



# Iodine deficiency and thyroid disorders

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**Iodine deficiency early in life impairs cognition and growth, but iodine status is also a key determinant of thyroid disorders in adults. Severe iodine deficiency causes goitre and hypothyroidism because, despite an increase in thyroid activity to maximise iodine uptake and recycling in this setting, iodine concentrations are still too low to enable production of thyroid hormone. In mild-to-moderate iodine deficiency, increased thyroid activity can compensate for low iodine intake and maintain euthyroidism in most individuals, but at a price: chronic thyroid stimulation results in an increase in the prevalence of toxic nodular goitre and hyperthyroidism in populations. This high prevalence of nodular autonomy usually results in a further increase in the prevalence of hyperthyroidism if iodine intake is subsequently increased by salt iodisation. However, this increase is transient because iodine sufficiency normalises thyroid activity which, in the long term, reduces nodular autonomy. Increased iodine intake in an iodine-deficient population is associated with a small increase in the prevalence of subclinical hypothyroidism and thyroid autoimmunity; whether these increases are also transient is unclear. Variations in population iodine intake do not affect risk for Graves' disease or thyroid cancer, but correction of iodine deficiency might shift thyroid cancer subtypes toward less malignant forms. Thus, optimisation of population iodine intake is an important component of preventive health care to reduce the prevalence of thyroid disorders.**

## Introduction: iodine deficiency disorders

Iodine deficiency impairs thyroid hormone production and has many adverse effects throughout the human life cycle, collectively termed the iodine deficiency disorders (panel 1).<sup>1</sup> Although goitre is the most visible effect of iodine deficiency, the most serious is cognitive impairment—normal concentrations of thyroid hormones are needed for neuronal migration, glial differentiation, and myelination of the central nervous system.<sup>2</sup> Because iodine deficiency continues to affect large populations, particularly in Africa and south Asia,<sup>3</sup> it is an important preventable cause of cognitive impairment.<sup>4</sup> Two recent systematic reviews<sup>5,6</sup> have confirmed the benefits of correcting iodine deficiency. The first systematic review looked at 89 studies that provided iodised salt to populations and recorded a significant 72–76% reduction in risk for low intelligence (defined as IQ <70) and an 8.2–10.5 point overall increase in IQ.<sup>5</sup> The second systematic review similarly concluded that iodine-sufficient children have a 6.9–10.2 point higher IQ than iodine-deficient children.<sup>6</sup> The International Child Development Steering Group identified iodine deficiency as a key global risk factor for impaired child development.<sup>7</sup> Although prevention of iodine deficiency early in life is the purpose of iodine programmes, variation in iodine intake is a major but underappreciated determinant of thyroid disorders in adults, which is the focus of this Review.

## Assessment, epidemiology, and iodine deficiency in industrialised countries

WHO has established recommended nutrient intakes for iodine (Panel 2).<sup>4</sup> The iodine status of populations can be assessed by using a biomarker of exposure, urinary iodine concentration (UIC), biomarkers of function, goitre, and thyroid function tests (table 1).<sup>8</sup> When assessing populations, UIC is the biomarker of choice;<sup>4</sup> it measures the latest iodine intake, because the kidney excretes more

than 90% of dietary iodine in the subsequent 24–48 h.<sup>8</sup> To classify national iodine status, WHO, UNICEF, and the International Council for the Control of Iodine Deficiency Disorders recommend the use of the median UIC, expressed as µg/L, from representative surveys (table 2).<sup>4</sup> The criteria for iodine intake outlined in table 2 are used throughout this Review. UIC surveys are often done in children because children are easy to reach through school-based surveys and their iodine status is generally representative of the adult population,<sup>9</sup> but not of pregnant women.<sup>10</sup> Although measuring UIC does not directly assess thyroid function, a deficient or an excessive median UIC in a population predicts a higher risk for the development of thyroid disorders.

National (n=121) or large subnational (n=31) UIC surveys have been done in 152 countries, representing 98% of the world's population (figure).<sup>11,12</sup> In 2014, iodine intake was adequate in 112 countries, deficient in 29 countries, and excessive in 11 countries.<sup>11</sup> During the past decade, the number of iodine-sufficient countries increased from 67 to 112, showing major progress.<sup>11</sup> A limitation of these data is that only a few countries have done national UIC surveys in pregnant women, a key target group. Large populous countries that are still iodine deficient include developing countries (eg, Ethiopia, Morocco, and Mozambique) and countries in transition (eg, Russia and Ukraine), but also several high-income countries (eg, Denmark, Italy, and the UK).<sup>11</sup> Moreover, in several high-income countries, including the USA and Australia, iodine intakes have decreased in the past 30 years.<sup>13</sup> Results of surveys suggest that many pregnant women in both developing and high-income countries, including the UK and the USA, have deficient iodine intakes.<sup>14,15</sup>

Iodine deficiency, unlike most micronutrient deficiencies, is not restricted to people in developing countries with poor diets. Iodine-deficient soils bring about the historic goitre belts of midwestern USA, southern Australia, the Alps and the Apennines in

Europe, and inland areas of England and Wales.<sup>13</sup> Diets are deficient in iodine in these areas unless iodine enters the food chain through addition of iodine to foods or dietary diversification introduces foods produced in iodine-sufficient regions. Unless iodised salt is available, the main source of iodine in typical diets in North America and Europe is dairy products, supplying up to 50% of intakes.<sup>13</sup> However, nearly all of the iodine in dairy products is adventitious. Milk has very low native iodine content, but iodine supplements given to cows, particularly in winter fodder, and residues of disinfectant iodophors used in dairying and transport end up in milk, boosting milk iodine concentrations.<sup>13</sup> Nevertheless, iodine intake from dairy might be decreasing, for several reasons. Government regulations that restrict the iodine concentration in cows' milk have led, in some countries, to a reduction in iodine concentrations in livestock supplements and to the replacement of iodophor disinfectants by chlorine-based compounds.<sup>13</sup> Also, some population groups might be drinking less milk, and organic milk might contain less iodine than milk from conventional dairying. Decreasing iodine intake from dairy products probably contributed to the re-emergence of iodine deficiency in Australia<sup>13</sup> and the UK in the last decade.<sup>16</sup>

## Iodine intakes and thyroid function in adults

### Adaptation of the thyroid to iodine deficiency

The relation between iodine intake and thyroid disorders in populations is U-shaped because both deficient and excessive iodine intakes can impair thyroid function. Moreover, even small increases in iodine intake in previously iodine-deficient populations change the pattern of thyroid diseases.<sup>17</sup> Thus, researchers undertaking epidemiological studies need to consider not only present intakes, but also the history of iodine intake of the population. Researchers also need to consider varying environmental and genetic factors that modify the effects of iodine intake on thyroid disorders. For example, white populations have a higher risk of autoimmune thyroiditis than Africans or Asians, and this makes white populations more susceptible to hypothyroidism if iodine intakes are excessive.<sup>18,19</sup>

If dietary iodine intakes are deficient, thyroid function is maintained by increasing thyroidal clearance of circulating iodine. Deficient iodine intake triggers secretion of thyroid-stimulating hormone (TSH) from the pituitary gland and increases the expression of the sodium-iodide symporter to maximise the uptake of iodine into thyroid cells.<sup>20</sup> The thyroid accumulates an increased proportion of ingested iodine, reuses the iodine from the degradation of thyroid hormones more efficiently, and this reduces renal clearance of iodine.<sup>20</sup>

In regions of mild-to-moderate iodine deficiency, overall serum thyroglobulin concentrations and thyroid size usually increase in the population, whereas serum TSH, tri-iodothyronine (T<sub>3</sub>), and thyroxine (T<sub>4</sub>) are often

still in the normal range.<sup>21–23</sup> There are usually no, or weak, associations between UIC and thyroid hormone concentrations, but UIC does correlate with serum thyroglobulin concentration and thyroid size.<sup>22</sup> In Denmark, median serum thyroglobulin concentration was significantly higher in adults with moderate iodine deficiency than in those with mild iodine deficiency, and salt iodisation decreased median thyroglobulin concentrations in both subpopulations and eliminated this difference.<sup>23</sup> In a population with mild iodine deficiency, many people develop simple diffuse goitre and some develop nodules.<sup>24</sup> Although often attributed to increased stimulation by TSH,<sup>24</sup> mean serum TSH concentration is usually not raised in populations with mild iodine deficiency, so the cause of diffuse goitre in the setting of mild iodine deficiency is unclear. Conversely, populations with mild-to-moderate iodine deficiency might have lower mean TSH concentrations than do sufficient populations.<sup>25–27</sup> This difference is explained by an increase in the prevalence of thyroid nodularity and multinodular toxic goitre in populations

### Panel 1: The iodine deficiency disorders and their health consequences, by age group<sup>1</sup>

#### All ages

- Goitre
- Increased susceptibility of the thyroid gland to nuclear radiation
- In severe iodine deficiency, hypothyroidism

#### 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
- Reduced work productivity
- Toxic nodular goitre; hyperthyroidism

### Panel 2: WHO recommendations for iodine intake by age or population group<sup>4</sup>

- Children 0–5 years: 90 µg per day
- Children 6–12 years: 120 µg per day
- Adults >12 years: 150 µg per day
- Pregnancy: 250 µg per day
- Lactation: 250 µg per day

	Age group	Advantages	Disadvantages	Application
Median urinary iodine concentration (µg/L)	School-aged children (6–12 years) and pregnant women	Spot urine samples are easy to obtain Relatively low cost External quality control programme in place	Not useful for individual assessment Assesses iodine intake only over the past few days Large number of samples needed to allow for varying extent of hydration in participants	See table 2
Prevalence of goitre measured by palpation (%)	School-aged children	Simple and rapid screening test Needs no specialised equipment	Specificity and sensitivity are low because of high interobserver variation; Responds only slowly to changes in iodine intake	Extent of iodine deficiency by prevalence of goitre: None: 0–4.9% Mild: 5–19.9% Moderate: 20–29.9% Severe: ≥30%
Prevalence of goitre measured by ultrasound (%)	School-aged children	More precise than palpation Reference values established as a function of age, sex, and body-surface area	Needs expensive equipment and electricity Operator needs special training Responds only slowly to changes in iodine intake	Extent of iodine deficiency by prevalence of goitre: None: 0–4.9% Mild: 5–19.9% Moderate: 20–29.9% Severe: ≥30%
TSH concentrations (mU/L)	Neonates	Measures thyroid function at a particularly susceptible age Low costs if newborn screening programme is in place Collection by heel stick and storage on filter paper is simple	Not useful if iodine antiseptics are used during delivery Needs a standardised, sensitive assay Should be taken at least 48 h after birth to avoid measuring physiological newborn TSH surge	A frequency of <3% of TSH concentration values >5 mU/L shows iodine sufficiency in a population (when samples collected >48 h after birth)
Serum or dried blood spot thyroglobulin (µg/L)	School-aged children	Collection by finger stick and storage on filter paper is simple International reference range available Measures improvement of thyroid function within weeks to months after iodine repletion	Expensive immunoassay Standard reference material is available, but wide interassay variation	Reference interval in iodine-sufficient children is 4–40 µg/L

TSH=thyroid-stimulating hormone.

**Table 1: Indicators of iodine status in populations<sup>4,8</sup>**

	Iodine intake	Iodine nutrition
<b>School-aged children and adults</b>		
<20 µg/L	Insufficient	Severe iodine deficiency
20–49 µg/L	Insufficient	Moderate iodine deficiency
50–99 µg/L	Insufficient	Mild iodine deficiency
100–299 µg/L	Adequate	Optimal
≥300 µg/L	Excessive	Risk of iodine-induced hyperthyroidism and autoimmune thyroid disease
<b>Pregnant women</b>		
<150 µg/L	Insufficient	..
150–249 µg/L	Adequate	..
250–499 µg/L	More than adequate	..
≥500 µg/L	Excessive	..
<b>Lactating women</b>		
<100 µg/L	Insufficient	..
≥100 µg/L	Adequate	..

**Table 2: Epidemiological criteria for assessment of iodine nutrition in populations based on median urinary iodine concentrations<sup>4,9</sup>**

with mild-to moderate iodine deficiency, particularly in adults older than 60 years. If multinodular toxic goitre is prevalent in a population, overall mean TSH concentration will be lowered.<sup>27</sup> In iodine-sufficient Chinese adults, a U-shaped relation has been reported between UIC and serum TSH concentration, with the lowest TSH concentration in the UIC range of 250–350 µg/L.<sup>28</sup>

In a population with moderate-to-severe iodine deficiency, mean serum TSH concentration often increases slightly whereas T<sub>4</sub> remains normal, and many individuals develop subclinical hypothyroidism.<sup>29,30</sup> As iodine deficiency becomes more severe, TSH might rise further whereas T<sub>3</sub> increases slightly or remains unchanged and T<sub>4</sub> decreases because of preferential secretion of T<sub>3</sub> by the thyroid in the setting of iodine deficiency.<sup>31</sup> Preferential secretion of T<sub>3</sub> occurs during iodine deficiency because the activity of T<sub>3</sub> is roughly four times that of T<sub>4</sub>, but T<sub>3</sub> needs only 75% as much iodine for its synthesis.<sup>20</sup> In moderate to-severe iodine deficiency, the concentration of serum TSH is usually inversely correlated with that of T<sub>4</sub>, but not with that of T<sub>3</sub>, suggesting closer feedback control of TSH secretion by T<sub>4</sub> than by T<sub>3</sub>.<sup>30,32,33</sup> In chronic, severe iodine deficiency, many individuals have elevated TSH concentrations and most, but not all, develop goitre.<sup>34</sup> If thyroidal iodine is exhausted, mean concentrations of T<sub>4</sub> and T<sub>3</sub> decrease, TSH concentration increases, and there is an increase in overt hypothyroidism in the population.<sup>35</sup>

**Goitre and nodularity**

The relation between iodine intake and risk for diffuse goitre also shows a U-shaped curve, with increased risk at deficient and excess intakes, whereas risk for nodular goitre seems to be increased only at deficient intakes. In a 5 year, prospective community-based survey in three rural Chinese cohorts—one with mild iodine deficiency

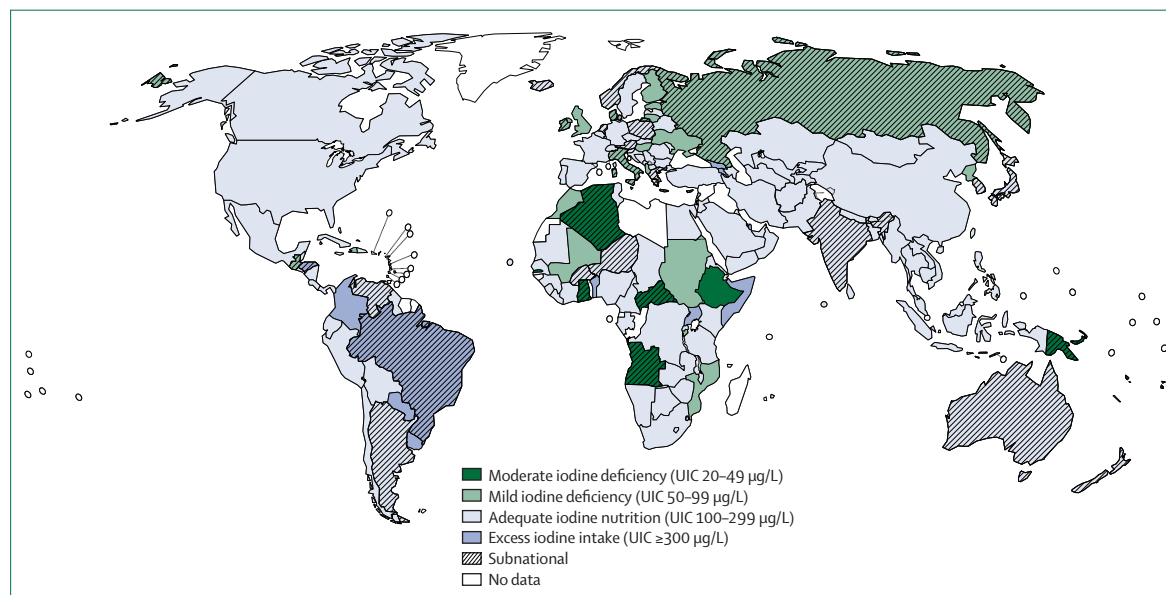
(median UIC 88 µg/L), one with more-than-adequate iodine intake from iodised salt (214 µg/L), and one with excessive iodine intake from high-iodine drinking water (634 µg/L)—the cumulative incidences of diffuse goitre were 7.1%, 4.4%, and 6.9%, respectively, and for nodular goitre were 5.0%, 2.4%, and 0.8%, respectively.<sup>36</sup> In Chinese adults, those consuming non-iodised salt had a significant 25–36% increased risk of thyroid nodules compared with those consuming iodised salt.<sup>37</sup> Results of a Danish study clearly showed a high prevalence of goitre in women aged 60–65 years old in an area where iodine intake was moderately low: 33% had an enlarged thyroid by ultrasound, 24% had palpable goitre, and 6% had undergone goitre surgery.<sup>37</sup> In Denmark, after 4 years of mandatory iodisation of salt in two regions—one with initially mild and one with initially moderate iodine deficiency—thyroid size decreased in all age groups, with the largest decrease in the area with initially moderate iodine deficiency.<sup>38,39</sup> The Pescopagano study included cross-sectional surveys of a rural Italian village before and after introduction of iodised salt.<sup>40</sup> Overall, the prevalence of goitre was lower after iodisation, mainly because of a reduction in diffuse goitre (10.3% vs 34.0%), and although the prevalence of nodular goitre decreased after iodisation in individuals aged 35 years or younger (3.8% vs 11.3%), it was unchanged in individuals aged older than 35 years.<sup>40</sup>

In summary, correction of iodine deficiency in adult populations, irrespective of severity, reduces mean thyroid size and the prevalence of diffuse goitre at all ages within a few years. Although iodine repletion usually does not reduce the prevalence of thyroid nodularity in adults older than about 50 years because of largely irreversible fibrotic changes in nodules, it does

reduce the risk for development of nodular disease in younger adults.

### Hyperthyroidism

Generally, populations with mild-to-moderate iodine deficiency have a higher prevalence of hyperthyroidism and lower mean serum TSH concentrations than do populations with optimum or excessive intakes. In a cross-sectional study,<sup>26</sup> a Danish population with deficient iodine intake (about 40–70 µg/day) had a 2.3 times higher lifetime risk for hyperthyroidism than an Icelandic population with excessive intakes (about 400–450 µg/day). The most common cause of hyperthyroidism in the Danish population was multinodular toxic goitre in adults older than 50 years, whereas most cases in the Icelandic population were caused by Graves' disease in adults younger than 50 years. Iodine deficiency seems to increase risk for multinodular toxic goitre by promoting growth and mutagenesis leading to the development of clusters of autonomous thyrocytes.<sup>41</sup> A cross-sectional study comparing two Danish cohorts with mild versus moderate iodine deficiency before iodisation reported a significantly increased incidence of hyperthyroidism in individuals with moderate iodine deficiency (96.7 vs 60.0 per 100 000 person-years). This higher incidence was mainly due to an increased prevalence of multinodular toxic goitre in the cohort with initially moderate iodine deficiency compared with the cohort with initially mild iodine deficiency; the prevalence of Graves' disease was similar between cohorts.<sup>42</sup> Compared with populations with sufficient iodine intakes, populations with moderate iodine deficiency also have an increased incidence of solitary toxic adenoma<sup>43</sup> and amiodarone-associated hyperthyroidism.<sup>42,44</sup>



**Figure:** National iodine status in 2014 based on the median urinary iodine concentration<sup>13,12</sup>  
UIC= urinary iodine concentration.

A rise in iodine intake in populations with iodine deficiency usually increases the incidence of hyperthyroidism. The increase tends to be greater and cases more severe if iodine fortification is excessive and the pre-existing iodine deficiency was severe. In Sudanese adults living in an area of endemic goitre, 3% developed overt hyperthyroidism and serum TSH concentration was less than 0.1 mU/L in 6–17% of subjects within 12 months after initiation of iodine prophylaxis.<sup>45</sup> Introduction of salt fortified with excessive concentrations of iodine to adults in Zaire with nodular goitre resulted in 7.4% of patients developing thyrotoxicosis, and in many, the disorder persisted for longer than 1 year.<sup>46</sup> Similarly, in Zimbabwe, introduction of over-iodised salt increased the prevalence of hyperthyroidism by three times.<sup>47</sup> Individuals at highest risk for development of hyperthyroidism are adults older than 60 years with nodular thyroid disease. Although most of these adults are euthyroid before iodisation, they might have radioactive iodine uptakes that are not suppressible and low serum TSH concentrations that do not respond to thyrotropin-releasing hormone.<sup>48</sup> Thyrocytes in these nodules can be insensitive to TSH control, and if the iodine supply is suddenly increased, these cells can overproduce thyroid hormone.

The increase in incidence hyperthyroidism after a properly monitored introduction of iodine into populations with mild-to-moderate iodine deficiency is transient because the resulting iodine sufficiency in the population reduces the future risk for the development of autonomous thyroid nodules. In Switzerland in 1980, iodine content of salt was raised from 7.5 to 15 ppm to correct mild iodine deficiency, and the median UIC increased from roughly 80 to 150 µg per g of creatinine.<sup>49</sup> During the first 2 years after this increase, the incidence of toxic nodular goitre rose by 12%, but regressed over the next 4 years to a stable concentration of only 25% of the initial incidence.<sup>49</sup> Results of surveys done a decade or more after introduction of iodised salt generally show low prevalence of hyperthyroidism in populations. For example, in the 5 year prospective Chinese study,<sup>50</sup> the cumulative incidence of hyperthyroidism was 1.4% in the cohort with deficient iodine intake, 0.9% in cohort with sufficient intake, and 0.8% in cohort with excessive intake; no significant differences in the incidence of overt or subclinical hyperthyroidism or Graves' disease between the three cohorts were reported.<sup>43,50</sup> In the Pescopagano study,<sup>40</sup> voluntary iodine prophylaxis significantly reduced the prevalence of hyperthyroidism due to toxic nodular goitre and toxic adenoma in adults older than 45 years, but no overall change in the prevalence of Graves' disease was noted.

When iodised salt was introduced into the Danish population, a transient increase in hyperthyroidism occurred: overall incidence increased from 102.8 to 138.7 cases per 100 000 people per year and most cases occurred in the area of previously moderate iodine

deficiency and in adults older than 40 years.<sup>51</sup> The increase was transient, and about 6 years after salt iodisation, incidence had decreased back to less than the pre-iodisation level.<sup>52</sup> Although an increase in incidence was also seen in adults younger than 40 years, the number of cases was much lower than in older adults; in younger adults this increased incidence was probably due mainly to Graves' disease. The number of new prescriptions of anti-thyroid drugs in younger adults, which increased for four years after iodisation,<sup>52</sup> also subsequently decreased, suggesting the initial increase in Graves' disease might have been due to earlier development of disease.<sup>52</sup> Salt iodisation did not change the incidence or presentation of Graves' orbitopathy in a hospital-based study in northern Denmark.<sup>53</sup> In a UK study,<sup>54</sup> patients with Graves' disease in remission were more likely to relapse if iodine exposure was excessive. A separate Danish report compared hyperthyroidism before and 4 years after salt iodisation and reported 50% lower rates of subclinical hyperthyroidism after iodisation and a trend towards lower rates of overt hyperthyroidism, both independent of age.<sup>55</sup>

In summary, differences in iodine intake have a large effect on the incidence and subtypes of hyperthyroidism in populations. Compared with adequate iodine intake, mild and moderate iodine deficiency in populations increases nodularity and thereby risk of hyperthyroidism, particularly in older adults. Introduction of iodised salt to deficient populations transiently further increases risk for hyperthyroidism, particularly if pre-existing iodine deficiency was severe and the programme results in excessive iodine intakes. Again, most of these new cases are due to thyroid autonomy. However, this effect is not seen in all studies, and this transient increase in risk might be reduced by gradual introduction of iodised salt at optimum levels of fortification. Because the prevalence of hyperthyroidism in a population eventually falls to lower than before iodisation, iodised salt in the long run might reduce thyrotoxicosis as a cause of atrial fibrillation and mortality in adults older than 65 years.<sup>56</sup> This represents a major public health benefit and should be considered in the determination of policies regarding salt iodisation in areas of mild-to-moderate iodine deficiency, such as the UK.

### Hypothyroidism

In populations with severe iodine deficiency, the prevalence of hypothyroidism is higher than in areas of optimum iodine intake.<sup>20</sup> However, in the setting of mild-to-moderate iodine deficiency, the prevalence of subclinical and overt hypothyroidism is generally lower than in areas of optimum or excessive iodine intake. In the cross-sectional study that compared adults in Denmark who had deficient iodine intake with adults in Iceland who had excessive iodine intake,<sup>26</sup> fewer cases of hypothyroidism were reported in the Danish population. In the cross-sectional study of two regions of Denmark

with mild or moderate iodine deficiency before salt iodisation,<sup>17</sup> the incidence of autoimmune hypothyroidism was roughly 50% lower in the region with moderate iodine deficiency. In the study of Danish adults before and 4 years after the introduction of mandatory iodisation of salt in two regions with previous mild or moderate iodine deficiency,<sup>57</sup> median serum TSH concentration was 16% higher in both regions across all ages after iodisation. In addition, the prevalence of subclinical hypothyroidism increased (mainly in young women) and, in the region with previous mild iodine deficiency only, a small overall increase in overt hypothyroidism was reported.<sup>57</sup> In the Danish registry study that tracked all new cases of overt hypothyroidism before and for the first 7 years after introduction of a national programme of salt iodisation,<sup>58</sup> the overall incidence rate of hypothyroidism modestly increased from 38.3 to 47.2 cases per 100 000 people per year, mainly in adults aged 20–59 years.

In the 5 year prospective Chinese study that compared cohorts with deficient, optimum, and excessive iodine intakes,<sup>50</sup> the cumulative incidence of overt hypothyroidism was not different (0.2%, 0.5%, and 0.3% respectively) but there was a significant increase in subclinical hypothyroidism in the areas of optimum and excessive intakes (0.2%, 2.6%, and 2.9% respectively). In the Pescopagano study,<sup>40</sup> the prevalence of hypothyroidism was higher after iodisation (5.0% vs 2.8% at baseline) mainly because of an increase in subclinical hypothyroidism in participants younger than 15 years. Whether subclinical hypothyroidism in areas with excessive iodine intake is a reversible phenomenon is unclear, but a reduction in iodine intake might normalise thyroid function in some cases.<sup>59</sup>

Higher mean TSH concentrations in populations with excessive iodine intake<sup>26,60</sup> could be explained by an increase in TSH concentration only in people with some extent of thyroid autoimmunity; alternatively, it could be explained by a more general phenomenon of iodine downregulation of thyroid function. In animal studies, prolonged excess iodine intake reduces pituitary type-2-deiodinase activity, and this reduction is associated with an increase in serum TSH concentration.<sup>61</sup> Individuals with autoimmune thyroiditis might develop hypothyroidism when exposed to excess iodine.<sup>62</sup> But many individuals living in areas with optimum or excessive iodine intake with raised serum TSH concentration do not typically have circulating thyroid antibodies,<sup>26,60</sup> possibly because some individuals with mild hypothyroidism and ultrasonographic changes consistent with thyroiditis do not have measurable thyroid antibodies.<sup>63</sup>

In summary, increasing iodine intakes in populations leads to a small increase mainly in the incidence of mild subclinical hypothyroidism; this increase seems to occur more often in individuals positive for thyroid antibodies. However, further research is needed to establish the mechanisms underlying this effect and the long-term

outcomes of subclinical hypothyroidism induced by iodine.

### Thyroid autoimmunity

A rapid increase in iodine intake can enhance thyroid autoimmunity,<sup>64,65</sup> possibly through increasing antigenicity of thyroglobulin,<sup>66</sup> but whether this increase is sustained is uncertain.<sup>65</sup> Conversely, several cross-sectional studies<sup>67,68</sup> have reported that thyroid autoimmunity is increased in populations with deficient iodine intakes, possibly because individuals with nodular goitre, which is more common in iodine deficiency, often have circulating thyroid antibodies. Thyroid antibodies are not highly prevalent in the USA population, despite many years of excessive iodine intake.<sup>19</sup>

In cross-sectional population studies in adults in Denmark before (median UIC 61 µg/L) and 4–5 years after (median UIC 101 µg/L) salt iodisation, the prevalence of thyroid-peroxidase antibodies greater than 30 U/mL increased from 14% to 24% and the prevalence of thyroglobulin antibodies greater than 20 U/mL increased from 14% to 20%, with the strongest increase in women aged 18–45 years and in those with low antibody titres before and after iodisation.<sup>69</sup> In the 5 year prospective Chinese study,<sup>50</sup> the cumulative incidence of autoimmune thyroiditis was 0.2% in the cohort with deficient iodine intake, 1.0% in the cohort with sufficient intake, and 1.3% in the cohort with excessive intake. However, no significant difference was recorded in the cumulative incidence of thyroid-peroxidase-antibody positivity or in the incidence of Graves' disease.<sup>50,70</sup> In that study, euthyroid participants who were thyroid-peroxidase-antibody positive at baseline and had excessive iodine intakes developed thyroid disorders more frequently (14.4%) than those who were antibody negative (3.3%).<sup>70</sup> In the Pescopagano study,<sup>40</sup> thyroid antibodies (thyroid-peroxidase antibodies and thyroglobulin antibodies) (20% vs 13%) and Hashimoto's thyroiditis (15% vs 3.5%) were more common after salt iodisation than before.

In summary, the link between iodine intake and thyroid autoimmunity is complex. Some studies have noted raised concentrations of thyroid antibodies in areas of excessive iodine intake, but others have not. However, large oral doses of iodine in iodine-deficient individuals might precipitate the development of thyroid antibodies, and individuals with autoimmune thyroiditis are at increased risk of hypothyroidism when exposed to excess iodine. Most surveys have reported modest increases in the occurrence of thyroid autoimmunity (albeit antibodies are at a low titre) in the wake of iodisation; whether these increases are transient is unclear.

### Thyroid cancer

The overall incidence of thyroid cancer in populations does not seem to be affected by the usual range of iodine intakes from dietary sources. A systematic

review<sup>71</sup> reported no association of thyroid cancer risk with dietary iodine intake: on the basis of two case-control studies done in populations with sufficient iodine intake and three ecological studies, the risk estimate range was 0.49–1.6. In addition, there was no association of thyroid cancer risk with fish consumption as a surrogate for dietary iodine intake: the risk estimate range was 0.6–2.2 (16 case-control studies).<sup>71</sup> An earlier pooled analysis of 13 case-control studies reported a significant decrease in thyroid cancer risk with high fish consumption in regions with endemic goitre (odds ratio 0.65, 95% CI 0.48–0.88) but not in iodine-rich regions (1.1, 0.85–1.5).<sup>72</sup> Although several ecological studies have suggested an increase in papillary thyroid cancer after the introduction of iodised salt to populations,<sup>71</sup> many confounding factors could account for this association, including other environmental factors and, more likely, increasing diagnostic intensity. During the past several decades in the USA, the prevalence of thyroid cancer has been steadily increasing,<sup>73</sup> but iodine intakes during the same period have decreased by about 50%.<sup>74</sup>

Differences in iodine intake between regions might affect the distribution of thyroid cancer subtypes: populations in areas of optimum iodine intake seem to have fewer of the more aggressive follicular thyroid cancers, but more papillary thyroid cancers.<sup>75–77</sup> A meta-analysis reported a ratio of papillary thyroid cancers to follicular thyroid cancers of 3.4–6.5:1 in areas of optimum iodine intake versus 0.19–1.7:1 in iodine-deficient areas.<sup>77</sup> Chronic iodine deficiency seems to be a risk factor for follicular thyroid cancer and, possibly, anaplastic thyroid cancer.<sup>78</sup> The major risk factor for goitre and nodularity is iodine deficiency, and both goitre and nodules are major risk factors for thyroid cancer in both men and women.<sup>79</sup> A pooled analysis of data up to 1998 reported a relative risk for thyroid cancer of 5.9 (95% CI 4.2–8.1) in individuals with a history of goitre and a much higher risk in those with a history of benign nodularity.<sup>80</sup> In China, the prevalence of the T1799A *BRAF* mutation, a risk factor for the development of papillary thyroid cancer and for tumour aggressiveness, was significantly higher in patients with papillary thyroid cancers in areas with excessive iodine intakes (median UIC >900 µg/L due to drinking water containing >100 µg/L iodine) than in iodine-sufficient areas (69% vs 53%).<sup>81</sup>

In summary, no strong evidence has shown that increases in iodine intake increase risk for thyroid cancer. Conversely, the correction of iodine deficiency might be beneficial in that it reduces goitre in populations, which is a major risk factor for thyroid cancer, and it might shift subtypes toward less malignant types of thyroid cancer. Also, in the setting of iodine sufficiency, in the event of nuclear fallout, doses of radioactive iodine to the thyroid would be lower than in an area of iodine deficiency, and the risk for development of thyroid cancer would therefore also be lower.<sup>82</sup>

## Prevention and treatment

In nearly all countries the best strategy to provide additional dietary iodine is the addition of iodine to salt: it is simple, effective, safe, and inexpensive.<sup>4</sup> Iodine can be added to salt in the form of potassium iodide (KI) or potassium iodate (KIO<sub>3</sub>). Because KIO<sub>3</sub> has increased stability in the presence of salt impurities, humidity, and porous packaging, it is the recommended form.<sup>4</sup> Iodine is usually added at a concentration of 20–40 mg iodine per kg salt, depending on local salt intake.<sup>4</sup> Worldwide, more than 70% of households in low-income countries are using iodised salt.<sup>3</sup> But in high-income countries, because 80–90% of salt consumption comes from purchased processed foods, the supply of iodine is not sufficient if only household salt is iodised.<sup>13</sup> Thus, the food industry has to be persuaded to use iodised salt in their products, either through advocacy or legislation. In Denmark and Australia, Governments have mandated that nearly all salt used by the baking industry be iodised.<sup>83,84</sup> In Switzerland, although not mandated, the iodised salt programme is successful because the food industry recognises it has an important part to play and voluntarily uses iodised salt in about 60% of processed foods.<sup>85</sup> At fortification concentrations (ppm) in foods, iodine does not cause sensory changes and, in most countries, the price difference between iodised and non-iodised salt is negligible. Salt iodisation is compatible with efforts to reduce salt consumption to prevent chronic diseases; iodisation methods can fortify salt to provide recommended iodine intakes even if salt intakes per head are reduced to less than 5 g per day.<sup>86</sup>

Notably, the UK and the USA do not have government policies on salt iodisation despite evidence of mild-to-moderate iodine deficiency in susceptible groups.<sup>14–16</sup> In view of the clear health benefits of maintaining normal iodine status in populations, a review of public health policies in these countries is urgently needed. In addition to salt iodisation, iodine supplementation during pregnancy and lactation should be strongly encouraged. Although recommended by professional guidelines in the USA,<sup>87–89</sup> prenatal supplements provided free of cost in the UK do not contain iodine.

## Conclusion and future research

As a population moves from severe iodine deficiency to mild iodine deficiency and then to iodine sufficiency, there is a shift from excess hypothyroidism to excess hyperthyroidism, which is transient, and then a small shift back towards excess mild subclinical hypothyroidism. Severe iodine deficiency causes hypothyroidism because, despite an increase in thyroid activity to maximise iodine uptake and recycling, iodine concentrations are simply not high enough to maintain thyroid hormone production. In mild-to-moderate iodine deficiency, the thyroid gland is able to compensate for deficient dietary intake by increasing thyroid activity, which maintains

### Search strategy and selection criteria

We searched PubMed, Web of Science, and the Cochrane Libraries for articles published in English, French, and German between 1960 and June 28, 2014 with the search terms “iodine deficiency”, “iodine excess”, “iodine status”, “iodised salt”, “urinary iodine”, “goitre”, “nodules” “hyperthyroidism”, “hypothyroidism”, “thyroid antibodies”, “thyroid autoimmunity”, and “thyroid cancer”. Articles were selected for this review if they were original research papers that reported novel findings.

thyroid hormone production, but at a price: in some individuals, chronic stimulation of the thyroid leads to thyroid nodularity and autonomy. This increase in nodularity subsequently increases risk of hyperthyroidism if iodine intakes are raised by supplementation or fortification. However, this increased risk of hyperthyroidism in the population is transient, as iodine sufficiency normalises thyroid activity resulting, in the long term, in reduced nodularity and autonomy. The small increase in mild subclinical hypothyroidism that occurs with a shift from deficient to optimum or excessive iodine intakes might be linked to an increased risk of thyroid autoimmunity and might also be transient, but more long-term studies are needed.

In conclusion, increasing iodine intake in populations with severe iodine deficiency is essential to reduce the prevalence of hypothyroidism and minimise the risk of fetal brain damage. Major benefits of increasing iodine intakes in populations with mild iodine deficiency are a decrease in the prevalence of goitre, thyroid autonomy and thyrotoxicosis in adults, and an increase in IQ in children.<sup>90–92</sup> These benefits occur at the expense of a small increase in the prevalence of mild subclinical hypothyroidism in adults, but this increase is easily correctable<sup>93</sup> and can be minimised by avoiding excessive intakes. Thus, iodised salt programmes should be carefully monitored to provide adequate iodine but avoid excess intakes in all population groups.

Future research priorities in iodine nutrition should include correlation of community iodine intake with long-term risk of thyroid disorders, and more precise definition of the limits of deficient and excessive iodine intakes that increase risk of thyroid disorders in populations. The modulation of this relation by genetic and environmental factors (pollutants and other micronutrient deficiencies) needs to be clarified. In iodine prophylaxis, efforts should focus on ensuring adequate iodine intake during pregnancy and infancy without causing excess intakes in the remainder of the population.

#### Contributors

MBZ and KB did the scientific literature review. MBZ wrote the first draft and KB edited the manuscript.

#### Declaration of interests

We declare no competing interests.

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