and SAM

Mark Manary and Meghan Callaghan-Gillespie

Protein is an important component of specialized foods to treat moderate acute malnutrition (MAM) and severe acute malnutrition (SAM). This is because wasting, the physiologic process that leads to acute malnutrition, is in large part reduction in the lean and functioning tissues of the body. It is generalized wasting of all organ systems that makes the wasted child more vulnerable. Protein is a category that represents all amino acids, the building blocks of almost all of the functional features of human cells. There are 11 essential amino acids, which cannot be synthesized endogenously, but must be absorbed from the gut. The term protein quality refers to the essential amino acid content of dietary protein. Aggregating the results from clinical trials with different foods with differing protein qualities used to treat MAM and SAM, correlations are seen between protein quality and rates of weight gain/recovery rates. Animal source proteins, in particular milk protein, are favored and prescribed as ingredients in foods to treat MAM and SAM. This is because the protein quality of milk is higher than that of plant proteins. Among plants, cowpea, common bean, and soybean have the most protein, the highest quality protein, and thus are candidates for foods for acute malnutrition. Clinical trials in SAM patients show that incorporation of milk protein causes greater weight gain and recovery. An interesting preliminary trial using crystallized amino acids to replace milk has shown some promise for the treatment of wasting but needs to be used in home-based therapy among young children before it can be recommended. MAM children, although less likely to die than SAM children, are deficient in essential amino acids and also require high protein quality to recover. Whenever specialized foods for wasting are considered, protein quality must be a key consideration.
Aggregated analyses of child growth in low-income countries reveal a remarkably consistent picture of serious growth failure compared to the WHO reference growth curves. Birth weight is generally lower by 0.5–1.0 Z-score. Young infants then grow reasonably well until about 3 m post-partum when they enter a period of precipitate decline compared to the WHO reference to reach −2 Z-scores and worse. By 24 m this decline halts and, in many settings, there follows a period of gradual catch-up (Fig. 1).

Low birthweight can be ascribed to numerous factors, especially small maternal size, which reflects the environmental effects in prior generations. Possible epigenetic mechanisms that might mediate these inter-generational effects are discussed by Silver elsewhere in this symposium.

A large proportion of the rapid growth deterioration in later infancy and the second year of life can be ascribed to infections and the wider nonspecific effects of living in an unhygienic environment. Despite never revealing themselves as clinical syndromes, the great majority of children in rural African settings are antibody positive to numerous pathogens (CMV, EB, HepB, *H. pylori*, and many more) by 24 m; these infections must take their toll.

Additional to these is a syndrome widely termed environmental enteric disease (EED) that combines gut leakage with a chronic inflammation leading to nutrient losses and cytokine-mediated growth retardation [1, 2].

The etiology of EED is still not entirely clear and probably results from a constellation of factors all related to poverty and pooled under the label of water, sanitation, and hygiene (WASH). Pathogens causing diarrhea play a contributory (though not necessarily dominant) role [3]. Alterations in the gut microbiota reflecting an inappropriately slow maturation toward the normal post-infancy profile [4] and/or a frank dysbiosis [5] each may play an additional role (Fig. 2).
Fig. 1. Life course of stunting in rural Gambians. (1) Fetal growth retardation. (2) Precipitate decline from 3 to 24 m. (3) Spontaneous catch-up in pre-schoolers. (4) Stability in childhood. (4a) Artifactual decline as reference standard children enter puberty earlier. (5) Pubertal catch-up. (6) Adult status. Adapted from Prentice [6].

Fig. 2. Genesis and pathophysiology of environmental enteric disease (EED).
Micronutrient deficiencies, and especially iron deficiency leading to anemia, are also caused in some part by infections and inflammation that impair both their absorption and utilization.

The rapid decline in stunting and anemia rates seen in many South American countries in the past 3 or 4 decades has been well documented in Brazil where it seems clear that concerted efforts involving improved water and sanitation facilities, improvements in breast-feeding rates, poverty reduction, and mothers’ education have all contributed to the excellent progress seen. In contrast, the disappointing effects of recent WASH intervention studies (presented in this symposium by Humphrey) emphasize the need for holistic approaches that encompass a wide range of environmental improvements in addition to nutrition-specific interventions.

References

The Gut Microbiome in Child Malnutrition

Ruairi C. Robertson

Undernutrition affects almost 25% of all children under the age of 5 worldwide and underlies almost half of all child deaths. Child undernutrition is also associated with long-term growth deficits, in addition to reduced cognitive potential, reduced economic potential, and elevated chronic disease risk in later life. Dietary interventions alone are insufficient to comprehensively reduce the burden of child undernutrition and fail to address the persistent infectious burden of the disease. Although the role of infections is well recognized in the pathogenesis of undernutrition, an emerging body of evidence suggests that commensal microbial communities, known as the microbiome, also play an important role [1].

Succession of the early-life gut microbiome critically regulates the structuring of the intestinal barrier, energy harvesting from nutrients, growth hormone signaling, colonization resistance, and immune tolerance against pathogens, among other pathways critically associated with healthy child growth. Hence, disturbance of the normal gut microbial ecosystem via undernourished diets or unhygienic environments, especially in the early phases of life, may perturb these critical pathways associated with child growth, thereby contributing to child undernutrition. Indeed, the programmed maturation of the gut microbiome in the first 2 years of life, as measured by the microbiome-for-age Z-score (MAZ), is highly predictive of healthy child growth [2]. Gut microbiome “immaturity” during this early life period is associated with undernutrition.

Stunting, a chronic form of undernutrition characterized by low height-for-age, is associated with compartmentalization of the intestinal tract, whereby commensal microbial taxa of oropharyngeal origin are found lower in the gastrointestinal tract [3]. It is hypothesized that the presence of these microbes outside of their ecological niche may stimulate a chronic inflammatory cascade leading to environmental enteropathic dysfunction (EED) and growth faltering. Preclinical studies have also demonstrated the essential role of the gut microbiome in linear growth via interaction with insulin-like growth factor 1 (IGF-1) and growth
hormone [4]. Wasting, a more acute form of child undernutrition, does not present with a consistent gut microbiome profile; however, a reduced MAZ is associated with severe wasting. MAZ fails to persistently recover following standard therapeutic feeding for severe wasting, suggesting that current feeding protocols are insufficient to restore the gut microbiome to a healthy state [2].

Interventions to target the gut microbiome in child undernutrition have yet to yield convincing beneficial effects. Antibiotics appear to exert beneficial effects for linear growth; however, their benefits for growth recovery following severe wasting remain inconclusive [5]. Furthermore, the threat of antimicrobial resistance limits the future potential for mass antibiotic usage for child growth. Some probiotics pose potential to reduce undernutrition-associated diarrhea and increase weight; however, future interventions must consider timing of probiotic interventions, colonization potential, and strain specificity. Fecal microbiome transplantation poses potential as a novel therapy to tackle severe wasting; however, it remains untested.

Research into the gut microbiome has led to novel therapies that have significantly improved both survival and quality of life in patients with chronic intestinal and metabolic disorders in high-income settings. This wealth of knowledge must now be applied with a global health perspective in LMIC in order to improve child mortality and undernutrition, both of which remain unacceptably high. With expanding knowledge from preclinical and observational studies, future research must begin to investigate microbiota-directed therapies, which pose real potential to reduce the mortality and morbidity associated with child undernutrition.

References

Intergenerational Influences on Child Development: An Epigenetic Perspective

Matt J. Silver

The link between poor maternal nutrition and suboptimal infant and child outcomes is well established, but underlying mechanisms are not well understood [1]. Modifications to the developing offspring epigenome (Fig. 1) are a plausible mechanism for the transmission of intergenerational signals that could extend to effects of paternal nutrition mediated by epigenetic modifications in sperm.

One widely studied epigenetic mark involves the addition of methyl groups to DNA. DNA methylation (DNAm) marks are faithfully copied across cell divisions and can influence gene expression without altering the underlying DNA sequence. DNAm plays a key role in establishing and maintaining cellular identity. The DNAm must, therefore, be extensively remodeled in the very early embryo where embryonic cells are first reset to a pluripotent state, prior to the establishment of cell type-specific marks following separation into the embryonic germ layers at gastrulation.

This has focused attention on the periconceptional period as a time when the establishment of epigenetic marks in offspring might be especially sensitive to differences in maternal (and potentially paternal) nutrition [2].

Some of the landmark work in this field has featured so-called “natural experiments” such as the Dutch Hunger Winter, where offspring were subject to short-lived but severe periods of nutritional challenge in utero [3]. Our work in a rural population in The Gambia in Sub-Saharan West Africa exploits another natural experiment, whereby fluctuations in energy balance and maternal nutrition exposures show a distinct bimodal pattern corresponding to dry and rainy seasons. We have shown, for example, that season of conception and blood levels of certain nutritional biomarkers in maternal blood plasma predict DNA methylation in infants at a number of metastable epialleles (MEs) – genomic regions where methylation is established stochastically in the early embryo [4]. Some
MEs have been linked to health-related outcomes, including a region in the \( POMC \) gene that is associated with obesity in children and adults [5]. The \( POMC \) gene is involved in the regulation of appetite, and evidence that \( POMC \) methylation is established in early life, is stable thereafter, and is associated with \( POMC \) expression positions this locus as a strong candidate for mediating links between early-life nutrition and the regulation of bodyweight in later life.

As with the studies described above, much of the work in human nutritional epigenetics focuses on the potential for DNA changes to mediate “intergenerational” signals, that is, methylation changes that arise as a result of direct exposure of the embryo or fetus to maternal factors. Intergenerational epigenetic effects potentially additionally encompass exposures in the paternal and grandmaternal generations since germ cells that give rise to the current generation could have been exposed \textit{in utero} (Fig. 2).

\begin{figure}
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\includegraphics[width=\textwidth]{fig1.png}
\caption{Epigenetic mechanisms may mediate links between early environmental exposures and health outcomes in later life (Image courtesy of US National Institutes of Health).}
\end{figure}
There is a great deal of interest in the possibility that epigenetic signals might also be transmitted across multiple generations – so-called transgenerational epigenetic inheritance. This would require epigenetic states to be maintained across epigenetic reprogramming events at conception and in primordial germ cells during gestation, but evidence for this is currently lacking in humans.

It is interesting to speculate whether epigenetic marks that are responsive to early maternal environment could have evolved to sense, record, and adapt the organism to its anticipated postnatal environment. This would require that environmentally responsive loci are under genetic control. Importantly, this might lead to disease through maladaptation, where there is a mismatch between the early environment encountered by the developing embryo and that experienced in postnatal life.

**Fig. 2.** Inter- and trans-generational epigenetic inheritance through the maternal (left) and paternal (right) lines.
References

The WASH Benefits Bangladesh, WASH Benefits Kenya, and SHINE Trials: A Summary of Their Findings

Rachel Makasi and Jean H. Humphrey

The WASH Benefits Bangladesh [1], WASH Benefits Kenya [2], and Sanitation, Hygiene, Infant Nutrition Efficacy (SHINE) [3] – Zimbabwe trials were cluster-randomized trials to test the independent and combined effects of improved water and sanitation/hygiene (WASH) and improved infant and young child feeding (IYCF) on child linear growth and hemoglobin concentration. The trials were designed as “proof of concept” studies [4, 5]: the goal was to implement our best effort to minimize fecal ingestion in the WASH arms and optimize infant diet in the IYCF arms. The WASH Benefits trials had 7 arms (water chlorination, sanitation [provision of an improved latrine], handwashing with soap [provision of two handwashing stations and soap], these 3 interventions together – WASH, IYCF (complementary feeding counseling and provision of 20 g small-quantity lipid-paste nutrient supplement [LNS]), WASH + IYCF, and a double-sized control arm which was passive in Bangladesh and active in Kenya. SHINE was a 2 × 2 factorial trial with 4 groups: WASH, IYCF, WASH + IYCF, and Standard of Care (SOC). Together the trials enrolled more than 19,000 pregnant women and measured their infants (15,500) at 18 months (SHINE) or 24 months (WASH Benefits) of age. All trials included behavior change communication based on published models of behavior change theory. Interventions were delivered by trained teams who lived in and were respected by the study communities. Interventions were delivered with high fidelity of implementation and achieved substantial contrast in WASH facilities and behaviors between WASH arms and non-WASH arms in all trials. Consumption of LNS in the previous 24 hours was >90% among children in the IYCF arms.

Results of these trials showed that in all three trials, the IYCF intervention improved length-for-age Z score (LAZ) by 0.13–0.26. In all three trials, the WASH interventions had no effect on linear growth. In Bangladesh, all the interventions except water chlorination alone reduced
diarrhea by 35–40%, while in the African sites, no intervention reduced diarrhea.

The increase in LAZ achieved by the IYCF intervention in all three trials is consistent with a large literature showing that complementary feeding interventions, on average, increase LAZ by 0.1 – 0.2. The failure of the WASH interventions in all three studies to improve linear growth is probably because the interventions implemented in these trials did not reduce exposure to environmental pathogens sufficiently to reduce linear growth faltering.

The reason why the WASH interventions reduced diarrhea in Bangladesh but not Kenya or Zimbabwe may be due to differences in the intensity of behavior change promotion: in Bangladesh, promoters visited participants 6 times per month (while households in the passive control group were visited only for outcome measurement), while in the African sites, promoters visit all participants monthly. It may be that very frequent behavior change promotion is required to achieve a high enough adherence to WASH behaviors to reduce diarrhea.

In summary, new innovative WASH interventions that are less reliant on behavior change and much more effective in reducing fecal exposure may be required to optimize child health and growth.

Reference

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