Best Practice & Research Clinical Endocrinology & Metabolism 24 (2010) 117–132

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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The impact of common micronutrient deficiencies on iodine and thyroid metabolism: the evidence from human studies

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Keywords:
iodine
iron
zinc
vitamin A
selenium
micronutrient deficiency
thyroid

Deficiencies of micronutrients are highly prevalent in low-income countries. Inadequate intake of iodine impairs thyroid function and results in a spectrum of disorders. Other common deficiencies of micronutrients such as iron, selenium, vitamin A, and possibly zinc may interact with iodine nutrition and thyroid function. Randomised controlled intervention trials in iodine- and iron-deficient populations have shown that providing iron along with iodine results in greater improvements in thyroid function and volume than providing iodine alone. Vitamin A supplementation given alone or in combination with iodised salt can have a beneficial impact on thyroid function and thyroid size. Despite numerous studies of the effect of selenium on iodine and thyroid metabolism in animals, most published randomised controlled intervention trials in human populations failed to confirm an impact of selenium supplementation on thyroid metabolism. Little evidence is available on interactions between iodine and zinc metabolism.

Background

Despite ongoing efforts to control micronutrient deficiencies in low-income countries, deficiencies in iodine, iron, zinc, and vitamin A remain major public health problems. In the recent *Lancet* series on maternal and child undernutrition, deficiencies of vitamin A and zinc were estimated to be responsible for 600 000 and 500 000 deaths per year, respectively, and a combined 9.8% of global childhood Disability-Adjusted Life Years (DALYs).[1] The effects of iron and iodine deficiencies on child deaths were estimated to be smaller, though their impacts on cognitive development, educability and future

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doi:10.1016/j.beem.2009.08.012

economic productivity potential are considerable.[1] Deficiencies of iron, zinc and vitamin A often co-exist[2], possibly because of similar causal factors, such as (1) inadequate dietary intake and/or absorption from predominantly plant-based diets; (2) sub-optimal breast feeding practices; (3) diseases that either induce excessive losses or impair use of the micronutrients; and (4) physiological states that increase requirements, such as periods of rapid growth during childhood and pregnancy.

Inadequate intake of iodine impairs thyroid function and results in a spectrum of disorders, including goitre, impaired cognitive development and congenital abnormalities, collectively referred to as iodine-deficiency disorders (IDDs). Unlike the micronutrient deficiencies mentioned above, iodine deficiency mainly occurs in regions of low soil iodine content. Most iodine is found in the oceans as iodide, and regions of glaciations, heavy rainfall and floods tend to have low iodine soil content, which leads to iodine deficiency in plants and animals grown on these soils. Consequently, populations in such areas that depend on locally grown foods are at risk of developing iodine deficiency.

Iodine and thyroid metabolism have been reviewed in detail elsewhere.[3] Briefly, iodine is essential for the human body because it is part of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). Iodine deficiency leads to increased thyroid-stimulating hormone (TSH) stimulation, increased iodine uptake, rapid iodine turnover and enhanced production of T_3 in relation to T_4.

Besides iodine, other micronutrient deficiencies adversely affect the thyroid.[4] The present review focusses on the impact of highly prevalent micronutrient deficiencies, such as iron, zinc and vitamin A, on iodine and thyroid metabolism in low-income countries. In addition to the micronutrients known to be of major public health concern[1], the impact of combined iodine and selenium deficiencies are also reviewed as both animal and human studies indicate that there are interactions.[5] The evidence from human studies are reviewed and summarised. When available, the evidence from randomised clinical trials is prioritised.

Iron

Prevalence of iron deficiency

Iron is essential for human health because of its capacity to participate in redox reactions and its role in oxygen transport in the body. Iron deficiency can adversely affect cognitive development in childhood[6], immune function[7] and pregnancy outcomes.[8] Iron deficiency is more likely to occur in populations that rely on plant-based diets, which have low iron bioavailability. Moreover, infections, such as hookworm, can lead to blood loss, which further aggravates the iron status.

The global prevalence of iron deficiency with or without anaemia is unknown, as most nutritional surveys measured anaemia prevalence only. In a recent publication by the World Health Organization (WHO), it is estimated that approximately 25% of the population worldwide suffers from anaemia, of which the prevalence is highest among pre-school children (47%), pregnant (42%) and non-pregnant women (30%).[9] Although anaemia results from a wide variety of causes, it is generally assumed that approximately half of the cases of anaemia are due to iron deficiency.[10] Thus, the prevalence of iron deficiency is estimated to be high, and it is likely that iron and iodine deficiency often co-exist. In surveys in school-age children in West and North Africa, 23–25% suffer from both goitre and iron deficiency anaemia (IDA).[11,12]

Evidence of interactions between iron and iodine deficiencies

Numerous studies in animals have shown that IDA impairs thyroid metabolism. IDA decreases plasma total T_4 and T_3 concentrations, reduces the peripheral conversion of T_4 to T_3 and may increase circulating TSH.[4,13] This section will review the evidence from clinical trials in humans regarding interactions between iron and iodine deficiencies. While the cross-sectional studies investigating the correlation between iodine deficiency and IDA found inconsistent results[4], randomised clinical trials provided stronger evidence, as described below.

The first intervention trial shedding light on this interaction was a study by Zimmermann et al.[12], which investigated the effect of a 200-mg oral dose of iodine, as iodised oil, in goitrous school-age children with ($n = 53$) or without IDA ($n = 51$) in western Côte d'Ivoire. Children with IDA had lower

weight, lesser height and higher mean TSH concentration at baseline. After 15 and 30 weeks, thyroid volume was significantly reduced and TSH and T_4 concentrations were significantly improved in the non-anaemic group compared with the IDA group ($P < 0.001$). This descriptive study suggesting a relation between IDA and iodine metabolism found that non-anaemic children responded more rapidly to iodine with regard to thyroid size and TSH concentration, and children with IDA responded mainly after co-administration of iron.[14]

Since this observation, more evidence from randomised trials has become available on the impact of iron deficiency on thyroid metabolism, as summarised in Table 1. The first trial was conducted in iron-deficient goitrous school children in western Côte d'Ivoire, who received either placebo or iron supplementation (60 mg per day 4 times per week) in addition to iodised salt consumed at home.[15] Haemoglobin and iron status at 20 weeks were significantly improved in the iron-supplemented group than in the placebo group ($P < 0.05$). At 20 weeks, the mean reduction in thyroid size in the iron-treated group was nearly twice that in the placebo group resulting in a goitre prevalence of 43% in the iron-treated group compared with 62% in the placebo group ($P < 0.05$). This study led to the conclusion that iron supplementation improves the efficacy of iodised salt in goitrous children with iron deficiency.

Eftekhari et al.[16] evaluated the impact of iron supplementation on thyroid metabolism in Iranian adolescent girls with iron deficiency. Using a 2×2 factorial study design, participants were randomised into four groups and provided with (1) a single oral iodine dose of 190 mg plus iron supplements (60 mg per day 5 times per week), (2) a single oral iodine dose of 190 mg at baseline plus placebo, (3) iron supplementation alone or (4) placebo only for 12 weeks. Indicators of iron status significantly increased in the two groups receiving iron compared with the two non-iron groups and urinary iodine concentration doubled in the two iodine groups. While there was no difference between groups in final free T_4 and T_3 and TSH concentrations, final concentrations of total T_4, total T_3 and T_3 resin uptake were significantly greater and reverse T_3 concentration was significantly less in the groups that received iron with or without iodine compared with the groups that did not receive iron. Although the authors did not provide the normal range for their analysis along with these results, based on an earlier publication by the same authors[17], initial and final concentration of thyroid metabolism indicators remained within the normal range throughout the study. Thus, although there is indication of an increase in concentration of some thyroid hormones by providing iron supplements to iron-deficient adolescent girls, the question remains whether there was an actual functional benefit on thyroid metabolism.

Because IDA reduces the efficacy of iodine prophylaxis, the co-fortification of iodised salt with iron was considered a potential solution, not only to prevent iron deficiency, but also to improve the efficacy of iodised salt in populations with a high prevalence of IDA. In a double-blind, controlled intervention trial, 6- to 15-year-old children were randomly assigned at the household level to receive either iodised salt (IS) or dual-fortified salt (DFS) for 9 months.[11,18] Both salts contained 25 μg iodine per gram of salt providing an average of 175–300 μg iodine per day. In addition, the DFS contained 1 mg iron per gram of salt as ferrous sulphate encapsulated with partially hydrogenated vegetable oil. In the DFS group, the haemoglobin and iron status improved significantly compared with that in the IS group ($P < 0.05$). The impact of providing iron along with iodine in salt on iodine and thyroid status indicators was similar to the findings in Côte d'Ivoire[15] described above. Although there was a significant reduction in thyroid volume from baseline to 40 weeks in both groups ($P < 0.05$), the goitre prevalence was significantly lower in the DFS group compared with the IS group ($P < 0.01$). Even more importantly, thyroid hormone status significantly improved in the DFS group compared with that in the IS group. At 20 and 40 weeks, mean T_4 was increased and the prevalence of hypothyroidism ($T_4 < 65$ nmol l^{-1}) was significantly reduced in the DFS group.

Zimmermann et al.[19] confirmed these findings in a second study using a different iron compound, micronised ferric pyrophosphate, to fortify the dual-fortified salt at ~2 mg iron per gram of salt. After 10 months of salt consumption during family meals, the iron status of school-age children in the DFS group was significantly improved compared with those in the IS group. The study confirmed that DFS could have a significantly larger effect on final mean thyroid volume than iodised salt due to the beneficial impact of iron on thyroid metabolism in iron deficient children.

To test the concept of DFS to control iron and iodine deficiency in various populations, three additional trials evaluated the impact of DFS on iron and iodine status of school-age children in Côte d'Ivoire[20] and India[21] and of families in India.[22] The studies found a significant increase of iron

Table 1
The impact of providing iron in addition to iodine on iodine status and thyroid metabolism in randomized double-blind controlled intervention trials.

Study (Ref)	Study population characteristics	Age group (yrs)	Duration of intervention	Iodine intervention	Iron intervention
Iodine supplementation or iodized salt and iron supplementation					
Hess et al., 2002[15]	Goitrous, iron-deficient school children in Côte d'Ivoire	5–14	16 wks	Iodized salt (10–30 ppm)[c]	Placebo
				Iodized salt (10–30 ppm)[c]	60 mg oral iron as ferrous sulfate; 4x/wk
Eftekhari et al., 2006[16]	Iron-deficient, non-anemic Iranian adolescent girls	15.7 ± 1.4	12 wks	Placebo	Placebo
				Placebo	60 mg oral iron as ferrous sulfate; 5x/wk
				190 mg single oral iodine dose	Placebo
				190 mg single oral iodine dose	60 mg oral iron as ferrous sulfate; 5x/wk
Dual fortified salt with iodine and iron					
Zimmermann et al., 2002[18] and 2003[11]	School children in northern Morocco	6–15	9 months	IS (25 μg iodine/g salt)	None
				DFS with 25 μg iodine/g salt	DFS providing 7–12 g iron/day as encapsulated ferrous sulfate
Zimmermann et al., 2004[19]	School children in northern Morocco	6–15	10 months	IS (25 μg iodine/g salt)	None
				DFS with 25 μg iodine/g salt	DFS providing ~18 mg iron/day as micronized ferric pyrophosphate

IS, iodized salt; DFS, dual fortified salt; na, not available; ns, no significant difference in final values between groups; SD, standard deviation,: TSH, thyroid-stimulating hormone; T_4, thyroxine.

[a] Sample size at baseline.

[b] Results are shown as mean ± SD or as median (range), except for the plasma ferritin concentration in the study by Zimmermann et al., 2004 [19], which is presented as geometric mean (−1 SD and +1 SD).

[c] Half of the children in both groups were randomly selected to receive a single oral iodine dose of 200 mg as iodized poppy seed. Except urinary iodine concentration, none of the other outcomes differed between these sub-groups and are therefore combined for presentation. The results for final urinary iodine concentration are shown for the groups receiving iodized salt only.

[d] P-value for the difference in final mean value between groups.

[e] P-value for the difference in final mean urinary iodine concentrations between groups receiving iodine compared to groups not receiving iodine.

[f] P-value for the difference in final value compared to iodine group.

[g] P-value for the difference in final value compared to placebo group.

[h] No significant difference between any of the treatment groups.

[i] P-value for the difference in final mean hemoglobin and mean serum ferritin concentrations between groups receiving iron compared to groups not receiving iron.

status[20,21] and reduction of anaemia prevalence[21,22] in the DFS groups compared with the IS group. Although the results on iodine status were inconsistent, final urinary iodine concentrations was significantly increased from baseline in Côte d'Ivoire[20] and in one of the two comparison groups in the children study in India[21], but not in the family study in India.[22] Neither thyroid volume nor thyroid hormone status was measured in these latter studies, so detailed results are not presented here.

Various mechanisms have been suggested for the interaction between iron and iodine deficiencies. Results from animal studies suggest that IDA may influence thyroid metabolism by altering the central nervous system control[23], decreasing T_3 binding to hepatic nuclear receptors[24] and reducing thyroid peroxidase activity[25], an enzyme essential for thyroid hormone synthesis. IDA could also impair thyroid metabolism through lowered oxygen transport.[26] It is likely that these mechanisms jointly contribute to the impairment of thyroid function in iron deficiency.

In summary, a series of randomised controlled trials consistently found a significant reduction in thyroid volume in iron-deficient school-age children when iron was provided along with iodised salt either as iron supplement[15] or included into DFS.[11,19] These findings suggest that a high prevalence of iron deficiency among children in areas of endemic goitre may reduce the effectiveness of iodised salt programmes. Thus, the prevention of iron deficiency is not only beneficial for iron-related outcomes, but also to improve the response to iodised salt. Further studies should evaluate the interaction of iron and iodine deficiencies in young children and pregnant women, the most vulnerable population groups.

Table 1 (*continued*)

Study group	Sample size[a]	Final urinary iodine concentration (μg/L)[b]	Final thyroid volume (mL)[b]	Final Total T_4 concentration (nmol/L)[b]	Final TSH concentration (mIU/L)[b]	Final hemoglobin concentration (g/L)[b]	Final plasma serum ferritin concentration (μg/L)[b]
Iodine supplementation or iodized salt and iron supplementation							
Iodine	81	125 (23–445)	5.1 (2.1–21.4)	104 ± 29	0.8 (0.2–4.2)	115 ± 10	67.1 ± 38.3
Iodine + Iron	85	110 (17–271)	4.3 (2.1–12.9) ($P < 0.01$)[d]	105 ± 25 (ns)	0.7 (0.7–4.2) (ns)	124 ± 9 ($P < 0.05$)[d]	80.2 ± 39.6 ($P < 0.05$)[d]
Placebo	22	120 (100–240)	na	108 ± 10	2.3 ± 0.4	129 ± 3	11.0 ± 0.3
Iron	23	120 (100–270)	na	121 ± 12 ($P < 0.001$)[f] ($P < 0.01$)[g]	2.7 ± 0.7	142 ± 6 ($P < 0.001$)[i]	16.8 ± 1.5 ($P < 0.001$)[i]
Iodine	25	260 (140–380) ($P < 0.001$)[e]	na	108 ± 12	2.6 ± 0.8	129 ± 5	10.8 ± 0.7
Iodine + Iron	24	280 (140–410) ($P < 0.001$)[e]	na	129 ± 19 ($P < 0.001$)[f,g]	2.5 ± 0.6 (ns)[h]	143 ± 4 ($P < 0.001$)[i]	17.6 ± 0.9 ($P < 0.001$)[i]
Dual fortified salt with iodine and iron							
Iodine	184	182 (14–474)	7.3 ± 2.4	85 ± 13	0.6 (0.3–1.9)	116 ± 12	17 ± 12
Iodine + Iron	183	189 (23–406) (ns)	5.7 ± 2.1 ($P < 0.05$)[d]	102 ± 17 ($P < 0.05$)[d]	0.7 (0.2–2.4) (ns)	127 ± 12 ($P < 0.02$)[d]	40 ± 25 ($P < 0.05$)[d]
Iodine	83	104 (22–1784)	6.9 ± 2.2	na	na	115 ± 8	15.0 (6.9, 28.1)
Iodine + Iron	75	97 (17–1356) (ns)	5.9 ± 2.3 ($P < 0.01$)[d]	na	na	128 ± 11 ($P < 0.01$)[d]	33.1 (12.5, 76.4) ($P < 0.01$)[d]

Selenium

Prevalence of selenium deficiency

Selenium content in foods is determined by the soil content, the use of selenium-containing fertilisers and agricultural practices, as soil pH and moisture determine the selenium uptake by the plant.[27] Absorption of selenium in humans is efficient and not regulated.[28] Thus, selenium deficiency occurs mainly in regions where selenium soil content is low. Several parts of the world (e.g., Denmark, Finland, New Zealand, eastern and central Siberia (Russia) and a long belt from northeast to southcentral China) are known for having very low amounts of selenium in their soils and, therefore, their food systems.[27]

Selenium functions largely through an association with proteins, known as selenoproteins. As selenocysteine, it is an integral component of two important enzymes – glutathione peroxidase (GPX) and iodothyronine deiodinase – that are present in many tissues, including the thyroid gland. The mechanism of the interactions between selenium and thyroid metabolism have been previously reviewed in detail.[29,30] Briefly, there are three types of deiodinases. Two 5′-deiodinases (5′DI and 5′DII) catalyse the activation of the prohormone T_4 to the thyromimetically active thyroid hormone T_3 and 5′DI is also involved in the degradation of reserve T_3.[5] The third selenocysteine-containing deiodinase inactivates thyroid hormones, both the prohormone T_4 and its active metabolite such as T_3 and 3,5-T_2.[30] GPX and thioredoxin reductase are expressed in thyroid tissue and protect the thyroid gland from hydrogen peroxide produced during the synthesis of thyroid hormone, thereby protecting against oxidative damage. In conditions of inadequate supply of both iodide and selenium, complex rearrangements of thyroid hormone metabolism enable adaptation by increasing retention of selenium in the brain, endocrine tissues, and especially in the thyroid gland and iodide in the thyroid.[29] Severe deficiencies of selenium and iodine co-exist in China, Southeast Asia, Russia, Egypt and Central and West Africa.[31]

Evidence of interactions between selenium and iodine deficiencies in humans

In populations with severe iodine deficiency, endemic cretinism, an extreme form of mental retardation, occurs in two forms: myxedematous cretinism and neurological cretinism.[32] The pathogenesis of cretinism is unclear, but iodine deficiency plays an important role since the disease can be prevented with iodine prophylaxis.[32] Epidemiological surveys suggest that concomitant iodine and

selenium deficiencies are present in settings where myxedematous cretinism is highly prevalent in Central Africa[33,34], leading to the hypothesis that selenium deficiency exposes the thyroid gland to free radical damage of hydrogen peroxide produced during thyroid hormone synthesis.[32] However, a similar association of iodine and selenium deficiencies in Tibet and in China does not lead to myxedematous cretinism, indicating that a number of other risk factors must play a role.[30]

The following section reviews evidence on randomised controlled intervention trials evaluating the impact of selenium supplementation on thyroid metabolism (Table 2). The first selenium supplementation trial was done in school children in the Democratic Republic of the Congo (formerly known as Zaire).[35] School children in this area had a mean serum selenium concentration of $27.1 \pm 13.9\ \mu g\ l^{-1}$ and a median urinary iodine concentration (range) of 25.4 (11.4–58.4) $\mu g\ l^{-1}$ indicating severe selenium and moderate iodine deficiency.[34] After 2 months of selenium supplementation (50 μg per day), selenium status increased significantly in the supplemented group, but not in the control group. Mean serum total T_4, free T_4 and reverse T_3 concentration fell significantly to 66%, 71% and 73% of the initial value with selenium supplementation without a concomitant rise in serum TSH concentration.[35,36] These data suggest that, in iodine-deficient areas, correction of selenium deficiency without iodine supplementation increases peripheral T_4 to T_3 conversion due to selenium-enhanced degradation of thyroid hormones by deiodination. Subsequent provision of iodised oil to all children normalised all thyroid hormone concentrations, but did not overcome the decrease of the T_4 concentration caused by selenium supplementation.[35] These findings led to the conclusion that selenium supplementation should not be provided without concomitant iodine prophylaxis in an area of co-existing iodine and selenium deficiency.

Moreno-Reyes et al.[37] investigated the impact of selenium supplementation in school-age children with Kashin–Beck osteoarthopathy in Tibet. Participants were severely iodine deficient at the beginning of the study (mean urinary iodine concentrations $\sim 12\ \mu g\ l^{-1}$). Four months prior to selenium supplementation, children in the placebo and the selenium group received 475 mg iodine as iodised oil by intramuscular injection. Selenium was provided orally for 12 months either daily (100 μg per day) or weekly (1 mg per week) depending on available supplies. Selenium supplementation significantly increased mean urinary selenium, mean serum selenium and mean serum GPX concentrations compared with the placebo group. Mean serum T_4 significantly increased and mean serum T_3 and TSH concentrations significantly decreased with intramuscular iodine injection in both the groups and were within the normal range 4 months after the iodine injection. However, the subsequent selenium supplementation did not affect thyroid hormone and TSH concentrations ($P > 0.05$). Although selenium deficiency in combination with iodine deficiency is considered a risk factor of Kashin–Beck disease[31], selenium supplementation had no effect on established Kashin–Beck disease, growth and thyroid function once iodine deficiency was corrected.[37]

Several studies investigated the impact of selenium supplementation on thyroid function in different population groups in industrialised countries, as summarised below (Table 2). In apparently healthy adults, daily selenium supplementation with doses ranging from 10 to 300 μg per day were provided for a duration of 1[38], 5[39,40], and 12 months.[41] The four studies that included the analysis of serum or plasma selenium concentration found a significant increase in the selenium-supplemented groups compared with the placebo group.[38–40] However, four out of five studies found no difference in thyroid hormone or TSH concentrations between groups.[38,40,41] Only one study with a small sample size ($n = 10$ per group) found a significant reduction in T_4 concentrations in the group receiving a daily dose of 10 μg selenium or all supplemented groups combined compared to the control group after 20 weeks of supplementation.[39] Subjects in these five trials had low selenium status at baseline in some[38–40] but not other studies.[40,41] Information on iodine status was not available. These findings suggest that the provision of selenium supplementation in apparently health adults in industrialised countries is unlikely to have an impact on thyroid hormone status.

Because of decreasing dietary selenium intakes in the UK, Rayman et al.[42] investigated the impact of various daily oral doses of selenium (100, 200 and 300 μg per day) for 6 months in 501 elderly. There was no difference in plasma selenium concentration between groups at baseline, but the overall mean was higher than expected ($91.3\ \mu g\ l^{-1}$ (95% confidence interval (CI): 89.2–93.3)). Information on iodine status was not available. Selenium supplementation significantly increased plasma selenium concentrations in the supplemented groups, but did not have an impact on any of the measured markers of thyroid function (serum TSH, total T_4, free T_4, total T_3, free T_3, total T_3:T_4, free T_3:T_4) after 6 months of supplementation, either unadjusted or after adjustment for baseline values, gender, age

Table 2
The impact of providing selenium supplementation on iodine status and thyroid metabolism in randomized double-blind controlled intervention trials.[a]

Study (Ref)	Study population characteristics	Age group (yrs)	Duration of intervention	Iodine intervention	Selenium intervention	Study group	Sample size[b]	Final urinary iodine concentration (μg/L)[c]	Final Total T_4 concentration (nmol/L)[c]	Final TSH concentration (mIU/L)[c]	Final or change in serum, plasma or blood selenium concentration (μg/L)[c,d]	Final erythrocyte GPX (IU/g Hb) or serum GPX concentration (U/L)[c,e]
Selenium supplementation without iodine												
Contempré et al., 1992[35]	School children in severely selenium deficient area of DR Congo	na	2 mo	None	Placebo	Placebo	22	na	55.1 ± 38.0	19.0 (1.6–221)	38.4 ± 19.3	3.8 ± 3.0
				None	50 μg selenium/day	Selenium	23	na	48.3 ± 23.7 (ns)[f]	7.2 (5.6–9.3) ($P < 0.001$)[f,g]	74.5 ± 22.5 ($P < 0.001$)[f,g]	5.8 ± 2.2 ($P < 0.05$)[f,g]
Olivieri et al., 1995[43]	Apparently healthy elderly in Italy	86 ± 7	3 mo	None	Placebo	Placebo	17	na	68.5 ± 10.4	0.99 ± 0.71	60.0 ± 15.8	4.1 ± 1.1
				None	100 μg selenium/day	Selenium	19	na	62 ± 10 ($P < 0.05$)[g]	1.18 ± 0.58 (ns)	105.8 ± 23.7 ($P < 0.05$)[g]	7.78 ± 2 ($P < 0.05$)[g]
Duffield et al., 1999[39,40]	Apparently healthy adults with low selenium status[h] in New Zealand	19–59	20 wks	None	Placebo	Placebo	10	na	99 ± 30	na	Plasma 66.3 ± 12.6	na
				None	10 μg selenium/day	10 μg Selenium	10	na	93 ± 10 ($p < 0.05$)[i]	na	83.7 ± 17.4 ($P < 0.005$)[j]	na
				None	20 μg Selenium/day	20 μg Selenium	11	na	88 ± 15	na		na
				None	30 μg Selenium/day	30 μg Selenium	10	na	90 ± 17	na		na
				None	40 μg Selenium/day	40 μg Selenium	11	na	89 ± 19	na		na
Thomson et al., 2005[40] (study a)[k]	Smoking adults with low selenium status[h] in New Zealand	19–52	20 wks	None	Placebo	Placebo	30	na	91 ± 32	na	Plasma 79.7 ± 12.6	na
				None	100 μg selenium/day	Selenium	30	na	98 ± 33 (ns)	na	105.0 ± 11.8 ($P < 0.001$)[g]	na
Thomson et al., 2005[40] (study b)[k]	Apparently healthy adults in New Zealand	18–65	21 wks	None	Placebo yeast	Placebo	81	na	88 ± 23	na	Plasma 90 ± 14.2	na
				None	200 μg selenium/day as yeast	Selenium	82	na	84 ± 22 (ns)	na	172.9 ± 23.7 ($P < 0.001$)[g]	na
Negro et al., 2007[44]	Italian pregnant women with TPOAb(+)	18–36	Beginning in an average at 12 wks gestation until 12 mo postpartum	None	Placebo	Placebo	74	na	na	na	Blood at delivery: 79[l] 12 mo post-partum: 79[l]	na
				None	200 μg selenium/day	Selenium	77	na	na	na	At delivery: 112[l] ($P < 0.01$)[m] 12 mo post-partum: 112[l] ($P < 0.01$)[m]	na
Hawkes et al., 2008[41]	Adult US men	18–45	48 wks	None	Placebo yeast	Placebo	20	na	92 ± 18	2.2 ± 1.1	na	na
				None	300 μg selenium/day as yeast	Selenium	22	na	92 ± 22 (ns)	2.0 ± 0.9 (ns)	na	na

(*continued on next page*)

Table 2 (*continued*)

Study (Ref)	Study population characteristics	Age group (yrs)	Duration of intervention	Iodine intervention	Selenium intervention	Study group	Sample size[b]	Final urinary iodine concentration (μg/L)[c]	Final Total T_4 concentration (nmol/L)[c]	Final TSH concentration (mIU/L)[c]	Final or change in serum, plasma or blood selenium concentration (μg/L)[c,d]	Final erythrocyte GPX (IU/g Hb) or serum GPX concentration (U/L)[c,e]
Rayman et al., 2008[42]	Elderly men and women in the UK	60–74	6 mo	None	Placebo yeast	Placebo	90	na	87.2 ± 18.0	1.23 ± 0.72	−2.6 (95% CI: −5.9–0.6)	na
				None	100 μg selenium/day as yeast	Low selenium	99	na	87.0 ± 16.4	1.23 ± 0.70	54.9 (95% CI: 49.5–60.4) ($P < 0.001$)[n]	na
				None	200 μg selenium/day as yeast	Moderate selenium	95	na	83.5 ± 14.5	1.27 ± 0.69	99.0 (95% CI: 91.6–106.4) ($P < 0.001$)[n]	na
				None	300 μg selenium/day as yeast	High selenium	84	na	81.6 ± 14.4 (ns)	1.18 ± 0.69 (ns)	133.2 (95% CI: 123.1–143.3) ($P < 0.001$)[n]	na
Iodine and selenium supplementation												
Moreno-Reyes et al., 2003.[37]	Tibetan school-aged children with Kashin-Beck disease	5–15	12 mo	475 mg iodine as iodized oil by intramuscular injection[o]	Placebo	Placebo	95	39	115[l]	1.7[l]	29 (17–50)	442 (269–726)
				475 mg iodine as iodized oil by intramuscular injection[o]	100 μg oral selenium/day or 1 mg oral selenium/wk[p]	Selenium	113	39 (ns)	111[l] (ns)	2.1[l] (ns)	61 (43–85) ($P < 0.001$)[g]	818 (629–1064) ($P < 0.001$)[g]

CI, confidence interval; GPX, glutathione peroxidase; na, not available; ns, no significant difference in final values between groups; TPOAb(+), tested positive for thyroid peroxidase antibodies.

[a] The study by Arthur et al.[38] is not presented in the table as detailed results were not published.

[b] Sample size at baseline.

[c] Results are shown as mean ± SD, as mean (range) except for the final TSH concentration by Contempré et al., 1992[35], which is given as geometric mean (range), or as mean (95% CI).

[d] Final concentration provided in all studies, except for the study by Rayman et al[42], which provided change in plasma selenium concentration.

[e] Results on GPX were presented as final erythrocyte GPX[35,43] or final serum GPX[37] concentrations.

[f] For the purpose of this review, P-values were calculated from the published results using a two-sided T-test. For final TSH concentrations, SD was estimated from range after log-transformation.

[g] P-value for difference in final values between groups.

[h] Low selenium status was defined as whole-blood selenium concentration <99.5 μg/L in the study by Duffield[39] and as whole-blood selenium concentration <94.8 μg/L and whole-blood glutathione peroxidase activities <20 units/g in study 1 by Thomson.[40]

[i] P-value for difference in final mean T_4 concentration between the control group and the group receiving 10 μg selenium/day, after adjustment for baseline value. No significant difference between any of the other groups.

[j] Mean plasma selenium concentration after 20 weeks combined for all supplemented groups was significantly different from placebo group. Data published by Thomson et al., 2005.[40]

[k] Additional information provided by the author.

[l] Results estimated from graph.

[m] P-value for difference in final blood selenium concentrations between selenium supplemented and placebo group at delivery and 12 mo postpartum.

[n] P-value for differences between all groups.

[o] Iodine injection given 4 months prior to start of selenium supplementation.

[p] Daily selenium supplement (100 μg/d) were given during the initial phase of the study. Due to logistical problems, selenium was later given weekly (1 mg/wk).

group and clinic location.[42] By contrast, a much smaller study in Italian elderly found decreased T_4 concentrations in the group ($n = 19$) receiving 100 μg selenium per day for 3 months compared with the placebo group ($n = 17$).[43]

Another study investigated the impact of selenium supplementation in Italian pregnant women at risk of postpartum thyroid dysfunction and permanent hypothyroidism because of positive tests for thyroid peroxidase antibodies (TPOAb(+)).[44] One group was randomly assigned to receive 200 μg selenium per day and the other daily placebo beginning at 12 weeks of gestation until 12 months postpartum. Women were recommended to consume iodised salt at home. Initial blood selenium concentration was $79.5 \pm 2.3\ \mu g\ l^{-1}$ and concentrations increased significantly in the group receiving selenium compared with those receiving placebo. Details on final T_4 concentrations were not published, but fewer women in the selenium group developed thyroid dysfunction (28.6% vs. 48.6%; $P < 0.01$) and permanent hypothyroidism (11.7% vs. 20.3%; $P < 0.01$) compared to the placebo group by 12 months postpartum.[44] Moreover, selenium supplementation reduced TPOAb titres and improved the ultrasound echogenicity pattern compared with the control group. The authors concluded that selenium supplementation during pregnancy and the first 12 months postpartum reduces the risk of thyroid inflammation in pregnant women with TPOAb(+).

In summary, iodine and selenium interact in multiple ways in thyroid metabolism.[30] Although there is some indication from animal studies and cross-sectional studies in humans that selenium deficiency can adversely affect thyroid function[32], randomised controlled trials investigating the impact of selenium supplementation on thyroid metabolism in various population groups found inconsistent results, but generally failed to confirm the hypothesis. The expected interaction may be too modest to be detected in randomised intervention trials, subjects were not sufficiently iodine and/or selenium deficient and/or adaptation of the thyroid metabolism may be able to sufficiently adapt to mild-to-moderate selenium deficiency. Interactions between selenium and thyroid metabolism may be a concern in areas of severe selenium deficiency[35] and high-risk population groups.[44]

Vitamin A

Prevalence of vitamin A deficiency

Vitamin A deficiency is the leading cause of childhood blindness and a major nutritional determinant of severe infection and mortality among children in low-income countries.[45] Although the health consequences of vitamin A deficiency are not well described beyond early childhood, data from several intervention trials indicate that vitamin A deficiency in women of reproductive age may increase morbidity and mortality during pregnancy and the early postpartum period.[46]

Vitamin A in food is present in various forms, of which the pre-formed retinol from animal source foods such as liver, eggs and dairy products is the most bioavailable dietary source of vitamin A. The absorption of pro-vitamin A carotenoids from plants is influenced by various factors.[47] Thus, populations relying mainly on plant-based foods are at increased risk of vitamin A deficiency.

According to one estimate[46], approximately 127 million preschool children and 7.2 million pregnant women are vitamin A deficient (serum or breast milk vitamin A concentrations $<0.7\ \mu mol\ l^{-1}$) worldwide, of whom about 45% live in South and Southeast Asia and 25–35% in Africa. Substantial efforts are ongoing to control vitamin A deficiency through bi-annual distribution of high-dose vitamin A capsules to children of 6–59 months of age.[48]

Evidence of interactions between vitamin A and iodine deficiencies in humans

Although there is little information on the co-existence of iodine and vitamin A deficiencies, in view of their high prevalence in low-income countries, it is highly likely that a substantial number of individuals are affected by both. As recently reviewed by Zimmermann et al.[49], vitamin A deficiency has multiple effects on thyroid metabolism. Vitamin A status modulates thyroid gland metabolism, peripheral metabolism of thyroid hormone and production of TSH by the pituitary. At the thyroid, vitamin A deficiency causes thyroid hypertrophy, reduces thyroidal iodine uptake, impairs synthesis of thyroglobulin and coupling of iodotyrosine residues to form thyroid hormone and decreases

Table 3
The impact of providing vitamin A in addition to iodine on iodine status and thyroid metabolism in randomized double-blind controlled intervention trials in school-aged children.

Study (Ref)	Study population characteristics	Age group (yrs)	Duration of intervention	Iodine intervention	Vitamin A intervention	Study group	Sample size[a]	Final urinary iodine concentration (μg/L)[b]	Final thyroid volume (mL)[b]	Final Total T_4 concentration (nmol/L)[b]	Final TSH concentration (mIU/L)[b]	Final serum retinol concentration (μmol/L)[b]	Final retinol-binding protein concentration (mg/L)[b]
Zimmermann et al., 2004[50]	School children with severe iodine deficiency and low vitamin A status[c] in Morocco	6–14	10 mo	IS (25 μg iodine/g salt)	Placebo capsule at 0 and 5 mo	Iodine	71	104 (22–1104)	6.2 (2.1–11.9)	119 ± 22	1.6 (0.3–3.0)	0.79 ± 0.11	20.6 ± 8.8
				IS (25 μg iodine/g salt)	Vitamin A capsule (200,000 IU retinyl palmitate) at 0 and 5 mo	Iodine + Vitamin A	67	99 (21–1124) (ns)	5.3 (2.2–12.4) ($P < 0.05$)[d]	116 ± 22 (ns)	0.9 (0.3–2.1) ($P < 0.01$)[d]	1.09 ± 0.13 ($P < 0.01$)[d]	30.2 ± 11.2 ($P < 0.05$)[d]
Zimmermann et al., 2007[51]	South Africa	5–14	6 mo	Placebo	Placebo	Placebo	88	88 (13–455)	3.29 (1.08–10.08)	99 ± 19	1.7 (0.7–4.1)	0.91 ± 0.21	RBP 20.5 ± 10.1
				Placebo	Vitamin A capsule (200,000 IU retinyl palmitate)	Vitamin A	115	97 (15–470)	2.91 (0.88–8.96) ($P < 0.05$)[f]	97 ± 16	1.1 (0.5–2.9) ($P < 0.05$)[f]	1.22 ± 0.21 ($P < 0.05$)[h]	30.3 ± 11.8 ($P < 0.05$)[h]
				191 mg single oral iodine dose	Placebo	Iodine	100	149 (1–1044) ($P < 0.05$)[e]	2.34 (0.87–9.97) ($P < 0.05$)[g]	100 ± 17	0.6 (0.3–4.6) ($P < 0.05$)[g]	0.91 ± 0.24	21.3 ± 13.1
				191 mg single oral iodine dose	Vitamin A capsule (200,000 IU retinyl palmitate)	Iodine + Vitamin A	101	175 (4–1567) ($P < 0.05$)[e]	2.50 (1.01–8.18) ($P < 0.05$)[g]	102 ± 18 (ns)	0.5 (0.4–2.9) ($P < 0.05$)[g]	1.19 ± 0.22 ($P < 0.05$)[h]	29.6 ± 14.3 ($P < 0.05$)[h]

IS, iodized salt; na, not available; ns, no significant difference in final values between groups.
[a] Sample size at baseline.
[b] Results are shown as mean ± SD or as median (range).
[c] Low vitamin A status was defined as serum retinol <1.05 μmol/L. Median urinary iodine concentration at baseline was 10 μg/L.
[d] P-value for difference in final values between the two treatment groups.
[e] P-value for difference in final values between groups receiving iodine and not receiving iodine.
[f] P-value for difference final value between vitamin A supplemented group and the other 3 treatment groups.
[g] P-value for difference in final value between the groups receiving iodine compared to placebo group.
[h] P-value for difference in final values between groups receiving vitamin A and not receiving vitamin A.

intrathyroidal T_3 and T_4. In the periphery, vitamin A deficiency increases total and free T_4 and T_3, reduces hepatic conversion of T_4 to T_3 and decreases T_3 uptake and binding.[49]

Only two well-designed randomised intervention trials have investigated possible interactions in humans (Table 3). In an area of severe iodine deficiency in northern Morocco, school children with low vitamin A status (serum retinol <1.05 μmol l^{-1}) were randomly assigned to receive placebo or a high-dose vitamin A capsule (200 000 IU as retinyl palmitate) at 0 and 5 months.[50] All children received iodised salt (25 μg per gram salt) for 10 months. Urinary iodine concentrations increased significantly from baseline to 10 months in both groups and serum retinol and retinol-binding protein concentrations increased significantly in the iodine + vitamin A group. The median TSH and thyroglobulin concentrations decreased significantly in the iodine + vitamin A group compared with the iodine group ($P < 0.01$), but there were no changes in mean total T_4, transthyretin and thyroid-binding globulin concentrations. At 10 months, there was a significant reduction in mean thyroid volume ($P < 0.05$) and goitre rate (52% vs. 64%, $P < 0.01$) in the iodine + vitamin A group compared with the iodine group. The authors concluded that in areas of concurrent iodine and vitamin A deficiencies, vitamin A supplementation along with iodised salt improves the efficacy of iodised salt.[50]

To follow-up on these findings, Zimmermann et al.[51] investigated the impact of iodine and vitamin A on thyroid metabolism in a double-blind, randomised controlled trial using a 2×2 factorial design in school children in South Africa. At baseline and after 3 months, children received either (1) two placebo tablets (placebo group), (2) a vitamin A capsule (200 000 IU as retinyl palmitate) and placebo (vitamin A group), (3) iodised oil (191 mg iodine) and a placebo (iodine group) or (4) iodised oil and a vitamin A capsule (iodine + vitamin A group). At baseline, 12% of children had serum retinol concentrations <0.7 μmol l^{-1}. The median urinary iodine was 74 μg l^{-1}, which indicated mild iodine deficiency. The goitre rate was 27%. Iodine status increased significantly from baseline after 3 and 6 months in the two groups receiving iodised oil compared with the other two groups. Similarly, serum retinol and retinol-binding protein concentrations significantly increased with the vitamin A capsules. Thyroid volume and TSH concentration decreased significantly more in the two groups receiving iodine compared with the other two groups not receiving iodine. Moreover, the vitamin A group also had a significantly reduced thyroid volume and decreased TSH concentration compared with the placebo group, indicating that vitamin A on its own had a beneficial impact on thyroid metabolism in these children. No difference between groups was found for total T_4 concentrations. The new finding of this study was that vitamin A supplementation alone in iodine-deficient children with mild vitamin A deficiency reduced circulating TSH, serum thyroglobulin and thyroid size without significantly affecting thyroid hormone concentrations. This implies that either the sensitivity of the thyroid to TSH increased with vitamin A supplementation or the metabolism of circulating thyroid hormone was altered to maintain their concentrations.

In summary, only two studies were identified that investigated the public health impact of controlling concurrent iodine and vitamin A deficiencies on thyroid metabolism. The first study in Morocco[50] found that providing vitamin A along with iodised salt improved the thyroid's response to the iodine prophylaxis in goitrous vitamin A-deficient children. The second study in an area of mild iodine and moderate vitamin A deficiency in South Africa[51] found no difference between the groups receiving either iodised oil alone or with concurrent high-dose vitamin A supplementation, although there was a significant impact of vitamin A supplementation alone on thyroid volume and TSH concentration. The varying results of these two studies could be due to differences in the severity of iodine deficiency, study duration, the type of iodine prophylaxis (iodised salt in Morocco and iodised oil in South Africa) or a combination of these factors. Further research is required to better understand the impact of concurrent iodine and vitamin A deficiency on thyroid metabolism, in particular, in young children and pregnant women, the most vulnerable population groups. The individual and joint public health impact of universal iodised salt and high-dose vitamin A supplementation programmes needs further assessment.

Zinc

Prevalence of zinc deficiency

Adequate zinc nutrition is essential for human health because of zinc's critical structural and functional roles in multiple enzymes that are involved in gene expression, cell division and growth, and

immunological and reproductive functions. As a consequence, zinc deficiency affects children's physical growth, and the risk and severity of a variety of infections.[52] As with iron and vitamin A, populations who depend mostly on plant-based diets are at increased risk of zinc deficiency due to the low bioavailability of zinc from plant sources. Additional factors that may exacerbate suboptimal zinc status, include increased faecal losses of zinc during diarrhoea[53] and malabsorption due to abnormalities in the intestinal tract, which are both likely to occur in low-income countries.[54]

Because so little information is available from nationally representative surveys on the prevalence of low serum zinc concentration or inadequate dietary zinc intake, current estimates of the extent of zinc deficiency must rely on the prevalence of stunting among children under 5 years of age.[55] Approximately 30% of children under 5 years of age worldwide are stunted (Height-for-age Z-scoare (HAZ)−2 SD with respect to the distribution of the reference population data).[56] WHO recommends using a prevalence of stunting greater than 20% of the population to indicate a public health concern.[57] The highest rates of stunting (>30%) are observed in countries in sub-Saharan Africa, South Asia, Southeast Asia and Central America indicating an increased risk of zinc deficiency in these populations.

Evidence of interactions between zinc and iodine deficiencies in humans

There are implications that zinc is also important for normal thyroid homeostasis. Zinc's role is complex and may include effects on both the synthesis and mode of action of the thyroid hormones.[58] However, results from animal studies are inconclusive.[4] Except for some specific studies of zinc supplementation on thyroid metabolism in children with Down's syndrome, which will not be summarised here, Pub Med searches did not identify any randomised controlled trials. Thus, findings of cross-sectional studies and one zinc-depletion study are summarised below. However, serum or plasma zinc concentration is unlikely to reflect an individual's true zinc status, except in cases of either relatively severe zinc deficiency or continuous consumption of zinc supplements, so misclassification of individual zinc status is possible.[59]

Cross-sectional studies investigating whether hypothyroid or hyperthyroid patients have abnormally low or abnormally high serum zinc concentrations, respectively, found inconsistent results.[4,60] No significant difference in thyroid hormone concentrations was found in six apparently healthy men with low serum zinc concentrations compared to eight apparently healthy men with high serum zinc concentration. However, serum T_4 concentration increased in the low zinc group following zinc supplementation.[61] In a cross-section of Iranian school children ($n = 1188$), no differences in thyroid hormone concentration and goitre rate were found in children with low and high serum zinc concentration.[62] By contrast, a study in Turkey found that goitrous men had significantly lower plasma zinc concentrations ($104 \pm 3\ \mu g\ dl^{-1}$; $n = 140$) than a comparison group of 140 non-goitrous men ($116 \pm 2\ \mu g\ dl^{-1}$, $P = 0.001$). However, the statistical analysis did not control for potential confounding factors.[63] No correlation was observed between zinc intake or serum zinc concentration and thyroid hormone concentrations in middle-aged and older European men and women ($n = 387$).[64] A moderate negative correlation was found only with total T_4 and red blood cell zinc concentrations ($r = -0.12$, $P < 0.02$, slope -0.026), which suggests that low zinc status may promote higher plasma total T_4 levels. In a 75-day zinc-depletion study of six young men, serum TSH, total T_4 and free T_4 concentrations tended to decrease during the period of low zinc intake (5.5 mg per day for 54 days), but only the reduction of free T_4 was significant ($P < 0.05$).[65]

In summary, existing studies found inconclusive evidence for interactions between zinc deficiency and thyroid metabolism, but they were based on relatively weak study designs. Because of the difficulties of assessing individual zinc status, it would be worth examining the impact of controlled zinc intervention trials on iodine and thyroid metabolism in population with an elevated risk of zinc deficiency.

Conclusion

Deficiencies of the micronutrients reviewed here are highly prevalent in low-income countries and each of them individually has serious adverse effects on health and welfare[1,66], in particular, during periods of rapid growth and pregnancy. Thus, the prevention of these micronutrients in populations at

risk should be of highest priority. Micronutrient deficiencies can be controlled individually through programmes such as salt iodisation[67] and high-dose vitamin A capsules[68] or in combination with other micronutrients. Examples of interventions with multiple micronutrients are fortification of staple foods[69] and complementary foods[70], or supplementation with a product targeting specific population groups as, for example, micronutrient supplements for pregnant women[71] and multiple micronutrients containing powders or pastes for young children.[72] The optimal approach will depend on numerous factors, such as the prevalence of micronutrient deficiencies, the target population group(s), potential adverse effects and the presence of other ongoing programmes, to only name a few.

As reviewed above, the prevention of one micronutrient deficiency may not only benefit the specific health outcomes related to that micronutrient, but may in fact increase the effectiveness of other micronutrient programmes. To the contrary, a micronutrient deficiency that is prevalent in a population may decrease the impact of an ongoing public health programme through interactions with the metabolism of another micronutrient. There is strong evidence for such an interaction between iron and iodine and thyroid metabolism. Randomised controlled intervention trials have repeatedly shown that providing iron along with iodine either as iron supplement[15] or as DFS[11,19] can benefit the iodine prophylaxis programme and result in significant improvements of thyroid metabolism. Similarly, but with slightly less evidence, vitamin A supplementation may not only benefit vitamin A-related outcomes, but also provide a beneficial impact on thyroid metabolism, either when given alone[51] or in combination with iodised salt.[50] Although much is known about the interactions between selenium, iodine and thyroid mechanisms[29], most published randomised controlled intervention trials failed to confirm an impact of selenium supplementation on thyroid metabolism. Because of concerns raised, giving selenium supplementation alone in iodine-deficient populations is not recommended[35], but more research is needed. Less evidence is available on interactions between iodine and zinc metabolism. Considering the observed interactions between common micronutrient deficiencies, an integrative approach in preventing micronutrient deficiencies seems advantageous, where possible.

Practice points

- In individuals with concurrent iodine and iron deficiency, both micronutrients should be provided.
- In individuals and populations with concurrent iodine and vitamin A deficiency, both micronutrients should be provided.
- In iodine-deficient individuals and populations, selenium should be provided only after iodine deficiency is corrected.
- The best approach for the prevention of iodine deficiency is generally by providing iodised salt, although iodised oil should be considered in some settings.[73] Multiple approaches are possible for delivering iron, vitamin A, zinc and selenium, such as supplementation, fortification and dietary diversification/modification[69,71,74–76], and specific strategies need to be developed in particular settings.

Research agenda

- Because most studies have been conducted in school children and non-pregnant adults, information is needed on interactions of common micronutrient deficiencies with iodine and thyroid metabolism in infants and pregnant women, the most vulnerable population groups, possibly using isotopic tracers.
- Large-scale effectiveness trials in carefully assessed individuals with specific deficiencies are needed to examine the impact of micronutrient intervention strategies on micronutrient status, functional outcomes and possible interactions with iodine and thyroid metabolism.

Acknowledgement

I appreciate valuable comments on the article provided by Kenneth H. Brown, Department of Nutrition, University of California, Davis, CA, USA and assistance provided by Rita Wegmüller, Institute of Food Science and Nutrition, Swiss Federal Institute of Technology, Zurich, Switzerland. Partial funding was provided by the International Zinc Nutrition Consultative Group (IZiNCG).

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