FOCUS

Like poverty, undernutrition and micronutrient deficiencies often occur as part of an intergenerational cycle

Ann Nutr Metab 2015;66(suppl 2):22–33

The Epidemiology of Global Micronutrient Deficiencies

by Regan L. Bailey et al.

Key insights

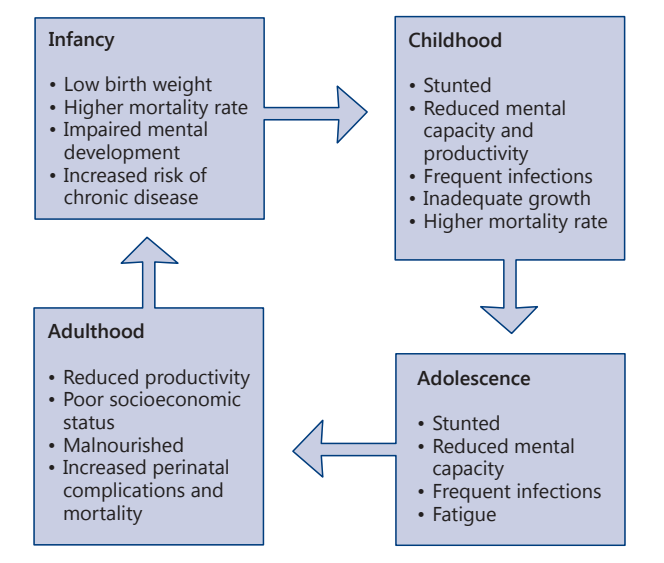
Micronutrient deficiencies (MNDs) have a direct impact on individuals and on societies, resulting in poorer health, lower educational attainment and decreased work capacity and earning potential. Nutrition is the most powerful adaptable environmental factor that can be targeted in order to reduce the burden of disease across an individual's entire life span. MNDs are preventable and the return on investment for the provision of micronutrients is high. Understanding how to interpret the biomarkers of MNDs alongside clinical and functional indicators is key to characterizing the global burden of MNDs and to identifying the optimal interventions.

Current knowledge

Around the world, pregnant women and children under 5 years of age are at the highest risk of MNDs. Iron, iodine, folate, vitamin A, and zinc deficiencies are the most widespread MNDs and are common contributors towards poor growth, intellectual impairment, perinatal complications, and increased risk of morbidity and mortality. Of greatest concern is the fact that the cycle of MNDs perpetuates across the generations, with far-reaching consequences on the future population.

Practical implications

Addressing MNDs has traditionally been accomplished through supplementation, fortification, and food-based approaches including dietary diversification. Of note, intervention in the first 1,000 days of life is most effective for breaking the cycle of malnutrition; however, a coordinated, sustainable commitment to scaling up nutritional interventions at the global level is needed. Supplementation is a cost-effective solution but does not address the root cause of the MND. Over the long term, food fortification may offer a more effective means to address MNDs, as it enables a larger segment of a population to be targeted.



Micronutrient deficiencies have consequences throughout an individual's life span and are perpetuated across the generations.

Recommended reading

Black RE, Victora CG, Walker SP, et al: Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427–451.

E-Mail karger@karger.com
www.karger.com/anm

Annals of Nutrition & Metabolism

Ann Nutr Metab 2015;66(suppl 2):22–33
DOI: 10.1159/000371618

Published online: June 2, 2015

The Epidemiology of Global Micronutrient Deficiencies

Regan L. Bailey[a, b] Keith P. West Jr.[b] Robert E. Black[b]

[a]Office of Dietary Supplements, National Institutes of Health, Bethesda, Md., [b]Department of International Nutrition, The Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Md., USA

Key Messages

- Nutrition is the most powerful adaptable environmental exposure to target in order to reduce the burden of diseases and death across the life span around the world. Micronutrient deficiencies (MNDs) have direct effects on individuals and indirect effects on societies. Globally, there have been substantial gains made to improve the nutritional status. However, there is still tremendous work to be done to reach all individuals with or at risk for MNDs.
- MNDs are preventable. The return on investment for provision of micronutrients is substantial. The choice of interventions should be based on the root cause and the scope and severity of the MND.
- Biomarkers of nutritional status can be influenced by infection and inflammation, which are common with MNDs. Understanding how to interpret biochemical indicators along with clinical and functional indicators is key to characterizing the extent of the global burden of MNDs.
- Ending the cycle of malnutrition is critical. Intervening during pregnancy and through the first 1,000 days is optimal. Multidimensional, coordinated, and sustainable strategies are needed to combat MNDs. Short- and long-term solutions are needed.

Key Words

Epidemiology · Micronutrient deficiencies · Vitamins · Minerals

Abstract

Micronutrients are essential to sustain life and for optimal physiological function. Widespread global micronutrient deficiencies (MNDs) exist, with pregnant women and their children under 5 years at the highest risk. Iron, iodine, folate, vitamin A, and zinc deficiencies are the most widespread MNDs, and all these MNDs are common contributors to poor growth, intellectual impairments, perinatal complications, and increased risk of morbidity and mortality. Iron deficiency is the most common MND worldwide and leads to microcytic anemia, decreased capacity for work, as well as impaired immune and endocrine function. Iodine deficiency disorder is also widespread and results in goiter, mental retardation, or reduced cognitive function. Adequate zinc is necessary for optimal immune function, and deficiency is associated with an increased incidence of diarrhea and acute respiratory infections, major causes of death in those <5 years of age. Folic acid taken in early pregnancy can prevent neural tube defects. Folate is essential for DNA synthesis and repair, and deficiency results in macrocytic anemia. Vitamin A deficiency is the leading cause of blindness worldwide and also impairs immune function and cell differentiation. Single

KARGER 125 years

E-Mail karger@karger.com

0250–6807/15/0666–0022$39.50/0

Regan L. Bailey
Office of Dietary Supplements, National Institutes of Health
6100 Executive Boulevard, Suite 3B01
Bethesda, MD 20892 (USA)
E-Mail baileyr@mail.nih.gov

MNDs rarely occur alone; often, multiple MNDs coexist. The long-term consequences of MNDs are not only seen at the individual level but also have deleterious impacts on the economic development and human capital at the country level. Perhaps of greatest concern is the cycle of MNDs that persists over generations and the intergenerational consequences of MNDs that we are only beginning to understand. Prevention of MNDs is critical and traditionally has been accomplished through supplementation, fortification, and food-based approaches including diversification. It is widely accepted that intervention in the first 1,000 days is critical to break the cycle of malnutrition; however, a coordinated, sustainable commitment to scaling up nutrition at the global level is still needed. Understanding the epidemiology of MNDs is critical to understand what intervention strategies will work best under different conditions.

Introduction

Micronutrient is the umbrella term used to represent essential vitamins and minerals required from the diet to sustain virtually all normal cellular and molecular functions [1]. While the required amounts of micronutrients are very small, micronutrient deficiency (MND) can have wide-range negative health impacts that will ultimately result in death if untreated. MNDs are common, affecting an estimated 2 billion people worldwide [2]. The most common deficiencies exist for vitamin A, folate, iron, iodine, and zinc; however, several other MND disorders exist. Coexistence of multiple MNDs frequently occurs. MNDs often occur as part of a cycle of malnutrition and may be coupled with protein or energy malnutrition. Pregnant women and their children 5 years of age and younger are the most vulnerable population subgroups. While most MND disorders can be reversed with provision of missing micronutrients, some deficiency disorders result in irreversible, lifelong consequences. The severity, timing, and the extent of the deficiency will determine its sequelae. Thus, a need exists for informed, evidence-based approaches to the prevention of MNDs at the global level. Understanding the epidemiology of MNDs is critical to understand what intervention strategies will work best under different conditions.

Defining Deficiency

The nutritional status of a micronutrient can be characterized along a continuum from deficiency to excess (fig. 1) [3]. The sufficiency status for micronutrients can be determined along this continuum using biomarkers, dietary intake data, or nonspecific functional indicators, like stunting or low birth weight. Ideally, MND is determined by a valid and reliable biomarker. Biomarkers are typically defined as biological measurements (i.e. blood, urine, etc.) that are used to indicate 'normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention' [4]. Unfortunately, biomarkers are not available for all, while other existing biomarkers are not practical or feasible for widespread assessment or for use outside the clinical setting. Furthermore, biomarkers may be influenced by inflammation, infection, hydration status, age, kidney function, and analytical method, all of which make their interpretation difficult. Finally, a number of issues exist concerning the use of cut points for biomarkers to determine deficiency and sufficiency as there is a distribution around the cut point, cut points may differ by many factors (e.g. by age group or by analytical method), and the selection of which cut point to use is problematic. National sur-

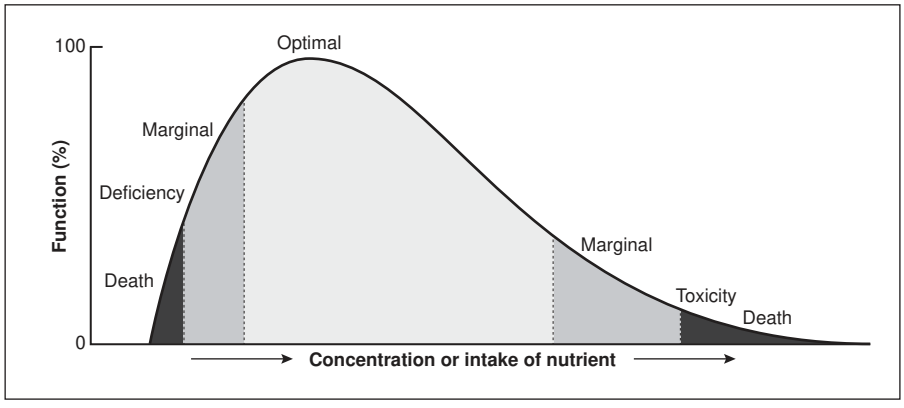


Fig. 1. Hypothetical micronutrient intake/status distribution.

Ann Nutr Metab 2015;66(suppl 2):22–33
DOI: 10.1159/000371618

veys containing dietary data are not routinely collected in most developing countries. Furthermore, databases needed to analyze reported intakes must be region specific and are often lacking or not up-to-date. The use of functional indicators to characterize the extent of MNDs is problematic because so many factors contribute to these public health problems. MNDs are commonly only one of the root causes of these types of indicators. Thus, in the absence of dietary or biomarker data, we can only assume that countries with a high burden of adverse functional physical indicators also have a high burden of MNDs.

Causes of MNDs

MNDs are only one form of undernutrition. Other forms of undernutrition are more readily visible and, for this reason, MNDs are often referred to as hidden hunger [5]. At the most basic level, MNDs, like all forms of undernutrition, occur due to insufficient intake or sufficient intakes combined with impaired absorption due to infection, disease, or inflammation [6, 7]. For infants, MNDs may result from maternal MND in utero or rapid postnatal growth [8]. The antecedents to these immediate causes for undernutrition are complex and can be fully appreciated by examining the 2013 UNICEF Conceptual Framework for the Determinants of Undernutrition (fig. 2) [6]. The underlying causes that contribute to the immediate causes include food insecurity, inadequate care or feeding practices, and an unhealthy environment with inadequate access to health services. Nutritional status is greatly impacted by infection [9]. Infection is the leading cause of child mortality [10]. Acute respiratory infection and diarrhea are the most common causes of infant mortality, and MNDs contribute greatly to the immune response [11]. Undernutrition is the leading cause of immunodeficiency worldwide [7].

The basic root cause of most undernutrition is poverty. As a result, low- and middle-income countries have the highest burden of MNDs; however, MNDs exist even in certain population groups in higher-income countries. The United Nation's Millennium Development Goals include eradicating extreme poverty and hunger as their priority goal [12]. Like poverty, undernutrition and MNDs often occur as part of an intergenerational cycle (fig. 3). During pregnancy and lactation, there are increased macro- and micronutrient requirements [13]. Pregnant mothers without optimal nutritional intakes have children with suboptimal nutritional status including impaired physical and mental development, setting the infant on a deleterious course of stunting, increased likelihood for infection, and developmental delays [14]. In time, these children themselves enter their reproductive years at a nutritional disadvantage and the cycle continues. Furthermore, adults with nutritional disadvantages often have a lower work capacity due to the early developmental delays mediated through a lack of education [14]. Thus, both malnutrition and poverty often track together and operate synergistically.

MNDs of Greatest Public Concern

Iron

Iron is a mineral that is an essential component of hemoglobin, myoglobin, enzymes, and cytochromes and is necessary for oxygen transport and cellular respiration [15]. Iron also is critical for optimal growth and cognitive function. Two forms of iron exist, namely heme and nonheme. Heme iron is found in animal sources, whereas nonheme iron is found in plants and used in fortification. Neither form of iron is highly bioavailable; heme iron bioavailability is estimated to be 12–25%, and nonheme iron is <5% bioavailable [1, 15]; however, with the exception of menstruating and pregnant women, iron in vivo is very highly conserved [15].

Acute respiratory infection and diarrhea are the most common causes of infant mortality, and MNDs contribute greatly to the immune response.

Iron deficiency is the most common MND in the world, affecting more than 30% of the world's population, an estimated 2 billion people [16]. Iron deficiency causes anemia and disrupts optimal function of both the endocrine and immune systems. Iron deficiency is particularly common during pregnancy because of increased requirements for fetal growth and development. Maternal iron deficiency is associated with low birth weight, premature delivery, and a host of perinatal complications, especially hemorrhage. Anemia is estimated to contribute to 20% of maternal deaths [16]. Children born to iron-deficient mothers are more likely to have low iron stores, to suffer from impaired physical and cognitive development, and to have suboptimal immune systems. Early-life iron status substantially influences human potential at the individual and country level [16–18]. Iron deficiency

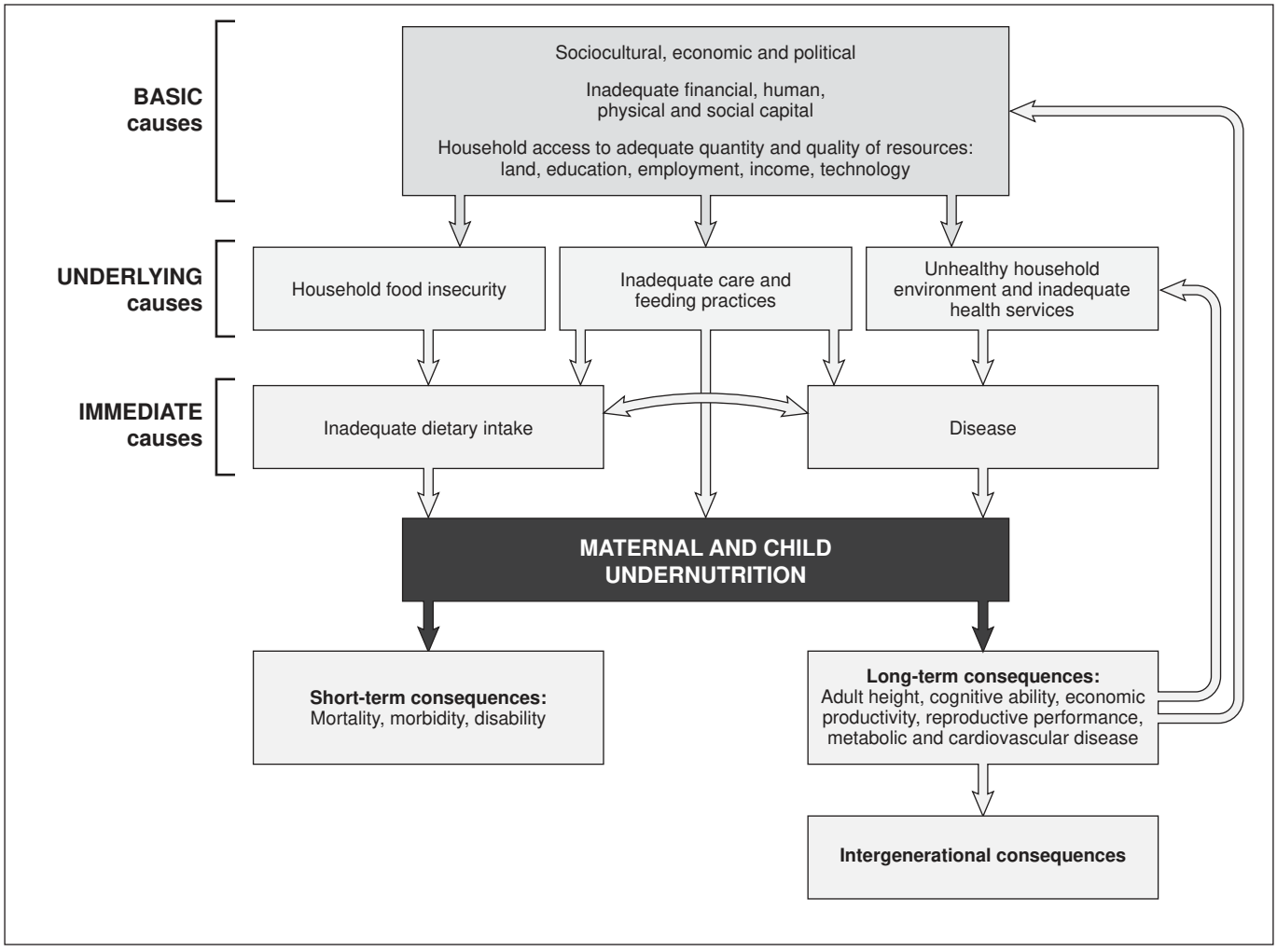


Fig. 2. Updated UNICEF Conceptual Framework for the Determinants of Undernutrition (adapted from UNICEF [6]).

may also be associated with enhanced absorption of environmental metal toxins such as cadmium [19].

Iron status is typically assessed through plasma ferritin, transferrin saturation, and hemoglobin concentrations. Ideally, all of these biomarkers are available to make an assessment; however, routinely, only 1 or 2 of these are available in screening and assessment. Hemoglobin is most often used to determine anemia. Ferritin is reflective of body iron stores; but, because it is also an acute-phase protein, ferritin will be elevated in acute or chronic disease, and tests may yield misleading results. Globally, the World Health Organization (WHO) estimates that 25% of the population (1.62 billion people; CI 1.50–1.74 billion) has anemia [16]. Preschool children (47.4%) and pregnant women (41.8%) have the highest prevalence overall. Africa (67.6 and 57.1%) and Southeast Asia (65.5 and 48.2%) have the highest burden of anemia in preschool children and pregnant women, respectively [16].

Women in perinatal life stages and their infants (<6 months of age) are considered to be at the highest risk for iron deficiency. Routine iron supplementation in pregnancy and infancy is recommended in areas without endemic malaria [20]. Iron supplementation in those with malaria may exacerbate the falciparum-related complications and mortality [20]. Recently, it has been proposed to dovetail efforts with iron nutriture in conjunction with malaria control programs [21]. Fortification programs with iron exist in several countries with the food vehicles of choice ranging from flours, dairy products, condiments, sugar, and salt to infant formulas. Fortification and supplementation may be appropriate for areas with high concentrations of vegetarians.

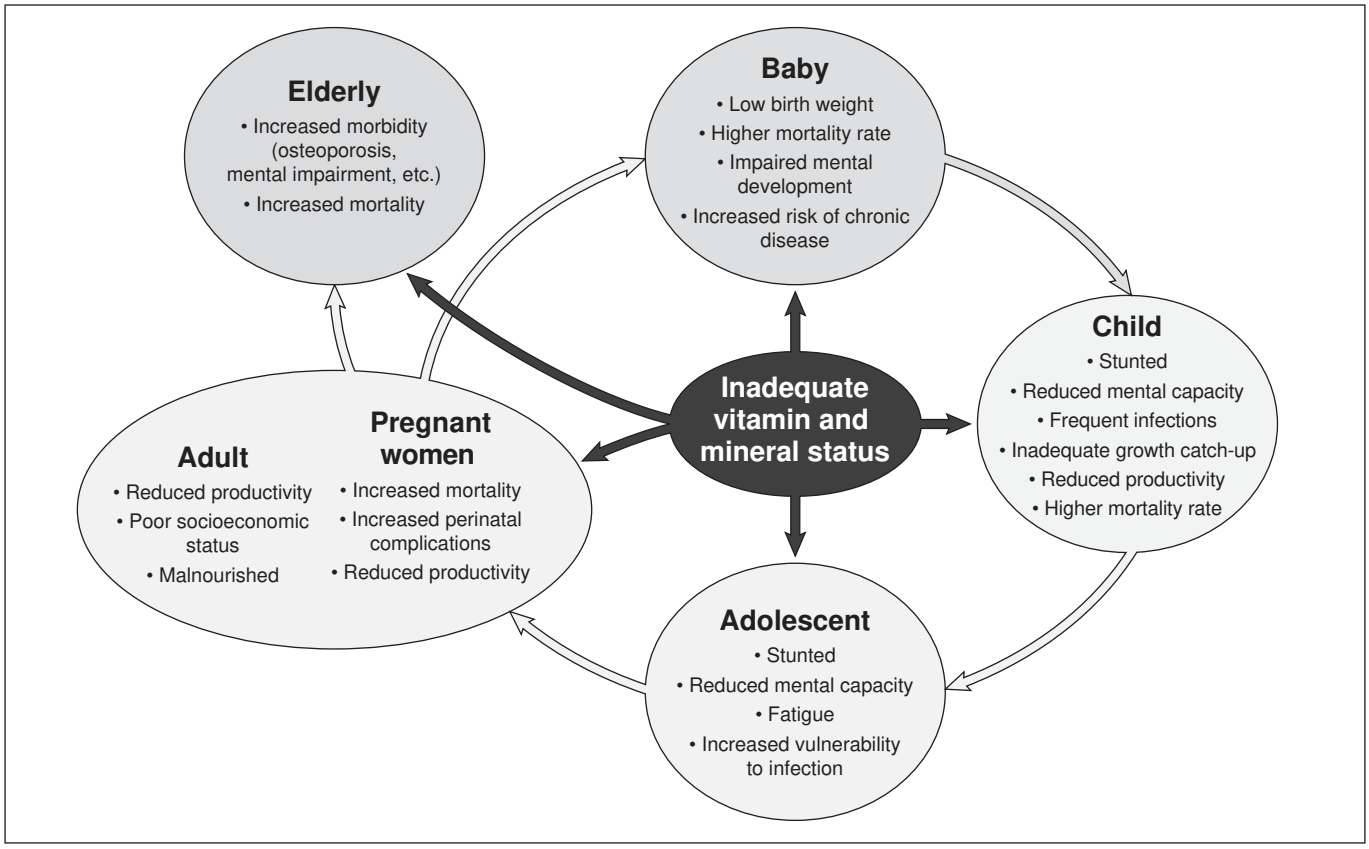


Fig. 3. The conceptual framework for the cycle of micronutrient inadequacies across the life span (adapted from ACC/SCN [14]).

Vitamin A

Vitamin A is a fat-soluble vitamin that has multiple roles in the body including vision, cell differentiation, immune function, reproduction, and organ and bone formation and growth. Vitamin A comes from animal sources in the diet preformed as retinol or retinyl esters, or from provitamin A carotenoids found in plant sources. Provitamin A carotenoids, which exhibit differential vitamin A activity, are converted to the active forms of the vitamin (retinal and retinoic acid) for use by the body.

Vitamin A deficiency (VAD) has been associated with increased rates and severity of infections and is a primary cause of childhood morbidity and mortality in the developing world, particularly in Africa and Southeast Asia [22]. VAD is the leading cause of preventable blindness in children. VAD causes xerophthalmia, a series of ocular manifestations like night blindness, Bitot's spots, and corneal ulcerations and lesions [1]. The WHO estimates that 250–500 million children are blind because of VAD, and half of these children will die within a year of vision loss. VAD is also common in pregnancy in lower-income countries with estimates ranging from 10 to 20%. Very little is known about older children and adults with regard to vitamin A status; however, because VAD tends to cluster in families, communities, and regions, we can assume that vitamin A status is low in areas with child and pregnancy burden. Subclinical VAD affects far greater numbers of individuals, particularly in Africa and Asia [23].

VAD is characterized using serum retinol, with hyporetinolemia defined as concentrations <0.70 μmol/l, clinical parameters determined via eye exam, and/or functional indicators like night blindness. Often, VAD occurs in clusters, so prevention and treatment schedules are in place to provide high-dose oral supplementation intermittently (i.e. semi-annually, every 4–6 months, etc.) based on age (beginning at birth), life stage, and severity of deficiency. Vitamin A can also be added as a fortificant to the food supply. For example, in Guatemala, vitamin A

is added to sugar [24] in addition to intermittent supplementation programs, together yielding a low rate of VAD determined by serum retinol [25]. Despite the Cochrane reviews limiting maternal, neonatal, and infant vitamin A supplementation in developing countries [26, 27], continued emphasis should be placed on vitamin A supplementation programs in Southeast Asia given the clearly documented effects on ocular health and mortality [22, 28, 29].

Iodine

Iodine is a trace mineral, and its primary function is in the synthesis of thyroid hormone. Approximately 60% of the total body pool of iodine is stored in the thyroid gland [30]. Thyroid hormone is necessary for regulation of human growth and development. Iodine in foods and dietary supplements is generally either in a salt or organic form [31]. The iodine content of many foods is dependent upon soil concentration of the element and fertilization and irrigation practices [15]. The iodine content of fish and seaweed is also highly variable [32]. Iodine stores in vivo during a sufficient state are estimated at 60 μg, and during deficiency, stores are much lower in the 10- to 20-μg range [30]. Iodine absorption and utilization can be impaired by the presence of goitrogens [33] or exposure to percolate, disulfides, and thiocyanates (from tobacco exposure) [34]. Hypothyroidism can occur in individuals when dietary intakes are lower than 10–20 μg daily, and it is frequently accompanied by goiter [15].

Thyroid hormones are essential for optimal fetal and postnatal central nervous system growth and development [35, 36]. Maternal iodine requirements increase by more than 50% during pregnancy to meet fetal needs and because of enhanced renal clearance of iodine and alternated iodine metabolism during pregnancy [37]. Maternal iodine deficiency, particularly when it occurs during early pregnancy, can lead to irreversible neurological complications and mental retardation in the offspring referred to as iodine deficiency disorder (IDD) [35]. IDD represents a spectrum of diseases affecting the entire life course. From infancy to adulthood, IDD includes goiters, impaired mental function, and hypo- or hyperthyroidism. At the most severe form, in utero iodine deficiency can result in cretinism [38].

Typically, iodine status is assessed via urinary iodine content because it is a reliable indicator of recent intake as approximately 90% of ingested dietary iodine is excreted in urine across the range of dietary intakes [30, 36, 39] and because renal clearance is relatively constant [40]. The WHO defines iodine insufficiency in children and adults as a median urinary iodine concentration of <100 μg/l. During pregnancy, different urinary iodine excretion rates may occur [41]; therefore, during pregnancy, sufficiency status is defined as a median urinary iodine concentration of 150–249 μg/l, with concentrations <150 μg/l defined as insufficient [42]. It is intuitive to think that thyroid hormones may serve as a biomarker of iodine status; however, thyroid hormones, with the exception of thyroglobulin [43], do not appear to be adequately sensitive to change in iodine status [44, 45].

Pregnant females and infants (<24 months of age) are the population groups at highest risk of iodine deficiency. As previously stated, in pregnancy, requirements are greatly increased, and infants have the highest requirements per kg of body weight of any age group [30]. Exclusively breastfed infants may also be at risk if not provided iodine in complementary foods [46]. While iodine is found in breast milk [15], its concentration is dependent on maternal intake and status [47, 48].

Globally, ~2 billion are estimated to have inadequate iodine status [49, 50]. As many as half of the European population (52%, 459.7 million people) is estimated to have inadequate iodine status and more than 500 million individuals are affected in Southeast Asia. While the group of highest concern is pregnant females, we have no global estimation of the burden of iodine deficiency in this group [51]. Approximately 30% (241 million) of the world's school-aged children have insufficient iodine intakes [52].

Universal salt iodization is the most practical strategy to reduce iodine deficiency globally.

Many countries of the world (~120 countries) have fortified table salt with iodine because iodine is found naturally in very few foods [53]. Salt is traditionally the food vehicle chosen for iodization because it is universally consumed at a relatively consistent intake level; the process of adding iodine to salt is very cheap at less than 5 cents per person per year. Global estimates from the UNICEF indicate that 68% of households have adequate table salt iodine [51]. Universal salt iodization refers to all salts used within a country, regardless if iodine is in table salt or in salt used by the food industry. Very few countries in the world have achieved universal salt iodization, and often, the food industry does not use iodized salt in food production [30]. Iodine can also be found in dietary supplements. Universal salt iodization is the most practical strategy to reduce iodine deficiency globally. Correcting

iodine deficiency does have some health risks for certain populations in terms of thyroid function and should be considered within the context of each country separately [38].

Folate

Folate is a generic term for multiple forms of the essential B vitamin. Folate naturally occurs in foods, whereas folic acid is a synthetic form of the vitamin that is used in fortified foods and in dietary supplements. Folic acid is much more bioavailable than folate naturally occurring in foods and when ingested is converted by dihydrofolate reductase to the dihydrofolate and then the tetrahydrofolate form of folate; these reduced compounds are identical to those that would arise from ingestion of natural folate. Folate is essential for synthesis of purines and thymidylate and, therefore, is involved in DNA synthesis, stability, and repair. Folate is also involved in one carbon metabolism and, as such, can alter DNA methylation, which is an important epigenetic determinant in gene expression, in the maintenance of DNA integrity, and in the development of mutations.

Folate deficiency can be determined by serum, plasma, or erythrocyte folate concentrations. Folate deficiency is very low in countries with mandatory or voluntary folic acid fortification programs [52]. Folate deficiency causes megaloblastic or macrocytic anemia and increases the likelihood for pregnancies affected by neural tube defects. The global prevalence of anemia secondary to folate deficiency is very low. Folate deficiency in pregnancy has also been associated with low birth weight, preterm delivery, and fetal growth retardation [53, 54]. Globally, only about 30% of women take folic acid supplements prior to conception [55]. No good estimates of global folate deficiency exist for those considered to be of highest risk: women of reproductive age, pregnant females, and young children [56].

Folic acid supplementation in the periconceptional period unequivocally reduces the occurrence of neural tube defects [57, 58]. For this reason, the governments of both the United States and Canada instituted national fortification programs with folic acid to enhance the diets of reproductive-aged females [59–61], and neural tube defect rates decreased in both the United States [62] and Canada [63–65]. Since this time, more than 75 countries have instituted folic acid fortification programs, and the amount of folic acid added varies by country [66]. Several more countries allow folic acid to be added to flour on a voluntary basis, while other countries fortify with iron and other B vitamins, but not with folic acid [67, 68]. Concerns exist about high exposure to folic acid through fortification practices and supplements among nontarget groups (i.e. females not in the reproductive age) like children, males, and the elderly.

Zinc supplementation during pregnancy is associated with a significant reduction in preterm births without an effect on infant birth weight.

Zinc

Zinc is an essential mineral that is involved in multiple aspects of cellular metabolism [69]. Zinc is required for the activity of more than 200 enzymes, and it is critical for immune system function, cell division, and protein and DNA synthesis [15]. Zinc is also required for normal growth and development from in utero until puberty. The human body has no long-term storage system for zinc, so consistent dietary intake is needed to sustain all of these functions and maintain the relatively small exchangeable zinc pool. Because of its diverse functions in vivo, it has been difficult to develop a single biomarker of zinc status; plasma zinc concentrations have been used, but this biomarker is nonspecific [69]. Zinc is primarily found in animal products and seafood. Similar to iron, zinc absorption is impaired by phytates, fiber, and lignins, all of which impair the bioavailability from nonanimal sources of zinc. Calcium and casein may reduce the bioavailability of zinc from cow's milk. Zinc is present in human breast milk.

Zinc status has been associated with reduced incidence, severity, and mortality due to diarrhea and respiratory and malarial infection (as summarized by Patel et al. [70] and Black et al. [71]). Infection is known to compromise dietary intake and micronutrient absorption, and diarrhea can contribute to losses in key micronutrients. A recent Cochrane review of randomized clinical trials (80 trials with 205,401 participants) in children 6 months to 12 years of age indicates a positive effect for zinc supplementation in reducing all-cause and infectious disease mortality and a small positive impact on linear growth [72]. A recent clinical trial in full-term infants in India receiving placebo or 5 mg zinc daily indicated a significantly higher skinfold thickness for infants in the treatment group when compared to the placebo group, without a difference observed in linear growth [73]. The

effect of zinc on anthropometry, but not linear growth, was also seen in a Peruvian clinical trial in which mothers were supplemented prenatally with zinc; infants born to zinc-supplemented mothers had greater weight gain, higher calf and chest circumference, and more calf muscle area than children born to mothers without zinc supplementation [74]. Zinc supplementation during pregnancy is associated with a significant reduction in preterm births without an effect on infant birth weight [75].

Supplementation as a strategy requires that provision of supplements is feasible and that adequate educational programs are in place to garner compliance.

Deficiency in zinc is thought to be one of the primary causes of morbidity in developing countries and, yet, surprisingly little is known about the status of the world [76]. Given the issues concerning the assessment of zinc status by biomarkers, estimates of inadequacy are largely based on the prevalence of child stunting, estimates of dietary intakes, and the availability of zinc from the food supply [76]. Globally, it is estimated that 17.3% of the population has inadequate zinc intakes, with the highest estimates in Africa (23.9%) and Asia (19.4%). Pregnant females and their young children are the highest-risk groups for zinc deficiency. Currently, the WHO and UNICEF recommend provision of zinc supplements for 10–14 days along with oral rehydration therapy for acute diarrhea; however, no routine supplementation recommendations currently exist for the prevention of zinc deficiency.

Multiple MNDs

Single MNDs rarely happen in isolation; more often, multiple MNDs are occurring simultaneously [1, 5]. Multiple MNDs appear to be mainly driven by a lack of food security, defined by the Food and Agriculture Organization (1996) at the World Food Summit as follows: 'when all people at all times have access to sufficient, safe, nutritious food to maintain a healthy and active life' [77]. Many factors contribute to food security and MNDs, including lack of available quality and diversity of foods, poverty in certain population groups, lack of access to health care and nutrition education, subsistence farming practices, volatile food prices, urbanization, high rates of infection (both acute and chronic), and issues with sanitation, climate change, and access to potable water [5, 78–80].

Estimates of multiple MNDs have been difficult to ascertain due to limitations in the available data. Muthayya et al. [5] estimated global hidden hunger indices for iron, vitamin A, and zinc together and determined that 18 of the 20 countries with the highest burden of multiple MNDs are in Africa, with Afghanistan and India (WHO region Asia) completing the list. Iodine may be the exception to the clustering of MNDs, and iodine deficiency is region specific and does not necessarily track with countries with a high hidden hunger [5]. However, deficiency in other micronutrients, like selenium, iron, and vitamin A, can exacerbate iodine deficiency by altering thyroid function [81–83].

Strategies and Interventions

Several options exist to combat MNDs, including supplementation, fortification, and food-based approaches like dietary diversification. The choice of intervention strategy or strategies should depend on the cause, severity, and scope of the MND. The intervention strategy should always try to eliminate the root cause and must be considered within the cultural preferences [2]. Understanding the sustainability and feasibility of interventions is critical a priori. Ensuring continued access to the intervention or strategy is of upmost importance depending on the intervention.

In general, supplementation is the approach to utilize when an MND is severe and requires a therapeutic approach to treatment, or for the purpose of prevention [2]. Supplementation can be daily or intermittently (i.e. 1–2 times per year). Widespread success has been achieved with vitamin A supplementation for the prevention of night blindness and infant mortality; the success is in part due to the intermittent requirements for supplementation (i.e. 1–2 times per year vs. daily). Supplementation as a strategy requires that provision of supplements is feasible and that adequate educational programs are in place to garner compliance. Ideally, supplementation is limited to these purposes because supplementation does not address the root cause of the deficiency. However, supplementation offers a relatively cost-effective short-term solution to MNDs. There are growing concerns that supplemental nutrients may exhibit different physiological responses and absorption than nutrients found in food; this has been noted for folic acid, zinc, and iron.

Food fortification is a more long-term strategy to combat MNDs than supplementation. Fortification differs

from supplementation in that most of the population is exposed to fortification, whereas supplementation is targeted toward certain individuals or groups. Fortification generally requires policy and procedural changes and engagement of the food industry and, thus, requires substantially more time to implement than supplementation. However, if an MND is widespread, fortification is the tool with the greatest capacity to reach the most within a country. The choice of the food vehicle is equally critical as the amount of fortificant to add; ideally, fortification will enhance the intakes at the lowest tail of the intake distribution without causing excessive intakes among those with already high intakes. Using more than one food vehicle and understanding the current intake patterns have been recommended to avoid excessive intakes of nutrients caused by fortification [84]. An emerging option for enhancing micronutrient intakes is by biofortification. Biofortification utilizes recombinant DNA technology or fermentation procedures to alter the micronutrient content, but not the appearance, taste, or smell, of an existing food or crop [85]. The use of nanotechnology to create new delivery systems and storage forms of micronutrients is also a rapidly evolving field [86, 87]. Continued monitoring of any widespread food fortification program is necessary.

An alternative to fortification of the food supply are home-based fortification systems in which micronutrients are added to foods that are already consumed within the home. This strategy, often called 'home fortification', avoids the policy and food industry involvement and allows for targeted intervention in individuals in need. Most often, home fortification involves adding multiple micronutrients to a semi-solid food prepared in the home. The micronutrients generally come in packets or sachets. Home-based fortification programs were ongoing in 22 countries as of 2011. In one trial in Pakistan, the use of home fortification with multiple micronutrients in children aged 6–18 months was associated with a significant decline in iron deficiency anemia but was also associated with increased rates of diarrhea [88]. A Cochrane review of home fortification suggests that home fortification with multiple micronutrients is effective for reducing anemia and iron deficiency but cautions that such products be used judiciously in areas with malaria as limited data exist at present. Issues have been raised concerning the compliance to home fortification systems and also concerning an increase in pollution due to the foil-lined packaging needed to preserve the micronutrients [89].

While optimal in terms of sustainability, changing the dietary patterns of individuals and communities may be difficult to achieve. Dietary diversification may not be possible due to limited food availability within certain regions. However, resources could be directed towards agricultural practices to change food availability; this is a sustainable mechanism to ensure access to a particular food or foods. However, a change in dietary patterns usually is not enough to ameliorate certain deficiencies such as iodine deficiency given that the root cause is the geographic location in which foods, animals, and seafood are produced. Food-based approaches can include additions or changes to complementary feeding practices when infants start to consume foods other than breast milk or infant formula. This transition period between liquid and solid nourishment is often accompanied by MND in developing countries. Provision of meals served outside the home, like school lunches, provides one opportunity to enhance micronutrient intakes of school-aged children. Several fortified food products exist to add micronutrients to the diet without changing dietary patterns, such as biscuits or noodles which have been delivered by aid programs either intermittently or consistently depending on the scope of the problem. Finally, if infection is the root cause of an MND, none of these intervention strategies alone would combat the problem of MNDs. In such instances, deworming or other public health control measures are needed [2]. Thus, those instituting interventions must adequately address all root causes of the MND in determining which strategy or combination of strategies to employ.

Resources could be directed towards agricultural practices to change food availability.

Economic Impact of MNDs

Given the widespread impacts that MNDs have across the life span, it is not surprising that they cause tremendous financial burdens to societies [71]. Adequate nutritional status is a primary building block of human capital [90, 91]. Early-life nutrition has long-lasting impacts on the individual and society, including poorer adult health, less educational attainment, diminished work capacity, and lower lifetime earning potential [71, 92]. An estimated 11% of the gross national product in Africa and Asia are lost each year secondary to the high burden of malnutrition. Estimates of increased earning potential due to early-life nutrition interventions are as high as 50% (e.g.

boys in Guatemala). For this reason, the Expert Panel for the Copenhagen Consensus Center determined nutrition through bundled micronutrient interventions as the top recommended global health issue to target resources toward in 2012.

Disclosure Statement

Regan L. Bailey and Keith P. West Jr. have no conflicts of interest to disclose. Robert E. Black presides on the governing boards of the Micronutrient Initiative and Vitamin Angels; he is also a member of the Creating Shared Value Advisory Council of Nestlé.

References

1 West KP, Stewart CP, Caballero B, Black RE: Nutrition; in Merson MH, Black RE, Mills AJ (eds): Global Health: Diseases, Programs, Systems, and Policies, ed 3. Burlington, Jones and Bartlett Learning, 2012, pp 271–304.
2 Committee on Micronutrient Deficiencies, Board on International Health, Food and Nutrition Board; Howson CP, Kennedy ET, Horwitz A: Prevention of Micronutrient Deficiencies: Tools for Policymakers and Public Health Workers. Washington, National Academy Press, 1998.
3 Food and Nutrition Board: Dietary Reference Intakes: Applications in Dietary Assessment. Washington, National Academy Press, 2000.
4 Strimbu K, Tavel JA: What are biomarkers? Curr Opin HIV AIDS 2010;5:463–466.
5 Muthayya S, Rah JH, Sugimoto JD, et al: The global hidden hunger indices and maps: an advocacy tool for action. PLoS One 2013; 8:e67860.
6 United Nations Children's Fund (UNICEF): Improving Child Nutrition: The Achievable Imperative for Global Progress. New York, UNICEF, 2013. http://www.unicef.org/infobycountry/indonesia_statistics.html#119 (accessed April 16, 2014).
7 Katona P, Katona-Apte J: The interaction between nutrition and infection. Clin Infect Dis 2008;46:1582–1588.
8 Zlotkin S: Micronutrient deficiencies and effect of supplements on correcting them. Nestle Nutr Workshop Ser Pediatr Program 2011;68:127–134; discussion 134–140.
9 Bhutta ZA, Das JK, Rizvi A, et al: Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet 2013;382:452–477.
10 Liu L, Johanson HL, Cousens S, et al: Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151–2161.
11 Bhutta ZA, Das JK, Walker N, et al: Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? Lancet 2013;381: 1417–1429.
12 United Nations Millennium Project: Millennium Development Goals. 2000. http://www.unmillenniumproject.org/goals/index.htm (accessed April 9, 2014).
13 Picciano MF: Pregnancy and lactation: physiological adjustments, nutritional requirements and the role of dietary supplements. J Nutr 2003;133:1997S–2002S.
14 ACC/SCN: Fourth Report on the World Nutrition Situation: Nutrition throughout the Life Cycle. Geneva, ACC/SCN in Collaboration with IFPRI, 2000.
15 Food and Nutrition Board: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, National Academy Press, 2001.
16 de Benoist B, McLean E, Egli I, Cogswell M: Worldwide Prevalence of Anaemia 1993–2005: WHO Global Database on Anaemia. Geneva, World Health Organization, 2008.
17 Lozoff B, Smith JB, Kaciroti N, et al: Functional significance of early-life iron deficiency: outcomes at 25 years. J Pediatr 2013;163: 1260–1266.
18 Flour Fortification Initiative, GAIN, Micronutrient Initiative, USAID, The World Bank, UNICEF: Investing in the Future: A United Call to Action on Vitamin and Mineral Deficiencies – Global Report 2009. Ottawa, 2009.
19 Silver MK, Lozoff B, Meeker JD: Blood cadmium is elevated in iron deficient US children: a cross-sectional study. Environ Health 2013;12:117.
20 World Health Organization: Conclusions and recommendations of the WHO consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas. Food Nutr Bull 2007; 28(4 suppl):S621–S627.
21 Stoltzfus RJ: Iron and malaria interactions: programmatic ways forward. Adv Nutr 2012; 3:579–582.
22 Sommer A, Tarwotjo I, Hussaini G, Susanto D: Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2:585–588.
23 World Health Organization: Global Prevalence of Vitamin A Deficiency in Populations at Risk 1995–2005. WHO Global Database on Vitamin A Deficiency. Geneva, World Health Organization, 2009.
24 Dary O, Martínez C, Guamuch M: Sugar fortification with vitamin A in Guatemala: the program's successes and pitfalls; in Freire WB (ed): Nutrition and an Active Life: From Knowledge to Action. Washington, Pan American Health Organization, 2005, pp 43–59.
25 INCAP/USAID: Sistema de Vigilancia de la Malnutrición en Guatemala (SIVIM). Presentation at the Latin American Congress of Nutrition, 2012. http://www.incap.int/index.php/es/publicaciones/doc_view/287-presentacion-sivin-slan-final (accessed August 16, 2014).
26 Gogia S, Sachdev HS: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less. Cochrane Database Syst Rev 2011; 10:CD007480.
27 Haider BA, Bhutta ZA: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries. Cochrane Database Syst Rev 2011;10:CD006980.
28 Tarwotjo I, Katz J, West KP Jr, et al: Xerophthalmia and growth in preschool Indonesian children. Am J Clin Nutr 1992;55:1142–1146.
29 Tarwotjo I, Sommer A, Soegiharto T, et al: Dietary practices and xerophthalmia among Indonesian children. Am J Clin Nutr 1982; 35:574–581.
30 Zimmermann MB: Iodine deficiency. Endocr Rev 2009;30:376–408.
31 Leung AM, Pearce EN, Braverman LE: Iodine content of prenatal multivitamins in the United States. N Engl J Med 2009;360:939–940.
32 Teas J, Pino S, Critchley A, Braverman LE: Variability of iodine content in common commercially available edible seaweeds. Thyroid 2004;14:836–841.
33 Doerge DR, Sheehan DM: Goitrogenic and estrogenic activity of soy isoflavones. Environ Health Perspect 2002;110(suppl 3):349–353.
34 Leung AM, Pearce EN, Braverman LE: Perchlorate, iodine and the thyroid. Best Pract Res Clin Endocrinol Metab 2010;24:133–141.
35 Zimmermann MB: Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. Am J Clin Nutr 2009;89:668S–672S.
36 Tayie FA, Jourdan K: Hypertension, dietary salt restriction, and iodine deficiency among adults. Am J Hypertens 2010;23:1095–1102.

37 Glinoer D: The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404–433.
38 Zimmermann MB, Jooste PL, Pandav CS: Iodine-deficiency disorders. Lancet 2008; 372:1251–2162.
39 Hurrell RF: Bioavailability of iodine. Eur J Clin Nutr 1997;51(suppl 1):S9–S12.
40 Alexander WD, Harden RM, Harrison MT, Shimmins J: Some aspects of the absorption and concentration of iodide by the alimentary tract in man. Proc Nutr Soc 1967;26:62–66.
41 Laurberg P, Andersen S, Bjarnadóttir RI, et al: Evaluating iodine deficiency in pregnant women and young infants – complex physiology with a risk of misinterpretation. Public Health Nutr 2007;10:1547–1552; discussion 1553.
42 World Health Organization, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders: Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination. A Guide for Programme Managers, ed 3. 2007. http://www.unicef.org/ukraine/2_Guide_for_IDD_managers_eng.pdf (accessed December 19, 2012).
43 Vejbjerg P, Knudsen N, Perrild H, et al: Thyroglobulin as a marker of iodine nutrition status in the general population. Eur J Endocrinol 2009;161:475–481.
44 Thomson CD, Colls AJ, Conaglen JV, et al: Iodine status of New Zealand residents as assessed by urinary iodide excretion and thyroid hormones. Br J Nutr 1997;78:901–912.
45 Paul T, Meyers B, Witorsch RJ, et al: The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism 1988;37:121–124.
46 Andersson M, Aeberli I, Wüst N, et al: The Swiss iodized salt program provides adequate iodine for school children and pregnant women, but weaning infants not receiving iodine-containing complementary foods as well as their mothers are iodine deficient. J Clin Endocrinol Metab 2010;95:5217–5224.
47 Semba RD, Delange F: Iodine in human milk: perspectives for infant health. Nutr Rev 2001;59:269–278.
48 Dorea JG: Iodine nutrition and breast feeding. J Trace Elem Med Biol 2002;16:207–220.
49 de Benoist B, McLean E, Andersson M, Rogers L: Iodine deficiency in 2007: global progress since 2003. Food Nutr Bull 2008;29:195–202.
50 Andersson M, Karumbunathan V, Zimmermann MB: Global iodine status in 2011 and trends over the past decade. J Nutr 2012;142: 744–750.
51 UNICEF: Progress for Children. 2007. http://www.unicef.org/progressforchildren/2007n6/index_41509.htm (accessed April 10, 2014).
52 Pfeiffer CM, Johnson CL, Jain RB, et al: Trends in blood folate and vitamin B-12 concentrations in the United States, 1988–2004. Am J Clin Nutr 2007;86:718–727.
53 World Health Organization: Conclusions of a WHO technical consultation on folate and vitamin B12 deficiencies. Food Nutr Bull 2007;29(2 suppl):S238–S244.
54 Tamura T, Picciano MF, McGuire MK: Folate in pregnancy and lactation; in Bailey LB (ed): Folate in Health and Disease, ed 2. Boca Raton, CRC Press, Taylor and Francis Group, 2010, pp 111–131.
55 Ray JG, Singh G, Burrows RF: Evidence for suboptimal use of periconceptional folic acid supplements globally. BJOG 2004;111:399–408.
56 McLean E, de Benoist B, Allen LH: Review of the magnitude of folate and vitamin B12 deficiencies worldwide. Food Nutr Bull 2008; 29(2 suppl):S38–S51.
57 Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet 1991;338:131–137.
58 Czeizel AE, Dudas I: Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327:1832–1835.
59 Food and Drug Administration: Food additives permitted for direct addition to food for human consumption; folic acid (folacin), final rule. Fed Reg 1996;61:8798–8807.
60 Food and Drug Administration: Food labeling: health claims and label statements; folate and neural tube defects. Fed Reg 1996;61: 8752–8781.
61 Food and Drug Administration: Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid. Fed Reg 1996;61:8781–8797.
62 Center for Disease Control and Prevention (CDC): Spina bifida and anencephaly before and after folic acid mandate – United States, 1995–1996 and 1999–2000. MMWR Morb Mortal Wkly Rep 2004;53:362–365.
63 Persad VL, Van den Hof MC, Dubé JM, Zimmer P: Incidence of open neural tube defects in Nova Scotia after folic acid fortification. CMAJ 2002;167:241–245.
64 Ray JG, Meier C, Vermeulen MJ, et al: Association of neural tube defects and folic acid food fortification in Canada. Lancet 2002; 360:2047–2048.
65 De Wals P, Rusen ID, Lee NS, et al: Trend in prevalence of neural tube defects in Quebec. Birth Defects Res A Clin Mol Teratol 2003; 67:919–923.
66 Flour Fortification Initiative, FFI Global Progress. 2012. http://www.ffinetwork.org/global_progress/ (accessed August 3, 2014).
67 Chen LT, Rivera MA: The Costa Rican experience: reduction of neural tube defects following food fortification programs. Nutr Rev 2004;62:S40–S43.
68 Food Safety Authority of Ireland: Currently No Need for Mandatory Fortification – Increased Folate Status Negates Mandatory Folic Acid Fortification at This Time. 2009. https://www.fsai.ie/news_centre/press_releases/11032009.html (accessed August 3, 2014).
69 King JC: Zinc: an essential but elusive nutrient. Am J Clin Nutr 2011;94:679S–684S.
70 Patel A, Mamtani M, Dibley MJ, et al: Therapeutic value of zinc supplementation in acute and persistent diarrhea: a systematic review. PLoS One 2010;5:e10386.
71 Black RE, Victora CG, Walker SP, et al: Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427–451.
72 Mayo-Wilson E, Junior JA, Imdad A, et al: Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age. Cochrane Database Syst Rev 2014;5:CD009384.
73 Radhakrishna KV, Hemalatha R, Geddam JJ, et al: Effectiveness of zinc supplementation to full term normal infants: a community based double blind, randomized, controlled, clinical trial. PLoS One 2013;8:e61486.
74 Iannotti LL, Zavaleta N, León Z, et al: Maternal zinc supplementation and growth in Peruvian infants. Am J Clin Nutr 2008;88:154–160.
75 Mori R, Ota E, Middleton P, et al: Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev 2012;7:CD000230.
76 de Benoist B, Darnton-Hill I, Davidsson L, et al: Conclusions of the Joint WHO/UNICEF/IAEA/IZiNCG Interagency Meeting on Zinc Status Indicators. Food Nutr Bull 2007;28(3 suppl):S480–S484.
77 Food and Agriculture Organization: Rome Declaration on World Food Security. 1996. http://www.fao.org/docrep/003/w3613e/w3613e00.HTM (accessed April 1, 2014).
78 Stewart CP, Iannotti L, Dewey KG, et al: Contextualising complementary feeding in a broader framework for stunting prevention. Matern Child Nutr 2013;9(suppl 2):27–45.
79 The other oil problem. The world's growing appetite for cheap palm oil is destroying rain forests and amplifying climate change. Sci Am 2012;307:10.
80 Carlson KM, Curran LM, Ratnasan D, et al: Committed carbon emissions, deforestation, and community land conversion from oil palm plantation expansion in West Kalimantan, Indonesia. Proc Natl Acad Sci USA 2012;109:7559–7564.
81 Zimmermann M, Adou P, Torresani T, et al: Persistence of goiter despite oral iodine supplementation in goitrous children with iron deficiency anemia in Côte d'Ivoire. Am J Clin Nutr 2000;71:88–93.
82 Zimmermann MB, Wegmueller R, Zeder C, et al: Dual fortification of salt with iodine and micronized ferric pyrophosphate: a randomized, double-blind, controlled trial. Am J Clin Nutr 2004;80:952–959.

83 Zimmermann MB, Jooste PL, Mabapa NS, et al: Vitamin A supplementation in iodine-deficient African children decreases thyrotropin stimulation of the thyroid and reduces the goiter rate. Am J Clin Nutr 2007;86:1040–1044.
84 Guamuch M, Dary O, Rambelson Z, et al: Model for estimating nutrient addition contents to staple foods fortified simultaneously: Mexico and Kampala data. Ann NY Acad Sci 2014;1312:76–90.
85 Rajasekaran A, Kalaivani M: Designer foods and their benefits: a review. J Food Sci Technol 2013;50:1–16.
86 Sonkaria S, Ahn SH, Khare V: Nanotechnology and its impact on food and nutrition: a review. Recent Pat Food Nutr Agric 2012;4:8–18.
87 Srinivas PR, Philbert M, Vu TQ, et al: Nanotechnology research: applications in nutritional sciences. J Nutr 2010;140:119–124.
88 Soofi S, Cousens S, Iqbal SP, et al: Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial. Lancet 2013;382:29–40.
89 De-Regil LM, Suchdev PS, Vist GE, et al: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. Cochrane Database Syst Rev 2011;9:CD008959.
90 Darnton-Hill I, Webb P, Harvey PW, et al: Micronutrient deficiencies and gender: social and economic costs. Am J Clin Nutr 2005;81:1198S–1205S.
91 Julia M: Adoption of the WHO Child Growth Standards to classify Indonesian children under 2 years of age according to nutrition status: stronger indication for nutritional intervention. Food Nutr Bull 2009;30:254–259.
92 Neufeld LM, Osendarp SJ: Global, regional and country trends in underweight and stunting as indicators of nutrition and health of populations. Nestle Nutr Inst Workshop Ser 2014;78:11–19.