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Micronutrient Deficiencies during the Weaning Period and the First Years of Life

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Influence of Food Intake, Composition and Bioavailability on Micronutrient Deficiencies of Infants during the Weaning Period and the First Year of Life

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Introduction

In recent years, the promotion of breast-feeding has received much attention. This emphasis, however, has overshadowed efforts in many developing countries to provide safe and nutritionally adequate complementary foods for infants and young children, and this critical aspect of young child feeding has been severely neglected. This is unfortunate in view of the overwhelming importance of complementary feeding practices and behaviors on the growth, development, health and wellbeing of young children. Indeed, the World Health Organization has urged that programs to improve complementary feeding practices and behaviors are given the highest priority [1].

It is now well established that at about 6 months of age, the supply of energy and certain nutrients from breast milk is no longer adequate to meet an infant's needs [2]. Consequently, complementary foods, preferably with a relatively high energy and nutrient density, must be provided after 6 months of age until the child is ready to consume the same foods as those consumed by the rest of the family members. Increasingly, research has shown that in developing countries and in some more affluent countries, the nutritional adequacy of these complementary foods is compromised in terms of their quantity and/or dietary quality [2]. Such inadequacies are especially serious

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for children less than 2 years of age, whose nutritional requirements at this time are higher per kilogram body weight than at any other time during the life cycle. The challenge of meeting these high requirements is exacerbated by the limited gastric capacity of infants ($\sim 30\text{--}40\text{ g/kg}$ body weight) [2], and the frequency with which meals can be provided, coupled in developing countries with high rates of infection.

Effect of Total Food Intake on Micronutrient Intakes

Several factors are known to affect the total amount of complementary foods consumed during the weaning period, and thus in turn the adequacy of micronutrient intakes. These factors have been reviewed in detail elsewhere [2–4], and are classified into three groups: caregiver behaviors; child-related factors, and dietary factors. Only the latter two will be considered here.

Child-Related Factors

Of the child-related factors, those related to appetite have received the most attention in part because of the repeated reports of poor appetite in young children in developing countries [4]. Studies have shown that appetite and, hence, food intake is often reduced during illness. Moreover, the incidence of illness, especially diarrhea, peaks during the second half of infancy, coinciding with the period when the contribution of complementary foods to total dietary requirements increases markedly [2].

Nonetheless, among Peruvian infants, $\sim 30\%$ of days with reported anorexia occurred regardless of the presence of other illnesses, suggesting that other important causes of anorexia exist [3, 4]. In these same infants, the energy intake from complementary foods was reduced by $\sim 25\text{--}35\%$ on those days when mothers reported poor appetite. Such a reduction in energy intake was probably accompanied by a concomitant decrease in micronutrient intakes, although the latter were not reported in this Peruvian study. In a community-based study in rural Malawi, a 30% reduction in energy intake from complementary foods for those infants whose mothers reported poor appetites [5] was accompanied by nearly a 33% reduction in iron, zinc, and vitamin A intakes.

Additional factors that may induce alterations in appetite and thus food intake are micronutrient deficiencies per se, specifically deficiencies of iron and zinc [2, 3]. Whether these effects are mediated by changes in physical activity, rates of infection, or direct changes in neuropeptides that control appetite is unknown. Some iron and zinc supplementation studies have reported increases in appetite or weight gain in response to additional iron or zinc [6].

Diet-Related Factors

The main dietary factors known to influence total complementary food intake are the frequency of feeding and the energy density, as well as the physicochemical, and organoleptic characteristics of the food [3, 4].

Feeding Frequency. In many developing countries infants may receive only 2–3 complementary feedings per day on average because they eat together with adult family members [2]. Experimental studies on fully weaned, recovering malnourished children have shown that a marked increase in energy intake can be achieved by increasing feeding frequency, when the level of energy density has been controlled [2–4].

Energy/Nutrient Density. Some studies have shown that children consume less food or formula (g/kg/day) as the energy densities of the complementary foods increase, thus apparently compensating in part, for the differing energy densities of their diets [2, 3]. Despite this apparent adjustment, however, the resultant total daily intakes of energy and micronutrients are increased when more energy-dense diets are consumed [3], provided micronutrient-containing sources of energy and not oil or sugar are used. Experimental studies have confirmed similar increases in total energy and thus micronutrient intakes after reducing the viscosity of stiff high-energy porridges by the addition of amylase-rich flours [3, 5, 8].

Food Variety. Increasing the variety of complementary foods may also enhance food intake, and thus in turn energy and micronutrient intakes. Underwood [9] and later Brown et al. [10] in an experimentally controlled study reported that, when children received a varied dietary regimen, they consumed ~10% more than when consuming monotonous diets.

Combined Strategies. A combination of these strategies discussed above can be used to increase food intake, and hence energy and micronutrient intakes during complementary feeding in developing countries. These may include increasing feeding frequency, probably to a maximum of 4 meals/day, increasing the energy/nutrient density of the complementary diets, and increasing the variety and tastefulness of nutritious foods in the diet. The choice of the most effective combination to implement will depend on the limitations of current feeding practices within the population group, as discussed by the WHO [2].

In a study in rural Malawi, a nutrition education intervention employed a combination of strategies to increase the amount of complementary foods consumed, and their energy and nutrient densities [5]. Results are shown in figure 1. Significant increases in the amount of complementary food consumed and the energy density of the diets in the intervention compared to the control group led, in turn, to higher intakes of energy, iron and zinc, as shown in figure 1.

Effect of Dietary Quality on Micronutrient Intakes from Complementary Foods

Poor dietary quality is often inherent in complementary foods in developing countries where the poor socioeconomic and environmental factors

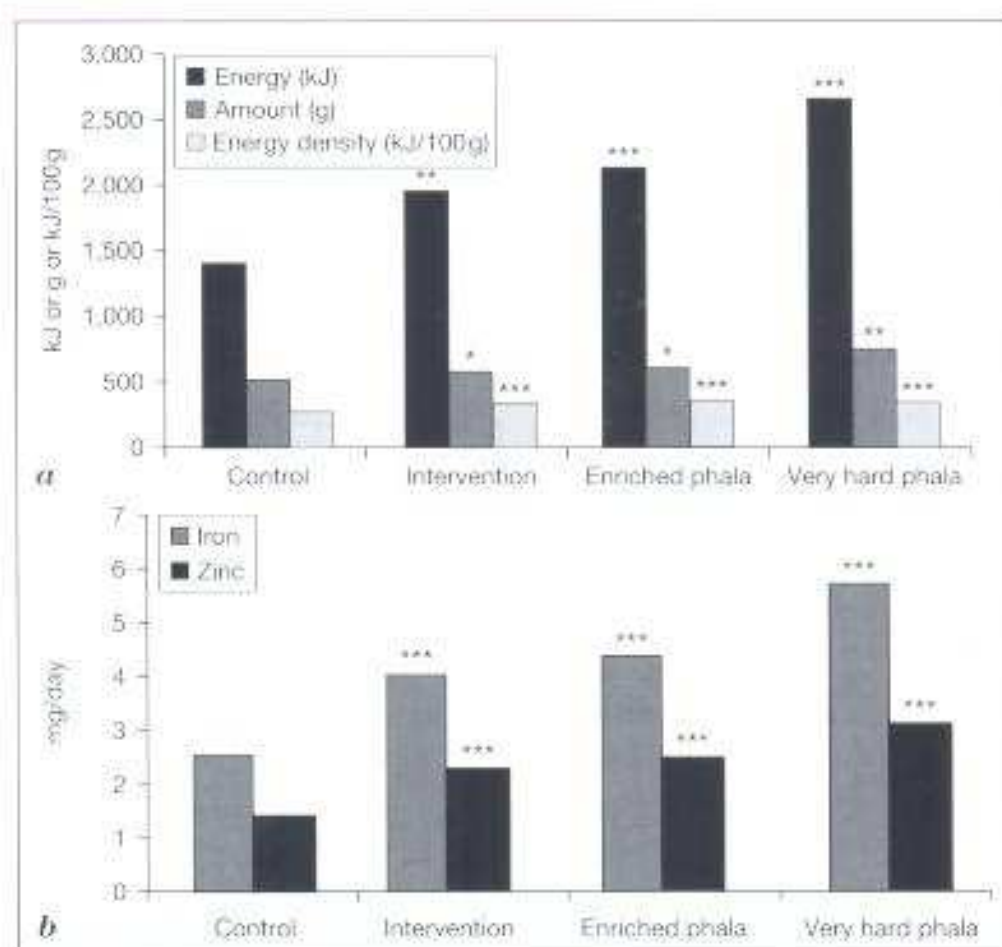


Fig. 1. Dietary intakes from complementary foods by Malawian children (9–24 months of age) compared between the control ($n = 40$) and intervention groups ($n = 71$) and users of enriched porridge (phala; $n = 34$) or very hard phala (16% dry matter; $n = 21$) on the day of dietary recall. **a.** The energy intake, amount, and energy density of the complementary diet are shown. **b.** The corresponding intakes of iron and zinc are shown. Data represent adjusted means with the number given above each column. Significant differences between control group and other groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (linear regression model controlling for age, sex, and whether intakes were considered by the mother to be usual or unusually poor).

limit the types of foods available [11]. Typically the complementary foods are based on starch-based staple foods (i.e. cereals, roots/tubers); very few sources of animal foods, rich sources of several key micronutrients, are included [12]. This pattern poses two important barriers to adequate micronutrient nutrition for weanlings. First, a low diversity of food sources, especially few animal-source foods, limits dietary quality as it decreases the chance of acquiring good food sources of all nutrients [13]. Secondly, the antinutrient content of plant-based staples such as unrefined cereals and legumes, pose further limitations to dietary quality through their negative impact on bioavailability [12].

Dietary Diversity

The relationship between the dietary diversity and dietary quality of complementary diets has been studied by several investigators [2, 5, 13, 14]. Results have confirmed that when complementary diets with a higher dietary diversity are consumed, micronutrient intakes (per day) and micronutrient densities (per 100-kcal) increase [13, 14]. Moreover, in Mexican preschoolers [15], lower rates of stunting were linked with more diverse diets, attributed to enhanced bioavailability of calcium, iron and zinc, compared to that from diets based on high phytate, maize-based tortillas. Promoting dietary diversity also provides infants with an important opportunity to appreciate different tastes and textures of food, both critical attributes for developing good eating habits in the future [2].

Micronutrient Bioavailability

It is noteworthy that the nutrients consistently reported to be most limiting in the complementary diets of infants in developing countries during the first years of life, calcium, iron, and zinc, and in some cases, vitamin A, are also those for which the reported inadequacies are often exacerbated by poor bioavailability. The latter arises because the complementary diets are predominantly based on cereals and legumes, especially in developing countries where consumption of animal source foods is low [2, 5, 12, 14]. Moreover, these plant-based complementary foods are often provided during the first 3 months, when they displace breast milk [2, 3, 5, 14]. Even in the more affluent countries, consumption of meat and fish during infancy is low [16, 17].

To date there have been very few *in vivo* isotope studies in humans that have measured the bioavailability of micronutrients in complementary foods; some exist for iron and zinc in complementary foods used in developed countries [18, 19]. Several dietary components modify the bioavailability of these limiting micronutrients: some enhance and others inhibit absorption. Of the dietary inhibitors, phytate is of particular concern for complementary foods based on cereals and legumes, depending on the preparation or processing methods used [2, 5, 12, 14, 19]. Phytate chelates certain minerals, and inhibits their absorption across the intestinal mucosa. The inhibition of zinc absorption by phytate is well established, and follows a dose-response effect. Phytate in unprocessed food is composed primarily of the hexa- and penta-inositol phosphate forms that inhibit zinc absorption [5, 12, 14]. Some processing methods (e.g. fermentation) can cause the dephosphorylation of the inositol phosphates to lower inositol forms (i.e., mono- to tetra-inositol phosphates) via microbial phytase enzymes, which do not have an inhibiting effect on zinc absorption. Soaking can also reduce the total content of phytate in cereal flours (e.g. maize and rice) and most legume flours because it is stored in a relatively water-soluble form, and hence can be removed by diffusion [5, 12, 14]. Phytate also inhibits non-heme iron absorption in cereal-based

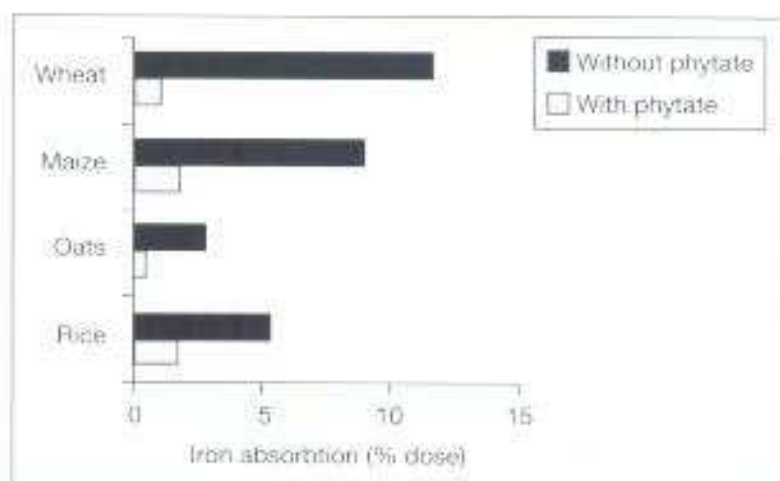


Fig. 2. Influence of phytic acid degradation on iron absorption from wheat, maize, oats, and rice porridges. Adapted from Hurrell et al. [19].

complementary foods [18, 19]. Even small amounts produce an inhibitory effect and, unlike zinc, the myo-inositol phosphates must contain less than 3 phosphate groups before iron absorption is no longer inhibited [20].

Any reduction in the total phytate content of complementary porridges based on cereals and legumes has the potential to enhance absorption of iron and zinc. This has been confirmed by two *in vivo* human stable isotope studies in which adults consumed tortillas or polenta prepared with a low phytic acid maize strain and wild-type unmodified maize [20, 21], and by a recent study by Hurrell et al. [19]. They demonstrated increases in iron absorption from porridges prepared from a variety of dephytinized cereals compared to those with their native phytate content. Dephytinization of rice, oat, maize and wheat porridges prepared with water resulted in 3- to 12-fold increases in iron absorption as shown in figure 2. In this study, the phytic acid was degraded by the addition of exogenous phytase, and iron absorption was measured in adult humans with an extrinsic-label radioiron technique.

The inhibitory effect of phytate on zinc absorption may be further exacerbated by high levels of calcium, which reduce the solubility of the phytate-mineral complex [12]. Some single meal isotopic studies suggest that high levels of calcium (both supplemental and dairy products) inhibit non-heme iron absorption, although whole diet studies have produced conflicting results [2]. The conflict may be due in part to differences in the iron status of the individuals being studied. However, the calcium content of most plant-based complementary foods is too low to have any detrimental effect [12].

Polyphenols and tannins are also important inhibitors of non-heme iron absorption; they form insoluble iron-phenolic compounds [19]. Complementary foods based on certain cereals (e.g. red sorghum and finger millet) and legumes (e.g. red kidney beans, black beans and black grams) may contain high levels of polyphenols. As well, beverages such as tea or coffee that contain

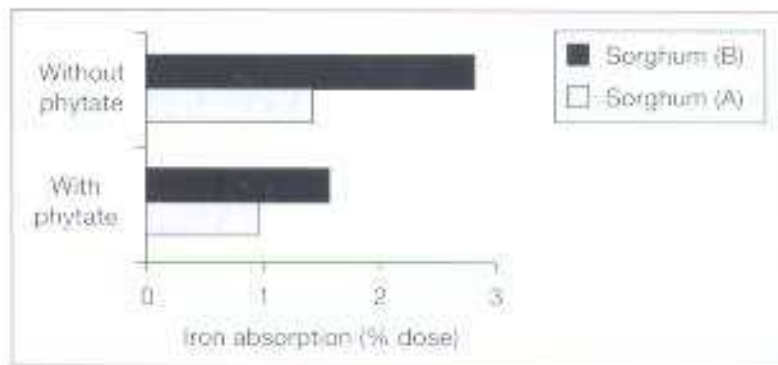


Fig. 3. Iron absorption from low (B) and high (A) tannin sorghum porridges with and without native phytate. Modified from Hurrell et al. [19].

polyphenols are sometimes introduced into an infant's diet, and have been associated with suboptimal iron status during infancy [22, 23]. The inhibitory effect of polyphenols on iron absorption was also demonstrated in the *in vivo* isotope study of Hurrell et al. [19] by comparing iron absorption after dephytinization of high-tannin and tannin-free varieties of sorghum. Results are shown in figure 3. A nearly 2-fold increase in iron absorption was observed in a tannin-free variety of dephytinized sorghum (B), whereas no significant increase in iron absorption occurred in the high-tannin dephytinized variety (A) [19].

Animal source foods play an important role in optimizing iron and zinc nutriture of weanlings. Apart from their high content of bioavailable heme iron and zinc, animal protein also has an enhancing effect on non-heme iron and zinc absorption [2, 12]. This has been confirmed by stable isotope studies comparing iron and zinc absorption in infants consuming vegetable or cereal-based complementary foods with those based on meat [24, 25].

Cellular animal protein also partially counteracts the inhibition by phytate on non-heme iron and zinc absorption [2, 12]. Hence, even the addition of a small amount of animal-source foods can play an important role in improving the bioavailability of both non-heme iron and zinc in complementary foods, and thus in turn iron and zinc nutriture during infancy. Nevertheless, intervention studies to examine the effect of the greater intake of meat as a complementary food on the iron and zinc status of infants have yielded inconsistent results [18]. Postulated reasons for the absence of any benefit may include that the iron and zinc nutriture of the infants was already adequate, and/or the study had insufficient power to detect any differences in the rate of iron or zinc deficiency between the 2 groups.

In view of the limited amount of *in vivo* absorption data from complementary foods based on human studies, the bioavailability of iron and zinc in complementary foods is often estimated from bioavailability algorithms. We have applied the bioavailability algorithms compiled by Murphy et al. [26] to estimate the intakes of available iron and zinc in the complementary

Table 1. Intakes of total iron and zinc, estimated available iron and zinc, phytate and phytate:zinc molar ratios (25th, 75th percentile) from complementary foods for Malawian infants

	Harvest season		Hungry season	
	6-8 months	9-11 months	6-8 months	9-11 months
Number	26 ^a	32	20	34
Iron, mg	1.2 (0.5, 2.5)	2.8 (1.8, 3.4)	1.5 (1.1, 2.4)	2.3 (1.5, 3.0)
Available iron, μg ^a	0.07 (0.03, 0.19)	0.20 (0.13, 0.31)	0.11 (0.06, 0.16)	0.15 (0.12, 0.22)
Available iron, %	5.5 (4.8, 6.6)	7.4 (5.7, 9.8)	5.7 (5.3, 8.2)	7.1 (5.9, 8.6)
Zinc, mg	0.7 (0.4, 1.7)	1.7 (1.0, 2.2)	1.0 (0.5, 1.5)	1.4 (0.9, 1.9)
Available zinc (basal), μg ^a	0.11 (0.05, 0.40)	0.34 (0.18, 0.43)	0.12 (0.07, 0.23)	0.18 (0.12, 0.27)
Available zinc, %	14.9 (12.1, 20.9)	19.9 (14.4, 24.5)	13.9 (10.6, 16.2)	12.5 (10.3, 15.4)
Available zinc (normative), μg ^a	0.11 (0.05, 0.38)	0.33 (0.18, 0.40)	0.12 (0.07, 0.21)	0.18 (0.12, 0.27)
Available zinc, % ^a	14.9 (12.1, 20.5)	18.5 (14.4, 22.2)	13.9 (10.6, 16.0)	12.5 (10.3, 15.4)
Phytate, mg, IP5+IP6	198 (112, 318)	332 (197, 474)	276 (175, 397)	432 (277, 605)
Phytate:zinc molar ratio	26 (14, 37)	20 (11, 31)	31 (25, 39)	32 (25, 39)

^aDetermined from total daily intakes. Modified from Hotz and Gibson [27].

maize-based diets of infants in rural Malawi at two seasons of the year: harvest and hungry season [27]. Table 1 summarizes the data on intakes of total and available iron and zinc for infants 6-8 and 9-11 months old. Details on their phytate:zinc molar ratios are also given; ratios over 15 are associated with a half-maximal absorption of zinc [12]. Note that the median estimated bioavailabilities of both iron (5.5-7.4%) and zinc (12.5-18.5%) for all age groups were low, attributed to the low intakes of both meat/fish/poultry protein (only 0-4% of iron from meat, poultry and fish) and ascorbic acid for iron, and the high phytate:zinc molar ratios for zinc. Indeed, nearly 60% of all meals consumed had a phytate:zinc ratio of >15. Note that most complementary foods based on unrefined cereals and legumes (per 100g as eaten) have phytate:zinc molar ratios of >15 [12].

To our knowledge, there are no *in vivo* studies on the bioavailability of copper, manganese, selenium, or iodine in complementary foods in developed

or developing countries. Lower copper absorption from infant cereals compared to milk has been reported using a weanling rat model, but the copper content of plant-based complementary foods is usually higher than the milk-based diets. Hence, it is unlikely that copper nutriture is of concern during infancy, unless infants are fed diets based on cow's milk alone [2].

For plant-based complementary foods with a low fat content, the bioavailability of fat-soluble vitamins A, D, E, and K and carotenoids may be compromised when breast-feeding ceases. Use of mild heat treatment (i.e. preparation of porridges) may release bound carotenoids from the food matrix and binding proteins, but if severe heat treatment is used, it can be detrimental. Fiber, especially the water-soluble fiber pectin, impairs β -carotene absorption by interfering with gastric emptying and with mixed-micelle formation [2]. Recent research has emphasized that the bioavailability of provitamin A β -carotene from plant sources is only half that of previous estimates [28]. Hence, if complementary diets do not include sources of pre-formed vitamin A from animal or dairy products, and concentrations of breast milk vitamin A content are low, deficits in vitamin A are likely to occur which cannot be overcome by the consumption of green leafy vegetables and orange-yellow fruits [28].

Evaluating the Nutritional Adequacy of Complementary Foods by Comparison with WHO Recommendations

The WHO [2] report on the estimated energy and nutrients needed from complementary foods for infants of various ages in developing countries has provided an opportunity to evaluate the nutritional adequacy of complementary foods. WHO has computed the theoretical energy and nutrient needs based on the difference between the age-specific energy and nutrient requirements and the energy and nutrients provided by breast milk, taking into account the volume and composition of breast milk consumed. The estimated needs have been compiled for low, average and high intakes of breast milk corresponding to mean -2 SD, mean, and mean $+2$ SD, respectively. Both estimated needs per day and per 100 kcal have been published; details are given in WHO [2]. Expressing the nutrient needs per 100 kcal (i.e. nutrient density) allows the identification of those nutrients most limiting in the diet because of inadequacies in total intake of complementary foods per se, or in the composition or quality of the complementary diet. As well, the adequacy of individual complementary foods to meet the estimated needs can be assessed by this method. An update of these calculations incorporating new energy and micronutrient requirements for infants is given by Dewey and Brown [3].

Comparison of micronutrient intakes (per day and per 100 kcal) from complementary foods based on assumed intakes [12] derived from data on gastric capacity [2] including actual intake data from a range of developing countries;

Table 2. Nutrient densities of complementary diets consumed by infants aged 6–8 months in seven countries compared to WHO desired densities

	WHO 1998	WHO 2002	Philippines	Bangladesh	Ghana	Malawi	Guatemala	Peru	USA
Age, months			6	6–8	6–8	6–8	6–8	6–8	6–8
Protein, g	0.7	1.0	1.7	1.9	3.3	2.3	2.2	2.6	2.6
Ca, mg	125	105	18	16	35	5	27	19	67
Fe, mg	4.0 ^b	4.5 ^b	0.5	0.4	1.2	0.8	0.5	0.4	3.6
Zn, mg	0.8	1.6	0.9	0.2	0.6	0.5	0.4	0.4	0.4
Vitamin A, µg RE	5	11	0.5	0	7	2	87	35	95
Thiamin, mg	0.04	0.08	0.02	0.04	0.07	0.08	0.04	0.04	0.14
Riboflavin, mg	0.07	0.08	0.02	0.04	0.03	0.04	0.06	0.07	0.18
Niacin, mg	1.1 ^b	1.7 ^b	0.30^a	0.9^a	0.8^a	0.7^a	0.4^a	0.5^a	1.5 ^a

Values in bold print indicate that the observed density is below the reference values for the average desired density for WHO [2, 30]. Modified from Dewey and Brown [3], Perlas [14] and Hotz and Gibson [27].

^aExcludes the contribution of dietary tryptophan to niacin synthesis.

^bMedium bioavailability of iron assumed.

as well as the USA [2, 3], has emphasized that for certain micronutrients the amount and density from complementary foods are consistently and substantially less than the corresponding WHO [2, 3, 29] recommendations. These nutrients have been defined as 'problem nutrients'. Based on recommendations by the WHO in 1998 [2] or in 2002 [30] for the desired nutrient density levels, tables 2 and 3 clearly show that calcium, iron, and zinc are problematic for infants aged 6–8 months, and calcium and iron for those aged 9–11 months, even when moderate bioavailability is assumed. Comparable deficits exist when micronutrient intakes per day are compared with the estimated needs defined by the WHO in 1998 [2] and 2002 [30] (data not shown).

Vitamin A, riboflavin, and niacin may also be a problem nutrients for some age groups and settings, as shown in tables 2 and 3. Note that for many developing countries, the bioavailability of iron and zinc in the complementary diets may be low rather than moderate, as assumed in tables 2 and 3, because such a large proportion of energy is provided by cereals, and intake of cellular animal protein is low [2, 14, 18, 27, 29].

Deficits may also occur in the complementary diets of infants living in more affluent countries, although methodological differences limit the comparisons that can be made. Again, the micronutrient deficits most frequently reported in the diets of breast-fed and weaned infants are those for zinc and iron [2, 3, 16–18, 27], attributed to low intakes of animal source foods. Inadequacies in intakes of vitamin D, vitamin E, and vitamin B₆ have also been reported in some studies of US, Swedish, or Finnish infants [2, 18, 31, 32]. Few other studies have reported intakes of vitamin D, E, and vitamin B₆ during infancy for comparison.

Table 3. Nutrient densities of complementary diets consumed by infants aged 9–11 months in seven countries compared to WHO desired densities

	WHO 1988	WHO 2002	Philippines	Bangladesh	Ghana	Malawi	Guatemala	Peru	USA
Age, months			10	9–11	9–11	9–11	9–11	9–11	9–11
Protein, g	0.7	1	1.7	2.5	3.1	3.7	2.7	2.6	3.4
Ca, mg	78	74	17	20	40	18	37	27	53
Fe, mg	2.4 ^a	3 ^b	0.5	0.4	1.3	0.8	0.6	0.4	1.2
Zn, mg	0.5	1.1	1.0	0.3	0.5	0.5	0.4	0.4	0.4
Vitamin A, µg RE	9	30	5	1	0	28	62	39	88
Thiamin, mg	0.04	0.06	0.02	0.05	0.06	0.07	0.05	0.04	0.1
Riboflavin, mg	0.04	0.06	0.02	0.05	0.02	0.04	0.06	0.07	0.08
Niacin, mg	0.9 ^a	1 ^a	0.35^a	1.0^a	0.7^a	0.8^a	0.5^a	0.5^a	1.1^a

Values in bold print indicate that the observed density is below the reference values for the average desired density [2, 33]. Modified from Dewey and Brown [3], Perlas [14] and Hotz and Gibson [27].

^aExcludes the contribution of dietary tryptophan to niacin synthesis.

^bMedium bioavailability of iron.

Deficits may also occur in manganese, iodine, and selenium, but accurate food composition data for these micronutrients are sparse, especially in developing countries [2]. Moreover, levels for iodine and selenium (as well as zinc) depend on soil trace element levels, so that unless region-specific food composition data are used to calculate intakes for these trace elements, or laboratory analysis is undertaken, an accurate assessment of their adequacy is difficult.

Caution must be used when extrapolating deficiencies based on dietary data alone, because the requirement estimates for some nutrients during infancy are uncertain, leading to large discrepancies among published requirement estimates [2, 3]. There is still considerable uncertainty regarding the nutrient composition values in the food composition databases used to calculate nutrient intakes, and in the concentrations of certain nutrients in breast milk. Nevertheless, these comparisons do suggest that complementary diets for infants aged between 6 and 12 months of age from both developing and more affluent countries are limiting at least in iron, zinc, and probably calcium [2, 3].

Are These Dietary Inadequacies Associated with Micronutrient Deficiencies during the Complementary Feeding Period?

It is evident from the discussion above that deficits in both the quantity and quality of complementary foods contribute to the coexistence of several micronutrient deficits. Nevertheless, studies examining interrelationships

Table 4. Prevalence of multiple biochemical micronutrient deficiencies

Biochemical index	Vietnam [35] (n = 160) 6–24 months	Indonesia [34] (n = 478) 4 months	Ghana [33] (n = 152) 6 months	New Zealand [16, 37] (n = 22) 6–12 months
Hemoglobin <110 g/l	46	57	30	52
Plasma ferritin <12 µg/l	—	20	17	13
Plasma Zn <10.7 µmol/l	36	17	4	32
Plasma retinol <0.7 µmol/l	46	54	38	—
RBC B-2 <200 µmol/l packed RBC	—	—	14	—
Urinary iodine <50 µg/l ^a	—	—	—	51

^aModerate iodine deficiency.

between dietary inadequacies and biochemical micronutrient deficits among weanlings, and adverse functional health outcomes are limited. Indeed, only a few studies have quantified the prevalence of multiple biochemical micronutrient deficiencies in weanlings, notably iron, zinc, vitamin A, and riboflavin; available results are summarized in table 2 [33–38]. Note that at least a third of the infants in each developing country represented have low hemoglobin concentrations indicative of anemia, compared to <4% in New Zealand [16]. In contrast, the prevalence of low serum/plasma retinol and serum/plasma zinc values varies markedly across countries. Biochemical data confirming deficiencies of iodine, selenium, riboflavin, niacin, and vitamin B₆ among weanlings are more limited [31, 33, 34; in the New Zealand study, 51% of the breast-fed infants had low urinary iodine concentrations, 37]. Note that some of these prevalence data are based on observational studies in which it is difficult to control for the adverse environmental factors (e.g. parasitic infections), or hereditary diseases (e.g. hemoglobinopathies) that may also have a detrimental effect on micronutrient status.

Very few of the studies in table 4 have examined relationships between micronutrient intakes from complementary foods and biochemical status, with the exception of Ghana [33] and New Zealand [16]. In Ghana [33], the intakes of iron, vitamin A, and energy from complementary foods were positively associated with plasma ferritin, plasma retinol, and zinc status, respectively, in infants at 12 months, whereas the intake of calcium from foods was negatively associated with zinc status. In New Zealand infants aged

Table 5. Multi-micronutrient efficacy trials of infants and their impact on biochemical status and growth

Country	n	Initial age months	Duration months	Study design	Effects on growth	Effects on micronutrient status
China [41]	164	6-13	3	V/M fortified vs. unfortified milk	NS	↑ Hb; ↓ Vit E; NS Vit A, riboflavin, Fe indices
Ghana [40]	208	6	6	Weanmix, ± V/M; Weanmix with fish powder; Fermented maize with fish powder vs. cross-sectional comparison group	NS among groups; ↑ Wt and ht in intervention vs. comparison group	↑ Vit A, ferritin (in V/M group only); NS Hb, riboflavin, Zn
Vietnam [35]	163	6-24	3	Fe, Zn, Vit A, Vit C weekly, daily or placebo	↑ Ht only in stunted children	↑ Hb, vit A, Zn
Guatemala [42]	250	6	8	BSC* + V/M, V/M, BSC or placebo	NS	NS vitamins A and E
Mexico [36]	319	8-14	12	V/M vs. placebo	↑ Ht in those <12 months at baseline	Not yet reported
Indonesia [43]	478	4	6	Fe + Zn; Fe, Zn; placebo	NS	↑ Hb in Fe; Fe + Zn; ↑ ferritin in Fe; Fe + Zn ↑ Zn in Zn; Fe + Zn

V/M = Vitamin/mineral; BSC* = bovine serum concentrate; Hb = hemoglobin; NS = not significant; Wt = weight; Ht = height. Modified from Dewey [44].

6-12 months, serum ferritin was positively associated with intakes of iron and vitamin C, but negatively with calcium and dietary fiber [16], while hair zinc was significantly associated with the proportion and absolute amount of energy provided by meat (Ferguson EL, personal commun.); iodine intakes could not be calculated because of the paucity of data on the iodine content of complementary foods in New Zealand.

Some randomized trials with micronutrient supplements or fortificants, notably iron, zinc, and/or vitamin A, provided singly or in combination, have demonstrated significant reductions in the prevalence of biochemical micronutrient deficiencies, based on hemoglobin, ferritin, serum retinol, and plasma zinc; reductions in the prevalence of low riboflavin biochemical indices have not been reported [33]. In some but not all of these studies, improvements in functional outcomes, mainly growth, have also been reported after supplementation or fortification with single [6, 38, 39] or multiple micronutrients [35, 40, 41], depending on the micronutrients, study group, and the setting; these studies have been summarized elsewhere [6, 44]. Table 5 summarizes the available efficacy trials of multiple micronutrients as supplements or fortificants that have measured both biochemical indices and growth [44].

The results in tables 4 and 5 confirm that biochemical micronutrient deficiencies, notably iron, zinc, and vitamin A, do exist among weanlings, sometimes concurrently in some settings, induced at least in part by micronutrient inadequacies during the complementary feeding period. Nevertheless, the results have not been consistent. In the single micronutrient supplement or fortificant studies, some of the discordant results may be due in part to the coexistence of multiple micronutrient deficiencies, which may suppress the effect of the micronutrient under study if it is not the first limiting micronutrient [36]. Additional factors that may also play a role in both the single and multiple micronutrient supplement or fortificant trials include differences in initial age and nutritional status of infants, duration of intervention, form and level of supplements or fortificants, study design, inadequate sample size, and constraints on growth due to infection, prenatal factors, and parenteral size [45].

Conclusions and Recommendations

It is apparent that inadequacies in iron, calcium, and zinc consistently arise in complementary diets used in both developing and affluent countries. In some countries, deficits in certain vitamins (e.g. vitamin A, riboflavin, niacin, vitamin B₆) and iodine and selenium may also occur, depending on the dietary staple used and the soil iodine and selenium levels.

Nevertheless, studies examining interrelationships between dietary and biochemical micronutrient deficits among weanlings, and adverse functional health outcomes are limited.

Several non-nutritional factors, notably infection, are known to exacerbate certain micronutrient deficiency states in weanlings, and confound such relationships. Hence, ensuring adequate intakes of readily available micronutrients in complementary foods alone may not necessarily ensure optimal growth, health and development during infancy and early childhood.

To accomplish the latter, a comprehensive and integrated approach is needed. Such an approach should emphasize nutrition prior to and during pregnancy, promote exclusive breast-feeding for about 6 months, followed by the use of micronutrient-dense complementary foods, and incorporate effective nutrition and health education messages. Only when a combination of such strategies is used can optimal growth, health, motor and cognitive development during infancy and early childhood in developing countries be expected.

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Discussion

Dr. Talbot: Thank you for your crystal clear presentation. I have a question about appetite. I know nutritionists have been very keen to cut that out, to see what is causing a decreased appetite. As a pediatrician I would always think that it is caused because a child is not feeling well, and feeling well in most of the settings you have been researching show with a high incidence of the infections, the weanlings in Malawi are I presume in a highly malarial region. Did you look at infections per se in your Malawian population in terms of COP or other infections parameters?

Dr. Gibson: No unfortunately we weren't able to collect blood samples in this particular trial in Malawi so we weren't able to examine infections. One of the things I didn't discuss in this presentation, which we all know is also very important in terms of appetite, is daily care practice, and we need to be much more attentive to caring practice. It became clear to us during our study in Malawi that also mothers need to be more proactive in terms of feeding sometimes.

Dr. Talbot: There was a point at which the frequency of feeds was increased. But how practical is that for an African mother who is already overburdened, has to get the shaving water for the husband in the morning, collect firewood, etc?

Dr. Gibson: I recognize that that might be a problem and having worked in Malawi I realize how busy the mothers are. However, before any of these strategies were actually implemented we carried out a lot of qualitative research to find out whether or not the strategies that we were proposing would be acceptable to the mothers, so none of these strategies were used unless they were acceptable to the mothers before we started, that is very important.

Dr. Abrams: I have a comment about calcium. You made it sound as if most weaning foods are calcium deficient. This points out that the British Recommended Nutritional Index of 520 mg for 9- to 11-month-olds is considerably greater than the US, i.e., 270, and the British number goes down to 350 at 12 months of age. If you look at some of the data collected since the British Recommended Nutritional Index was developed, 520 mg/day is a very high estimate of what most infants of 9-11 months of age need. So I am not sure if the amount of calcium in infant weaning foods may not be as far off. Now I recognize that bioavailability is a problem, but there is a huge calcium gap and the US recommendations are, I think, the more current understanding of the bone growth in 9- to 11-month-old infants.

Dr. Gibson: Thank you very much for the comment. Agree, and it is actually reassuring to hear that the gap is probably not as bad as it looks from the data available.

Dr. Goesby: I am a bit confused by one of the aspects of your presentation which is not related to micronutrient but to energy because up to now all of what I have read

about energy density and food intake show that when you increase energy density you reduce the overall amount of food, although insufficiently to reduce the energy intake. You said that when energy density is increased the quantity of food is increased as if there was no satiation effect of the energy density. Could you explain how you came to this conclusion?

Dr. Gibson: There have been very elegant experimental control trials to investigate this effect. The earlier literature was quite confusing because it was very difficult to separate the changes in energy density and feeding frequency. In fact more recent studies have clearly shown that you can in fact increase energy intake if you increase energy density [1], and in Malawi one of the things that we did to ensure that the increased energy density food, which was 16% dry matter, was acceptable for the infants was actually to use some germinated cereal so that the viscosity of the porridge prepared as 16% dry matter was similar to that of 7% dry matter.

Dr. Specker: With regard to the calcium recommendations for infants, in the US the adequate intake levels of calcium for 0–6 months were based on the calcium content of human milk and the average amount of human milk consumed per day in the exclusively breast-fed infant. The recommended intake for 6–12 months was based on intakes from human milk and what the normal US infant receives from complementary foods. The recommendations were not based on any functional indicator for calcium.

Dr. Neufeld: I have two comments. One is methodological really. You reported that poor appetite as perceived by the mother was predictive of intake, and I have to ask what would be the possible role of maternal responsive feeding? If we assume that the mother perceives and interacts with her child in a certain way, then she would perceive the lower appetite of the child. In terms of measuring this we must find a way to classify a mother's interaction with her child, the whole caregiving, in order to really understand that relationship. We have just recently finished a trial in Mexico, a multiple micronutrient supplementation trial, comparing multiple micronutrients and iron and vitamin A, and the results are not encouraging. We finished the trial in September and we are analyzing results, but I think we are really going to need to think about how to deal with multiple deficiencies in these countries because it looks as though supplementation with multiple micronutrients is not going to be the answer, at least not in our settings.

Dr. Gibson: That is very true and this is one of the reasons why in the final slide I suggested that we look at the multiple micronutrients specific for the setting. But perhaps in fact it would be preferable to use additional micronutrients as fortificants rather than supplements, which is probably a much more promising way to proceed. Even better in my view is to try and ensure that mothers have available to them foods that meet nutrient needs without even having to fortify. But from our study in Malawi even with our interventions which involved 4 different strategies, although we achieved an increase in intake of most nutrients in many cases, it was still not sufficient to meet the estimated needs. So we came to the conclusion that in this setting in Malawi, particularly for iron and zinc, there would be a problem. This was partly because the mothers had such limited access to flesh foods; their only source of animal protein was fish and that really constrained our efforts to try and produce a complementary food that would meet all the estimated needs of those infants.

Dr. Gebre-Medhin: One of the striking points you made is the very high occurrence of micronutrient deficiency in Sweden with the complementary feeding. If I understood you correctly, if that is the case this must be looked at in relation to the fact that we have the best growth ever published anywhere in Sweden, lowest mortality, lowest morbidity, highest quality of life, and the rest, and the figure that you gave very clearly put Sweden among the highest examples of deficiency.

Dr. Gibson: I am glad you raised that point, and of course it is very much dependent on the cutoff that we use. In terms of hemoglobin there is a lot of doubt or discussion

about the cutoff that we should be using to classify infants with anemia. So that might be some of the reason. In terms of New Zealand, where we saw a large proportion of children with urinary iodine deficiency, this is certainly a reemerging problem, as it is in Tasmania. In New Zealand one of the reasons for this is because dairy industries have stopped using iodine so that the iodine content of foods, dairy products particularly, has decreased, and although there is iodized salt in the country it is not mandated and mothers do not recognize the importance of using iodized salt and they are using less salt. This has just been presented to the Ministry of Health in New Zealand and they have a special committee to address this concern about the reemergence of iodine deficiency. In some developed countries, certainly in New Zealand and Tasmania, iodine deficiency is going to become a reemerging problem.

Dr. Tollboom: I looked at your figures on the weanlings aged 6-8 and then 9-11 months old in Malawi. I am a bit confused about the definition of weaning.

Dr. Gibson: I may have been responsible for that confusion. In fact those infants that I showed you were still being breast-fed, so all the data that I showed you were for infants who were still being breast-fed.

Dr. Tollboom: Then you assume the breast milk intake on data from the literature. Are there any ways that we can increase breast-feeding because in Zambia we found that in the 2nd year of life breast milk still contributes about 45% of the energy needs of children and protein about 40%. So is there any way apart from good complementary food to improve lactational performance regarding micronutrients?

Dr. Gibson: I am afraid I really can't answer that question. I know that a fully breast-fed infant after 6 months still cannot meet its estimated needs for all nutrients. After 6 months there are certain nutrients that they do require even if they are breast-fed fully. So breast milk itself does not meet the requirements for certain nutrients after 6 months of age. In New Zealand unfortunately most mothers go back to work so breast-feeding frequently actually drops off dramatically by 3 months.

Dr. Tollboom: Do you think the mother is a good vehicle to increase the micronutrient intake of her infant? We have said that mothers should be supplemented with vitamin A, giving all the supplements to a lactating mother rather than to putting it in a fortified food?

Dr. Gibson: I think that it is very unlikely that mothers in New Zealand are vitamin A-deficient.

Dr. Tollboom: I mean the mothers in Malawi.

Dr. Gibson: That may well be the case, but I think in addition we still need to ensure that there is vitamin A in a complementary food.

Dr. Zlotkin: I would like to discuss the concept of using meat as a complementary food. You showed that the group with the highest meat intake still had a significantly inadequate intake of iron and zinc. In Canada, in the communities one would expect to be the least likely to be iron-deficient are our native communities where in fact hunting is of major importance and deer and moose meat are major components of the diet. Yet if you look at the prevalence of iron deficiency among infants between 6 and 12 months of age in Canada in that population, it is around 35% compared to the rest of the country where it is around 5 or 6%. I looked at this a bit more carefully and in fact the populations do use meat, but they use it either as a dilute broth or, among the Inuit population, the mother actually chews the food and provides the chewed food to her infant, and I imagine that actually as the mother chews and swallows the juices of the meat the infant actually receives very little meat. The only studies that I have ever seen that actually demonstrated that meat as a complementary food can prevent anemia are those in which commercial meat products were fortified with iron. In fact we did a study that was published in the *Canadian Journal of Public Health* which showed that the combination of jar meat products and infant cereal could prevent anemia [2]. So my question is do you really think that a recommendation to include more meat in

a complementary food strategy is actually going to work to prevent iron deficiency anemia?

Dr. Gibson: That is a very important question. In fact we are about to embark on a study in New Zealand looking exactly at that question. And indeed when we looked closely in the literature we could not find any study in which they had set out to try to encourage meat consumption that showed a positive effect on reducing iron-deficiency anemia either [3, 4]. I still think, however, that meat certainly might have an impact on the zinc status of the children. In New Zealand the amount of meat given to infants after 6 months is incredibly small, in fact negligible. In New Zealand most of the cereals that are given to infants are not infant cereals at all; Weatabix is given which until recently has not been fortified with iron. So we have a problem with iron deficiency in New Zealand weanlings and toddlers [5]. One of the arms of our study does include a meat group, so we will see.

Mr. Peruvanta: Just to follow up on this point, I don't think that we are saying that meat is not a food to recommend. I think the problem is that a young infant just cannot eat enough meat to be able to consume the needed amount of iron from meat. Last year, as you recall, Gleason [6] did some modeling of different types of diets, looking at what the iron intake should be for a child less than 12 months. Essentially the bottom line was that, depending on the combination but assuming the children were to consume meat as the main source of their iron intake, they would have to eat approximately 150 g meat/day to meet their iron needs. So it is basically not feasible for children to consume that much meat in a day, not to say that they shouldn't consume meat, it is just how much they can consume.

Dr. Gibson: I would just like to elaborate on that. In fact Dr. Ferguson is the principal investigator for this study on meat we are doing in the toddlers. She has worked with Dr. Briand's group in Paris, so she is very aware of the problems associated with meeting the iron needs of infants. Her group has spent about 9 months developing special recipes, testing them with toddlers, to find recipes that they actually will eat. They have measured the amounts of meat that they are willing to consume in this pilot study, and at the beginning of next year we will embark on this study using the piloted recipes on these toddlers to see whether or not we can find a positive effect.

Dr. Specker: Since it appears that it is so hard to get this much iron into an infant's diet, what is the functional indicator for iron deficiency? It seems that if it is so unreasonable to get it in their diet, it might be that the requirement is set too high.^a

Dr. Gibson: Dr. Lozoff will talk about that tomorrow morning.

Dr. Barclay: I would like to underline your statement that it is very important not to assume that micronutrient deficiencies are all the same. We hear a lot about iron, vitamin A and iodine, but we have done studies in West Africa showing that in fact these three micronutrients are not major problems. The major micronutrient deficiencies in this area are calcium, zinc and B vitamins [7]. The data you presented show a difference in the response in girls and boys. We have also done a study on zinc fortification and shown that in boys the growth response is greater than in girls [8]. Do you think this is because boys have a greater requirement for growth or is there another explanation?

Dr. Gibson: One of the explanations in the literature suggests that it may be associated with the fact that males have a higher percentage of total body weight comprised of muscle, which in turn contains a greater content of zinc than fat [9]. Additionally, the growth rate of males is generally higher than females, so their zinc requirements are probably greater.

Dr. Gøtzte Medboe: I would like to come back to this issue of the assessment of iron status using hemoglobin and the Swedish material that you showed. The Swedish children have a high prevalence of exclusive breast-feeding, iron-enriched or iron-supplemented formula, follow-on formula, porridges, and they even get meat from about

4–5 months, they grow well, have a very good morbidity and no mortality, and yet we have these figures that you showed us today. Unless that issue is resolved I think we are going to be in very serious trouble. I think this cutoff point that you mentioned will have to be taken into account before we go ahead. Don't you agree?

Dr. Gibson: I think we need to validate the cutoff points that we can use for designating anemia in infancy, and as Dr. Lommerdal discussed earlier today there is a lot of discussion going on about what levels we should use and also the immaturity of the infants in the first 6 months. At that age it changes a lot so I think we have to bear that in mind when we are looking at these sorts of interpretation.

Dr. Lozoff: A couple of factors may be relevant to the discussion of the right amount of iron for babies. Even though we say that babies were well nourished during human evolution, babies in countries like the US or Sweden are bigger, and they grow more rapidly. It is possible that they are exceeding the capacity of breast milk iron to keep up. The other factor is the introduction of cereal due to agriculture. Although this was a big advance for humans, it may have worsened the situation with regard to iron. So you can think of some circumstances in which breast milk, despite tremendous advantages, might not totally meet iron needs. There are other considerations as we talk about the functional effects of iron deficiency. Different things may be required for good function now, compared to previous times. Thus, the behavioral benefits of good iron status might not have had a major impact under other conditions. These are hesitations before accepting the argument that because anemia was commonly observed in breast-fed infants in Sweden, the cutoffs might be wrong.

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