Iodine-deficiency disorders

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2 billion individuals worldwide have insufficient iodine intake, with those in south Asia and sub-Saharan Africa particularly affected. Iodine deficiency has many adverse effects on growth and development. These effects are due to inadequate production of thyroid hormone and are termed iodine-deficiency disorders. Iodine deficiency is the most common cause of preventable mental impairment worldwide. Assessment methods include urinary iodine concentration, goitre, newborn thyroid-stimulating hormone, and blood thyroglobulin. In nearly all countries, the best strategy to control iodine deficiency is iodisation of salt, which is one of the most cost-effective ways to contribute to economic and social development. When iodisation of salt is not possible, iodine supplements can be given to susceptible groups. Introduction of iodised salt to regions of chronic iodine-deficiency disorders might transiently increase the proportion of thyroid disorders, but overall the small risks of iodine excess are far outweighed by the substantial risks of iodine deficiency. International efforts to control iodine-deficiency disorders are slowing, and reaching the third of the worldwide population that remains deficient poses major challenges.

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Introduction

Iodine (atomic weight 126·9 g per atom) is an essential component of the hormones produced by the thyroid gland. Thyroid hormones, and therefore iodine, are essential for mammalian life. Iodine (as iodide) is widely but unevenly distributed in the earth's environment. Most iodide is found in the oceans (about 50 µg/L), and iodide ions in seawater oxidise to form elemental iodine, which is volatile and evaporates into the atmosphere and returns to the soil by rain, completing the cycle. However, the cycle of iodine in many regions is slow and incomplete, and soils and groundwater become deficient in iodine. Crops grown in these soils will be low in iodine concentration, and man and animals consuming food grown in these soils become deficient in iodine.[1]

In plants grown in deficient soils, iodine concentration might be as low as 10 µg/kg of dry weight, compared with about 1 mg/kg in plants from iodine-sufficient soils. Iodine-deficient soils are common in inland regions, mountainous areas, and places with frequent flooding, but can als-o occur in coastal regions.[2] Iodine deficiency in populations residing in these areas will persist until iodine enters the food chain through addition of iodine to foods (eg, iodisation of salt) or dietary diversification introduces foods produced in iodine-sufficient regions.

The native iodine content of most foods and beverages is low, and most commonly consumed foods provide 3–80 µg per serving.[3–7] Major dietary sources of iodine in the USA and Europe are bread and milk.[3,4] On the basis of direct food analysis, mean intake of dietary iodine is about 140 µg per day in Switzerland and 100–180 µg per day in Libya.[3,6] Boiling, baking, and canning of foods containing iodated salt cause only small losses (≤10%) of iodine content.[8] Iodine content in foods is also determined by iodine-containing compounds used in irrigation, fertilisers, and livestock feed. Iodophors used for cleaning milk cans and teats can increase the native iodine content of dairy products;[9] few data are available for the bioavailability of iodine or potential health risks from these iodophors. Traditionally, iodate was used in bread making as a conditioner for dough, but it is being replaced by non-iodine-containing conditioners.

Iodide is rapidly and nearly wholly absorbed (>90%) in the stomach and duodenum.[5] Iodate, widely used in iodisation of salt, is reduced in the gut and absorbed as iodide. Organically bound iodine is typically digested and the released iodide absorbed, but about 75% of an oral dose of the thyroid hormone thyroxine is absorbed intact. Thyroid clearance of circulating iodine varies with iodine intake: in situations with adequate iodine supply, 10% or less of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency, this percentage can exceed 80%.[10] Under normal circumstances, plasma iodine has a half-life of about 10 h, but this time is

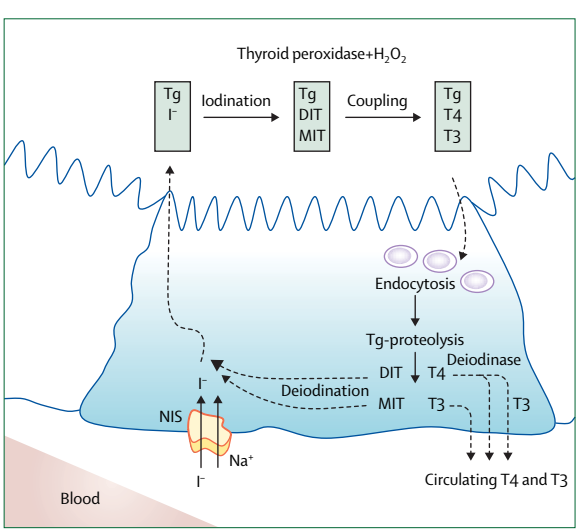

Figure 1: **Iodine pathway in the thyroid cell**
Iodide (I^-) is transported into the thyrocyte by the sodium/iodide symporter (NIS) at the basal membrane and migrates to the apical membrane. I^- is oxidised by the enzymes thyroperoxidase (TPO) and hydrogen peroxidase (H_2O_2) and attached to tyrosyl residues in thyroglobulin (Tg) to produce the hormone precursors iodotyrosine (MIT) and di-iodotyrosine (DIT). Residues then couple to form thyroxine (T4) and tri-iodothyronine (T3) within the Tg molecule in the follicular lumen. Tg enters the cell by endocytosis and is digested. T4 and T3 are released into the circulation, and iodine on MIT and DIT is recycled within the thyrocyte.

reduced in iodine deficiency. During lactation, the mammary gland concentrates iodine and secretes it into breastmilk to provide for the newborn infant.[11]

The body of a healthy adult contains 15–20 mg of iodine, of which 70–80% is in the thyroid. In chronic iodine deficiency, the iodine content of the thyroid might fall to less than 20 µg. In iodine-sufficient areas, the adult thyroid traps about 60 µg of iodine per day to balance losses and maintain synthesis of thyroid hormone. The sodium/iodide symporter transfers iodide into the thyroid at a concentration gradient 20–50 times that of plasma (figure 1).[12] Iodine consists of 65% and 59% of the weights of thyroxine (T4) and tri-iodothyronine (T3), respectively. Turnover is slow: the half-life of T4 is about 5 days and for T3, 1·5–3 days. The released iodine enters the plasma iodine pool and can be taken up again by the thyroid or excreted by the kidney. More than 90% of ingested iodine is ultimately excreted in the urine. Iodine deficiency is the main cause of endemic goitre, but other dietary substances (termed goitrogens) that interfere with thyroid metabolism can aggravate the effect (table 1).[22] Most goitrogens do not have a major clinical effect unless there is coexisting iodine deficiency.

Table 2 shows recommendations for daily iodine intake by age group. The iodine requirement during pregnancy is increased because of a rise in maternal T4 production to maintain maternal euthyroidism and transfer of thyroid hormones to the fetus; iodine transfer to the fetus, especially in late gestation; and a likely increase in renal iodine clearance.[24]

	Mechanism
Foods	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides; they are metabolised to thiocyanates that compete with iodine for thyroidal uptake[13]
Cruciferous vegetables such as cabbage, kale, caulifower, broccoli, turnips, rapeseed	Contain glucosinolates; metabolites compete with iodine for thyroidal uptake[13]
Soy, millet	Flavonoids impair thyroid peroxidase activity[14,15]
Industrial pollutants	
Perchlorate	Competitive inhibitor of the sodium/iodine symporter, decreasing iodine transport into the thyroid[16]
Others (eg, disulphides from coal processes)	Reduce thyroidal iodine uptake[13]
Smoking	An important goitrogen; smoking during breastfeeding is associated with reduced iodine concentrations in breastmilk; high serum concentration of thiocyanate due to smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast[17]
Nutrients	
Selenium deficiency	Accumulated peroxides might damage the thyroid, and deiodinase deficiency impairs thyroid hormone synthesis[13,18]
Iron deficiency	Reduces haeme-dependent thyroperoxidase activity in the thyroid and might blunt the efficacy of iodine prophylaxis[19,20]
Vitamin A deficiency	Increases TSH stimulation and goitre through decreased vitamin A-mediated suppression of the pituitary TSHβ gene[21]

TSH=thyroid-stimulating hormone.

Table 1: **Goitrogens and their mechanism**

	Iodine intake (µg per day)
US Institute of Medicine recommendations[5]	
Infants 0–12 months*	110–130
Children 1–8 years	90
Children 9–13 years	120
Children ≥14 years+adults	150
Pregnancy	220
Lactation	290
WHO recommendations†[1,23]	
Children 0–5 years	90
Children 6–12 years	120
Children ≥12 years+adults	150
Pregnancy	250
Lactation	250

*Adequate intake. †Recommended nutrient intake. ‡Recommended daily allowance.

Table 2: **Recommendations for iodine intake by age or population group‡**

Pathophysiology of deficiency

Iodine deficiency has many adverse effects on growth and development in animals and man. These effects are collectively termed iodine-deficiency disorders (panel), and are common in human beings.[25] They result from inadequate thyroid hormone production due to insufficient iodine.

Thyroid enlargement (goitre) is the classic sign of iodine deficiency, and can take place at any age, even in newborn babies. It is a physiological adaptation to chronic iodine deficiency. As the iodine intake falls, secretion of thyroid-stimulating hormone (TSH) increases in an effort to maximise uptake of available iodine, and TSH stimulates thyroid hypertrophy and hyperplasia. Initially, goitres are characterised by diffuse, homogeneous enlargement, but over time nodules often develop (figure 2). Many thyroid nodules derive from a somatic mutation and are of monoclonal origin;[27] the mutations seem to be more likely to result in nodules under the effect of a growth promoter, such as iodine deficiency. Iodine deficiency is associated with a high occurrence of multinodular toxic goitre, mainly seen in women older than 50 years.[28]

The most serious adverse effect of iodine deficiency is damage to the fetus. Maternal thyroxine crosses the placenta before onset of fetal thyroid function at 10–12 weeks and represents up to 20–40% of T4 measured in cord blood at birth.[29] Normal amounts of thyroid hormones are needed for neuronal migration and myelination of the fetal brain, and insufficient iodine irreversibly impairs development of the brain.[30] Severe iodine deficiency during pregnancy increases risk of stillbirths, abortions, and congenital abnormalities.[31–33] Iodine treatment of pregnant women in regions of severe deficiency reduces fetal and perinatal mortality and improves motor and cognitive performance of the offspring.[34,35] Severe iodine deficiency in utero causes a

condition called cretinism, which is characterised by gross mental retardation along with varying degrees of short stature, deaf-mutism, and spasticity.[1,25] Two distinct types—neurological and myxoedematous—have been described (figure 3), which might also present as a mixed form. In areas of severe iodine deficiency, cretinism can affect 5–15% of the population. Iodine prophylaxis has completely eliminated the occurrence of new cases of cretinism in previously iodine-deficient Switzerland and other countries, but it continues to arise in isolated regions of western China.[36]

The potential adverse effects of mild-to-moderate iodine deficiency during pregnancy are unclear. Maternal subclinical hypothyroidism (an increased concentration of TSH in the second trimester) and maternal hypothyroxinaemia (a free thyroxine concentration <tenth percentile at 12-week gestation) are associated with impaired mental and psychomotor development of the offspring.[37,38] However, in these studies, maternal thyroid abnormalities were not likely to be due to iodine deficiency. In Europe, several randomised controlled trials of iodine supplementation in mild-to-moderately iodine-deficient pregnant women have been done.[39] Iodine reduced maternal and newborn thyroid size, and, in some, decreased maternal TSH. However, none of the trials showed an effect on maternal and newborn total or free thyroid hormone concentrations, which is the most important outcome,[40] and none measured long-term clinical outcomes, such as maternal goitre, thyroid autoimmunity, or child development.

Although iodine deficiency in utero impairs fetal growth and brain development, its postnatal effects on growth and cognition are less clear. Cross-sectional studies of moderate-to-severely iodine-deficient children have generally reported impaired intellectual function and fine motor skills; two meta-analyses estimated that populations with chronic iodine deficiency showed a reduction in their intelligence quotient of 12·5–13·5 points.[41,42] However, observational studies are often confounded by other factors that affect child development, and these studies could not distinguish between the persistent effects of in-utero iodine deficiency and effects of current iodine status. Investigators in several randomised trials have examined the effect of iodine supplementation on the cognitive performance of children, but their results are equivocal, and methodological difficulties restrict their interpretation.[43] In a controlled trial of 10–12-year-old moderately iodine-deficient Albanian children who received 400 mg of iodine as oral iodised oil or placebo, iodine treatment substantially improved processing of information, fine motor skills, and visual problem-solving ability compared with those given placebo.[43] Thus, in children born and raised in areas of iodine deficiency, cognitive impairment is at least partly reversible by iodine repletion.[43]

Data from cross-sectional studies on iodine intake and child growth are mixed, with most studies showing modest positive correlations.[44] In five Asian countries, household access to iodised salt was correlated with increased weight-for-age and mid-upper-arm circumference in infancy.[45] However, results from controlled intervention studies of iodised oil alone and iodine given with other micronutrients have generally not shown effects on child growth.[44] In iodine-deficient children,

***Panel:* Health consequences of iodine deficiency**[1,25,26]

- All ages: goitre including toxic nodular goitre; increased occurrence of hypothyroidism in moderate-to-severe iodine deficiency; reduced occurrence of hypothyroidism in mild-to-moderate iodine deficiency; enhanced susceptibility of the thyroid gland to nuclear radiation
- Fetus: abortion, stillbirth, congenital anomalies, perinatal mortality
- Neonate: infant mortality; endemic cretinism
- Child and adolescent: impaired mental function; delayed physical development
- Adults: impaired mental function; overall, moderate-to-severe iodine deficiency causes subtle but widespread adverse effects in a population secondary to hypothyroidism, including decreased educability, apathy, and reduced work productivity, resulting in impaired social and economic development

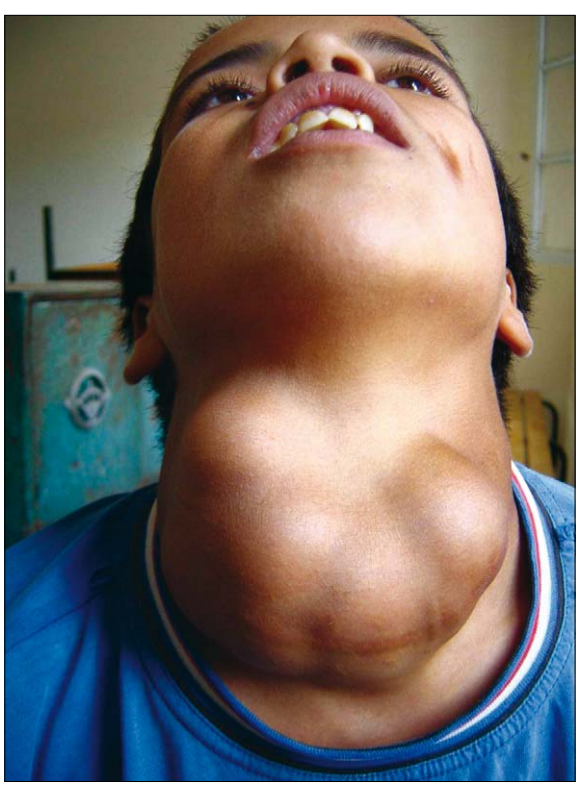

Figure 2: **Large nodular goitre**
Photograph of a 14-year-old boy in 2004 in an area of severe iodine-deficiency disorders in northern Morocco, with tracheal and oesophageal compression and hoarseness, probably due to damage to the recurrent laryngeal nerves.

impaired thyroid function and goitre were inversely correlated with insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3) concentrations.[46] Investigators in controlled trials reported that iodine repletion increased IGF-1 and IGFBP-3 and improved somatic growth in children.[44]

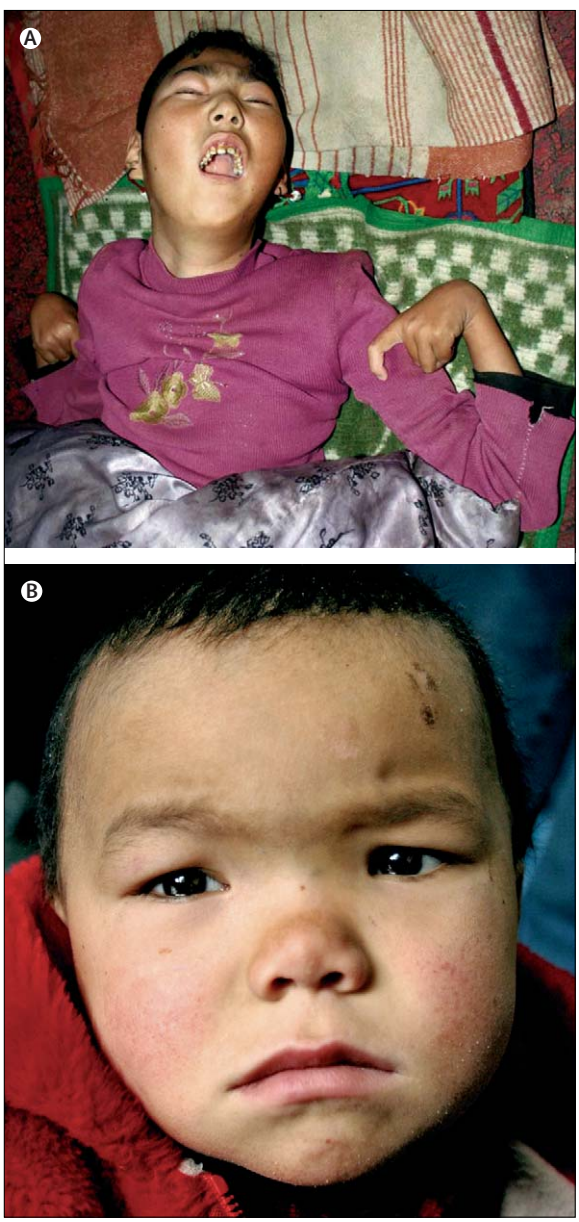

Figure 3: **Cretinism**
(A) Neurological cretinism in a 9-year-old girl (photograph, 2007) from western China shows three characteristic features: severe mental deficiency together with squint, deaf mutism, and motor spasticity of the arms and legs. The thyroid is present, and frequency of goitre and thyroid dysfunction is similar to that noted in the general population. (B) Myxoedematous cretinism in a 7-year-old girl (photograph, 2008) from western China with the characteristic features: severe mental retardation; short stature (height 106 cm); profound hypothyroidism; incomplete maturation of the face with wide-set eyes, mild strabismus, saddle-nose deformity, and mandibular atrophy; and thickened, dry skin and hair. The thyroid typically shows atrophic fibrosis.

Epidemiology

Only a few countries—eg, Switzerland, some of the Scandinavian countries, Australia, the USA, and Canada—were completely iodine sufficient before 1990. Since then, worldwide, the number of households using iodised salt has risen from less than 20% to more than 70%, strikingly reducing iodine deficiency.[47] This effort has been spurred by a coalition of international organisations—including International Council for Control of Iodine Deficiency (ICCIDD), WHO, Micronutrient Initiative, and UNICEF—working closely with national iodine-deficiency disorders control committees and the salt industry; this informal partnership was established after the World Summit for Children in 1990 and has been funded by Kiwanis International, UNICEF, the Bill & Melinda Gates Foundation, and country aid programmes. In 2007, WHO estimated that nearly 2 billion individuals have an insufficient intake of iodine, including a third of all school-aged children (table 3).[49] The lowest prevalence of iodine deficiency is in the Americas (10·6%), where the proportion of households consuming iodised salt is the highest in the world (about 90%). The highest prevalence of iodine deficiency is in Europe (52%), where the household coverage with iodised salt is the lowest (about 25%), and many of these countries have weak or non-existent control programmes for iodine-deficiency disorders.

As shown in figure 4, iodine deficiency remains a public-health problem in 47 countries. However, progress has been made since 2003; 12 countries have progressed to optimum iodine status and the percentage of school-aged children at risk of iodine deficiency has decreased by 5% (figure 5). However, iodine intake is more than adequate, or even excessive, in 34 countries, an increase from 27 in 2003.[49] In Australia and the USA, two countries that were previously iodine sufficient, iodine intakes are falling. Australia is now mildly iodine deficient,[52] and in the USA, the median urinary iodine is 145 μg/L, which is still adequate but half the median value of 321 μg/L noted in the 1970s.[53,54] These changes emphasise the importance of regular monitoring of iodine status in countries, to detect both low and excessive intakes of iodine.

Several limitations to WHO's data for prevalence exist. First, extrapolation from a population indicator (median urinary iodine) to define the number of individuals affected is not straightforward—eg, a country in which children have a median urinary iodine concentration of 100 μg/L would be classified as being iodine sufficient, yet at the same time 50% of the children would be classified as having inadequate iodine intakes. Second, nationally representative surveys depict only 60% of the worldwide population included in WHO data, and subnational data might underestimate or overestimate the extent of iodine deficiency.[49] Last, data from nearly all countries are insufficient to estimate the prevalence of iodine deficiency in pregnant women.

Household coverage by iodised salt in south Asia is only 49%. More than 17 million babies in this region are born every year unprotected from brain damage because of iodine deficiency; this is about 40% of all unprotected births worldwide.[55] There are major challenges to increasing coverage of iodised salt in the region, including the presence of a large number of small, local salt producers, inadequate monitoring, or insufficient political commitment. In India, despite intensive efforts to promote iodised salt, only about half the population is covered, and coverage is especially poor in low socioeconomic populations.[56–58] Iodised salt is unavailable in many rural markets, or salt sold as iodised is poorly or incompletely iodised, or both. In 1997, in a move to increase the consumption of iodised salt, the Government of India banned the sale of non-iodised salt for human consumption. However, in September, 2000, the Government of India lifted the ban, which led to a 12% decrease in the coverage of iodised salt nationwide.[58] Only after intense advocacy by international and national partners did the Government of India reimpose the ban in May, 2006.

64% of households in sub-Saharan Africa use iodised salt, but coverage varies widely from country to country.[50] In countries such as Sudan, Mauritania, Guinea-Bissau, and The Gambia, coverage is less than 10%, whereas in Burundi, Kenya, Nigeria, Tunisia, Uganda, and Zimbabwe, it is more than 90%. Several countries have absent or weak legislation on iodised salt, and in those with legislation, the stipulated iodine content for salt ranges from 20 parts per million (ppm) to 100 ppm. As a consequence, iodine status in sub-Saharan Africa varies from obvious iodine deficiency in countries such as Ethiopia, Sierra Leone, and Angola, to iodine excess in the Democratic Republic of the Congo, Uganda, and Kenya.[59,60] Many sub-Saharan countries have outstanding programmes, including Nigeria, which has been recognised as the first African country to successfully eliminate iodine deficiency.[61]

The control of iodine-deficiency disorders in sub-Saharan Africa poses several challenges. In many countries, attempts to effectively implement or enforce, or do both, iodised-salt programmes have been derailed by conflict, famine, and political instability.[62] Emphasis should be placed on the education of government leaders and the public, formation of national coalitions for iodine-deficiency disorders, and generation of country-specific information about iodine status. Countries with legislation requiring 80–100 ppm of iodine in salt should reduce to 20–40 ppm,[1] and they should improve their monitoring of iodine status. Last, taking into account repackaging and selling of non-iodised salt in the informal sector, as has been done in South Africa,[63] will further improve salt-iodisation programmes.

Assessment and diagnosis

Four methods are generally recommended for assessment of iodine nutrition (table 4): urinary iodine concentration, goitre rate, serum TSH, and serum thyroglobulin.[72] These indicators are complementary, in that urine iodine concentration is a sensitive indicator of recent iodine intake (days) and thyroglobulin shows an intermediate response (weeks to months), whereas changes in the goitre rate show long-term iodine nutrition (months to years).

	Population with urinary iodine <100 µg/L*		Proportion of households with access to iodised salt†
	As proportion of general population (all age groups)	As proportion of school-age children (6–12 years)	
Africa	41·5% (312·9)	40·8% (57·7)	66·6%
Americas	11·0% (98·6)	10·6% (11·6)	86·8%
Eastern Mediterranean	47·2% (259·3)	48·8% (43·3)	47·3%
Europe	52·0% (459·7)	52·4% (38·7)	49·2%
Southeast Asia	30·0% (503·6)	30·3% (73·1)	61·0%
Western Pacific	21·2% (374·7)	22·7% (41·6)	89·5%
Total worldwide	30·6% (2000·0)	31·5% (263·7)	70·0%

Data for general population and all school-aged children are shown in parentheses (in millions). *On the basis of population estimates for 2006 from reference 48. †These numbers do not include data for non-UNICEF countries (eg, the USA and western Europe). ‡193 WHO member states.

Table 3: **Prevalence of iodine deficiency in 2007[49] and percentage of households with access to iodised salt[50] by WHO regions‡**

For national, school-based surveys of iodine nutrition, the median urinary iodine from a representative sample of spot urine collections from about 1200 children (30 sampling clusters of 40 children per cluster) can be used to classify a population's iodine status (table 5).[1] However, the median urinary iodine is often misinterpreted. Individual iodine intakes and, therefore, spot urinary iodine concentrations are highly variable from day-to-day,[65] and a common mistake is to assume that all individuals with a spot urinary iodine of less than 100 µg/L are iodine deficient. To estimate iodine intakes in individuals, 24-h collections are preferable, but difficult to obtain. An alternative is to use the age-adjusted and sex-adjusted iodine to creatinine ratio in adults, but this ratio also has limitations.[73] Creatinine might be unreliable for the estimation of daily iodine excretion from spot samples, especially in malnourished individuals in whom creatinine concentration is low. Daily iodine intake for population estimates can be extrapolated from urinary iodine concentrations, with estimates of mean 24-h urine volume and on the assumption of an average iodine bioavailability of 92% by:[5]

$$\text{urinary iodine } (\mu g/L) \times 0{\cdot}0235 \times \text{bodyweight (kg)} = \text{daily iodine intake } (\mu g)$$

Using this formula, a median urinary iodine concentration of 100 µg/L corresponds roughly to an average daily iodine intake of 150 µg.

When palpation is used, goitre is present when each thyroid lobe has a volume greater than the terminal

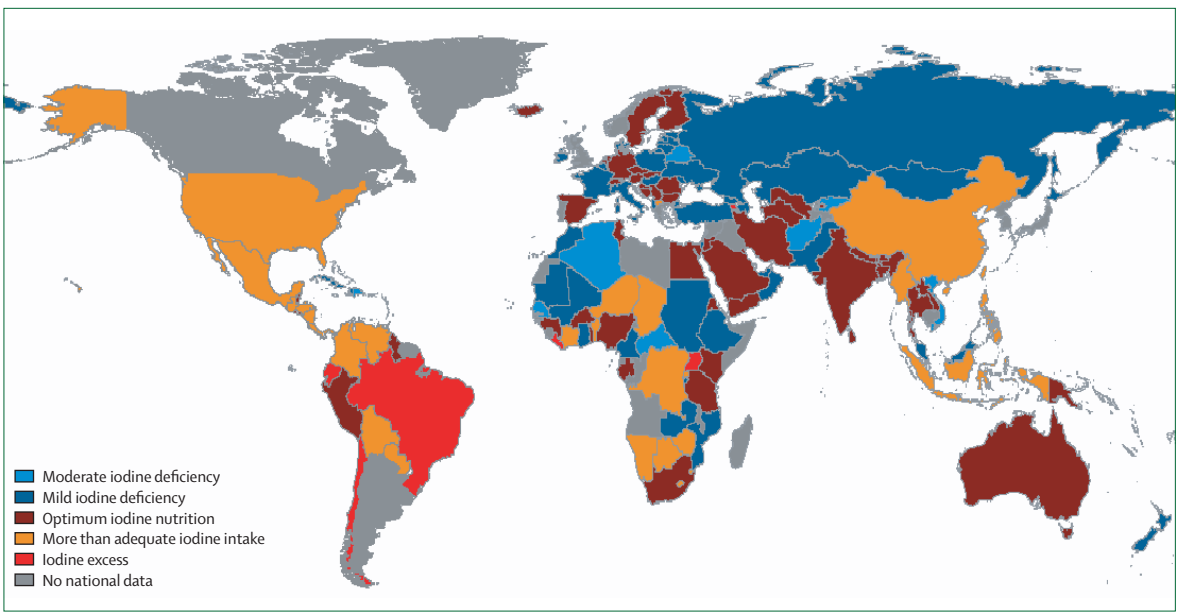

Figure 4: **Iodine nutrition based on the median urinary iodine concentration, by country**[49,51]

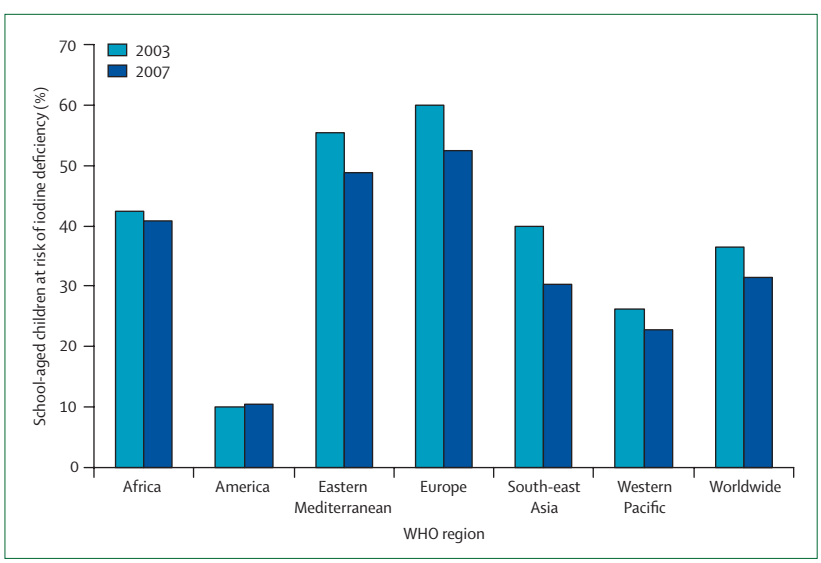

Figure 5: **Prevalence of iodine deficiency in school-aged children (defined as a urinary iodine concentration <100 µg/L) by WHO region and worldwide, 2003–07**[49,51]

phalanx of the thumbs of the patient being examined. Grade 1 goitre is palpable but not visible when the neck is in the normal position, and grade 2 goitre is clearly visible when the neck is in a normal position.[1] In areas of endemic goitre, although the thyroid size predictably decreases in response to increases in iodine intake, thyroid size might not return to normal for months or years after correction of iodine deficiency.[67] During this transition period, the goitre rate is difficult to interpret, because it indicates both a population's history of iodine nutrition and its present status. Moreover, palpation of goitre in regions of mild iodine deficiency has poor sensitivity and specificity; in such areas, measurement of thyroid volume by ultrasound is preferable for the classification of goitre.[66] A sustained salt-iodisation programme will reduce the goitre rate by ultrasound to less than 5% in school-aged children,[69] which shows the disappearance of iodine deficiency as an important public-health problem.[1]

Thyroid hormone concentrations are generally poor indicators of iodine status. In iodine-deficient populations, serum T3 and TSH rise or remain unchanged, and serum T4 usually falls. However, these changes are often within the normal range, and the overlap with iodine-sufficient populations is large enough to make thyroid hormone concentrations an insensitive measure of iodine nutrition.[1] However, TSH is a sensitive indicator of iodine status in the newborn period.[69] Compared with adults, the thyroid in newborn babies contains less iodine but has higher rates of iodine turnover. So when iodine supply is low, maintaining high iodine turnover needs enhanced TSH stimulation, and thus TSH concentrations increase in iodine-deficient infants for the first few weeks of life. This condition is termed transient newborn hyperthyrotropinaemia, and newborn TSH obtained 3–4 days after birth is a sensitive indicator of iodine nutrition (table 4).[69]

Treatment and prevention

In nearly all regions affected by iodine deficiency, the most effective way to control iodine deficiency is through salt iodisation.[1] Universal salt iodisation is used to describe the iodisation of all salt for human (food industry and household) and livestock consumption. Although the ideal universal salt iodisation, even in countries with successful salt-iodisation programmes, is rarely achieved because food industries are often reluctant to use iodised salt, and many countries do not

iodise salt for livestock. Salt iodisation is the recommended strategy for control of iodine-deficiency disorders because salt is consumed by virtually everyone; its intake is fairly consistent through the year; its production or importation is restricted to a few sources in many countries; iodisation technology is simple and inexpensive to implement; addition of iodine to salt does not affect its colour or taste; and quantity of iodine in salt can be monitored simply during production and retailing, and in the household.

WHO/UNICEF/ICCIDD recommend that iodine is added at a concentration of 20–40 mg iodine per kg salt, dependent on local salt intake.[1] Iodine can be added to salt in the form of potassium iodide or potassium iodate. Because potassium iodate has higher stability than does potassium iodide in the presence of salt impurities, humidity, and porous packaging,[74,75] it is the recommended form in tropical countries and those with low-grade salt.[1] Iodine is usually added after the salt has been dried. Two techniques are used: (1) the wet method, in which a solution of potassium iodide is dripped or sprayed at a regular rate on to salt passing on a conveyor belt; (2) the dry method, in which potassium iodide or potassium iodide powder is sprinkled over the dry salt. In an optimum situation, packaging of salt should be in low-density polyethylene bags. In a multicountry study, high humidity combined with porous packing resulted in up to 90% losses of iodine in a year's storage in high-density polyethylene bags compared with 10–15% from low-density polyethylene bags.[75]

Salt iodisation remains the most cost-effective way to deliver iodine and to improve cognition in iodine-deficient populations.[76] For example, in Sierra Leone, if current rates of iodine deficiency remain unchanged over the next 5 years, the present value of future productivity losses due to intellectual impairment from in-utero iodine deficiency will exceed US$42·5 million.[60] Worldwide, the cost of salt iodisation per year is estimated at $0·02–0·05 per child covered, and the cost per child's death averted is $1000 and per disability-adjusted life year gained is $34–36 (figure 6).[78] Alternatively, before widespread salt iodisation, the yearly potential losses attributable to iodine deficiency in the developing world have been estimated as $35·7 billion, compared with an estimated $0·5 billion yearly cost for salt iodisation—ie, a 70 to 1 benefit to cost ratio.[79]

Bread can be an effective vehicle for iodine intake by including baker's salt enriched with iodine.[80] Although iodising drinking water or irrigation water can also be effective,[81,82] the high cost and complexity of monitoring are disadvantages. Iodine-containing milk is a major adventitious source in countries such as Switzerland and the USA,[3,4] because of the use of iodophors in the dairy industry rather than the deliberate addition of iodine. In Finland, iodine-fortified animal fodder has increased the iodine content of foods derived from animal sources. In countries affected by iodine-deficiency disorders, whenever possible, iodine should be routinely added to complementary foods to provide 90 µg of iodine per day.[83]

	Age group	Advantages	Disadvantages	Application
Urinary iodine concentration (µg/L, median)	School-aged children, adults, and pregnant women	Spot urine samples are easy to obtain Low cost External quality control programme in place[64]	Not useful for individual assessment Assesses iodine intake only over the past few days Meticulous laboratory practice needed to avoid contamination Sufficiently large number of samples needed to allow for varying degrees of patient hydration[65]	See table 5
Goitre rate by palpation (%)	School-aged children	Simple and rapid screening test Needs no specialised equipment	Specificity and sensitivity are low because of a high interobserver variation[66] Responds only slowly to changes in iodine intake[67]	Degree of IDD by goitre rate:[1] 0–4·9% (none) 5–19·9% (mild) 20–29·9% (moderate) ≥30% (severe)
Goitre rate by ultrasound (%)	School-aged children	More precise than palpation[66] Reference values established as a function of age, sex, and body surface area[68]	Needs expensive equipment and electricity Operator needs special training Responds only slowly to changes in iodine intake	Degree of IDD by goitre rate:[1] 0–4·9% (none) 5–19·9% (mild) 20–29·9% (moderate) ≥30% (severe)
TSH (mU/L)	Newborn babies	Measures thyroid function at particularly susceptible age Minimum costs if congenital hypothyroidism screening programme is already in place Heel-stick method to obtain sample, and storage on filter paper is simple	Not useful if iodine antiseptics used during delivery[69] Needs standardised sensitive assay Should be taken by heel-prick at least 48 h after birth to avoid physiological newborn surge	<3% frequency of TSH values >5 mU/L indicates iodine sufficiency in a population[70]
Serum or whole blood thyroglobulin (µg/L)	School-aged children and adults	Finger-stick approach to obtain sample, and storage on filter paper is simple International reference range available[71] Measures improvement in thyroid function within several months after iodine repletion	Expensive immunoassay Standard reference material is available, but needs validation	Reference interval in iodine-sufficient children is 4–40 µg/L[71]

IDD=iodine-deficiency disorders. TSH=thyroid stimulating hormone.

Table 4: **Indicators of iodine status by age group**

In some regions, iodisation of salt might not be practical for control of iodine deficiency, at least in the short term. This difficulty might arise in remote areas where communication is poor or where there are many small-scale salt producers. In these areas, iodised oil supplements can be used.[1] Iodised oil is prepared by esterification of the unsaturated fatty acids in seed or vegetable oils and addition of iodine to the double bonds.[84] It can be given orally or by intramuscular injection.[85] The intramuscular route has a longer duration of action than does oral administration, which is more common because it is simple. Usual oral doses are 200–400 mg iodine per year and are often targeted at women of childbearing age,[35] pregnant women,[34,35] and children (table 6). Iodised oil given in the first and second trimesters of pregnancy reduced the frequency of neurological abnormalities and improved developmental test scores during 7 years, compared with supplementation later in pregnancy or treatment after birth.[86] However, the disadvantages are an uneven concentration of iodine in the body over time and the need for direct contact with individuals, resulting in increased costs.

Iodine can also be given as potassium iodine or potassium iodate as drops or tablets. Single oral doses of potassium iodide monthly (30 mg) or every 2 weeks (8 mg) can provide adequate iodine for school-aged children.[87] Lugol's iodine, containing about 6 mg of iodine per drop, and similar preparations are commonly available as antiseptics in rural dispensaries in developing countries and offer another simple way to deliver iodine locally. Whether giving preterm infants supplemental iodine prevents morbidity and mortality is uncertain.[88] In countries or regions where a salt-iodisation programme covers 90% or more of households and has been sustained for 2 years or more, and the median urinary iodine concentration shows iodine sufficiency (table 5), pregnant and lactating women do not need iodine supplementation.[23] In iodine-deficient countries or regions that have weak distribution of iodised salt, supplements should be given to pregnant women, lactating women, and infants according to the strategy outlined in table 6.

	Iodine intake	Iodine nutrition
School-aged children		
<20 µg/L	Insufficient	Severe iodine deficiency
20–49 µg/L	Insufficient	Moderate iodine deficiency
50–99 µg/L	Insufficient	Mild iodine deficiency
100–199 µg/L	Adequate	Optimum
200–299 µg/L	More than adequate	Risk of iodine-induced hyperthyroidism in susceptible groups
>300 µg/L	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnant women		
<150 µg/L	Insufficient	..
150–249 µg/L	Adequate	..
250–499 µg/L	More than adequate	..
≥500 µg/L	Excessive*	..
Lactating women†		
<100 µg/L	Insufficient	..
≥100 µg/L	Adequate	..
Children <2 years of age		
<100 µg/L	Insufficient	..
≥100 µg/L	Adequate	..

There is no information about iodine nutrition for pregnant and lactating women in the WHO assessment table. *The term excessive means in excess of the amount needed to prevent and control iodine deficiency. †In lactating women, the numbers for median urinary iodine are lower than the iodine requirements, because of the iodine excreted in breastmilk.

Table 5: **Epidemiological criteria for assessment of iodine nutrition in a population based on median or range of urinary iodine concentrations,[1,23] or both**

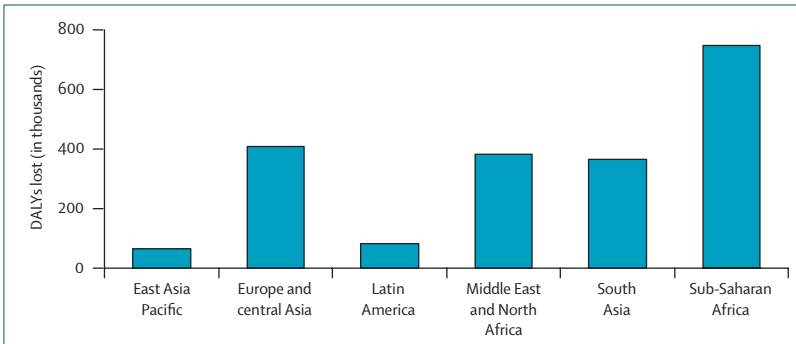

Figure 6: **Disability-adjusted life years (DALYs) (thousands) lost due to iodine deficiency in children younger than 5 years of age, by region[77]**
A DALY is calculated as the present value of the future years of disability-free life that are lost as a result of the premature deaths or cases of disability that arise in a particular year.

Toxic effects of excess intake

Most people who are iodine sufficient are remarkably tolerant to high dietary intakes of iodine. Iodine intakes of up to 1000 µg per day are well tolerated by most adults, since the thyroid is able to adjust to a wide range of intakes and regulates the synthesis and release of thyroid hormones.[89] In children, chronic intakes of 500 µg per day or more are associated with increased thyroid volume, which is an early sign of thyroid dysfunction.[90] European and US expert committees have recommended tolerable upper intakes for iodine (table 7), but caution that individuals with chronic iodine deficiency might respond adversely to intakes lower than these. Table 5 shows the WHO/UNICEF/ICCIDD recommendations for more-than adequate and excess iodine intake for monitoring populations consuming iodised salt.

An increase in iodine intake in populations with chronic iodine deficiency might precipitate iodine-induced hyperthyroidism.[92] Iodine-induced hyperthyroidism has been reported in the introductory phase of several universal salt-iodisation programmes, including in Zimbabwe and the Democratic Republic of the Congo due to excessively iodised salt. It mainly affects older adults with longstanding nodular goitre whose iodine intake is rapidly increased. Thyrocytes in nodules often become insensitive to TSH control, and

	Iodine supplementation
Women of childbearing age	One yearly oral dose of 400 mg of iodine as iodised oil, or a daily oral dose of iodine as potassium iodide should be given, so that the total iodine intake meets the RNI of 150 µg per day of iodine
Women who are pregnant or lactating	One yearly oral dose of 400 mg of iodine as iodised oil, or a daily oral dose of iodine as potassium iodide should be given, so that the total iodine intake meets the new RNI of 250 µg per day of iodine Iodine supplements should not be given to a woman who has already been given iodised oil during her pregnancy or up to 3 months before her pregnancy started
Children aged 0–6 months	One oral dose of 100 mg of iodine as iodised oil, or a daily oral dose of iodine as potassium iodide should be given so that the total iodine intake meets the 90 µg per day requirement of iodine Should be given iodine supplements only if the mother was not supplemented during pregnancy or if the child is not being breastfed
Children aged 7–24 months	One yearly oral dose of 200 mg of iodine as iodised oil as soon as possible after the child is 7 months old, or a daily oral dose of iodine as potassium iodide should be given so that the total iodine intake meets the RNI of 90 µg per day of iodine

In areas where less than 90% of households use iodised salt and the median urinary iodine concentration is less than 100 µg/L in schoolchildren.[23] RNI=recommended nutrient intake.

Table 6: **Recommendations for iodine supplementation in pregnancy and infancy**

if iodine supply is suddenly increased, these autonomous nodules might overproduce thyroid hormone.[93] Symptoms of iodine-induced hyperthyroidism include weight loss, tachycardia, muscle weakness, and skin warmth, without the ophthalmopathy of Graves' disease. This hyperthyroidism is nearly always transient, and the incidence reverts to baseline after 1–10 years of intervention. However, it is dangerous when superimposed on underlying heart disease, and might be lethal.[92] Its prevention includes careful monitoring of salt iodine amounts and training of regional health staff in identification and treatment.

To investigate the effects of iodine intake on thyroid disorders in China, a prospective 5-year survey was done in three rural communities with mildly deficient, more-than adequate (previously mild deficient iodine intake), and excessive iodine intake (median urinary iodine excretion of 88 µg/L, 214 µg/L, and 634 µg/L, respectively).[94,95] High iodine intakes did not increase rates of overt hypothyroidism or hyperthyroidism, but did increase cumulative incidence of subclinical hypothyroidism (0·2%, 2·6%, and 2·9%, respectively) and autoimmune thyroiditis (0·2%, 1·0%, and 1·3%, respectively). In most people, these disorders were not sustained.

Investigators have documented the pattern of thyroid disease after careful introduction of iodised salt in Denmark. Pedersen and others[96,97] prospectively identified new cases of overt hypothyroidism and hyperthyroidism in Denmark before and for the first 6–7 years after introduction of iodised salt. There was a moderate increase in the incidence rate of overt hypothyroidism (relative risk 1·35; 95% CI 1·11–1·66) that occurred mainly in young and middle-aged people with previously moderate iodine deficiency. The overall incidence of hyperthyroidism also increased from 102·8 to 138·7 per 100 000 per year. But by contrast with iodine-induced hyperthyroidism, many of the new cases were seen in young adults (20–39 years), and were presumably of autoimmune origin. Modest differences in iodine intake in populations do not affect incidence of thyroid cancer or the distribution of its subtypes.[98] Overall, the small risks of iodine excess are far outweighed by the substantial risks of iodine deficiency such as pregnancy loss, goitre, and mental retardation.[99]

	EC/SCF, 2002[91] (µg per day)	US Institute of Medicine, 2001[5] (µg per day)
1–3 years	200	200
4–6 years	250	300
7–10 years	300	300
11–14 years	450	300
15–17 years	500	900
Adult	600	1100
Pregnant women >19 years	600	1100

EC/SCF=European Commission/Scientific Committee on Food.

Table 7: **Tolerable upper intake amount for iodine (µg per day) by age group**

The future

The International Classification of Diseases' steering group identified iodine deficiency as one of four key worldwide risk factors for impaired child development, for which the need to intervene is urgent.[100] But controlling iodine-deficiency disorders in the remaining third of the global population at risk will not be easy. Although the key contributors to successful national programmes have been identified,[1] reaching economically disadvantaged groups living in remote regions and convincing small-scale salt producers to iodise their salt are major challenges.[101] An important strategy will be to strengthen national coalitions that include government partners, national and international agencies, the health-care sector, and salt producers. In countries that have begun iodised-salt programmes, sustainability will become a major focus. These programmes are fragile and need a long-term commitment from governments. In several countries where iodine deficiency had been eliminated, salt-iodisation programmes fell apart and iodine deficiency recurred.[102] Children in iodine-deficient areas are susceptible to even short-term lapses in iodised-salt programmes.[103] To achieve this goal, countries should monitor the state of their iodine nutrition every 3 years and report to the World Health Assembly about their progress.[104]

Advocacy should focus on damage to reproduction and cognitive development. Governments need to understand the serious effects of iodine deficiency; many still equate iodine deficiency with goitre, which is a cosmetic problem and thus a low priority. Iodine-deficiency disorders are the most important cause of preventable mental retardation worldwide, and their elimination can contribute to at least five of the Millennium Development Goals:[105] (1) eradicate extreme poverty and hunger; (2) achieve universal primary education; (3) reduce child mortality; (4) improve maternal health; and (5) develop a worldwide partnership for development. The World Bank strongly recommends that governments invest in micronutrient programmes, including salt iodisation, to promote development, concluding: "Probably no other technology offers as large an opportunity to improve lives at such low cost and in such a short time."[106]

Conflict of interest statement

We declare that we have no conflict of interest.

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