


## Review

# Optimizing Growth: The Case for Iodine

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**Abstract:** Iodine is an essential micronutrient and component of thyroid hormone. An adequate dietary iodine intake is critical to maintain and promote normal growth and development, especially during vulnerable life stages such as pregnancy and early infancy. The role of iodine in cognitive development is supported by numerous interventional and observational studies, and when iodine intake is too low, somatic growth is also impaired. This can be clearly seen in cases of untreated congenital hypothyroidism related to severe iodine deficiency, which is characterized, in part, by a short stature. Nevertheless, the impact of a less severe iodine deficiency on growth, whether in utero or postnatal, is unclear. Robust studies examining the relationship between iodine and growth are rarely feasible, including the aspect of examining the effect of a single micronutrient on a process that is reliant on multiple nutrients for optimal success. Conversely, excessive iodine intake can affect thyroid function and the secretion of optimal thyroid hormone levels; however, whether this affects growth has not been examined. This narrative review outlines the mechanisms by which iodine contributes to the growth process from conception onwards, supported by evidence from human studies. It emphasizes the need for adequate iodine public health policies and their robust monitoring and surveillance, to ensure coverage for all population groups, particularly those at life stages vulnerable for growth. Finally, it summarizes the other micronutrients important to consider alongside iodine when seeking to assess the impact of iodine on somatic growth.

**Keywords:** iodine; growth; iodine deficiency; thyroid function



**Citation:** Rigutto-Farebrother, J. Optimizing Growth: The Case for Iodine. *Nutrients* **2023**, *15*, 814. <https://doi.org/10.3390/nu15040814>

Academic Editors:  
Vincenzo Triggiani and  
Giuseppe Lisco

Received: 30 December 2022  
Revised: 29 January 2023  
Accepted: 3 February 2023  
Published: 5 February 2023



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## 1. Introduction

Growth is a multi-factorial process. Adequate macro- and micronutrient intake, socioeconomic status, environmental and sanitary conditions, as well as culture, all impact on the risk of sub-optimal growth in a population [1–4]. Growth faltering in early life, if uncorrected, may compromise height in adulthood leading to permanent stunting. Stunting has far-reaching adverse consequences, including poor educational performance, lost productivity and low wages as an adult [3]. Though perhaps often more associated with cognition through its implication in the development of the brain, iodine is also a critical micronutrient for somatic growth. It exerts its effects via thyroid hormone (TH), being an integral and essential component. TH regulates vital processes in the body from the agglomeration of fetal cells after conception [1] through to the maintenance of cellular energy and metabolism in adulthood [1], and the role of iodine in skeletal formation and development via thyroid hormone is known [5]. However, inadequate iodine intakes may result in low serum TH concentrations.

Iodine deficiency disorders (IDD; Table 1) are well described and can be as severe as congenital hypothyroidism and miscarriage in pregnancy [6]. Growth can also be impaired: in particular, stunting is marked in myxedematous congenital hypothyroidism caused by severe iodine deficiency during gestation [4,7]. However, the precise effect of iodine on growth trajectories in individuals subject to a lesser degree of iodine deficiency is not as clear.

**Table 1.** Iodine deficiency disorders.

Life Stage Group	Health Consequences of Iodine Deficiency	
Fetus	Failed pregnancy	
	Stillbirth	
	Congenital anomalies	Goiter
Neonate	Perinatal mortality	Hypothyroidism
	Endemic congenital hypothyroidism	Increased susceptibility to nuclear radiation
	Infant mortality	
Child, Adolescent	Impaired mental function	
	Delayed physical development	
	Iodine-induced hyperthyroidism	
Adult	Impaired mental function	
	Iodine-induced hyperthyroidism	
Neonate	Failed pregnancy	
	Stillbirth	
	Congenital anomalies	
	Perinatal mortality	

Adapted from [6].

This is partly because somatic growth is difficult to adequately assess in nutrition intervention studies. Not only because growth is so multifactorial, as outlined above, thereby making it difficult to assess the effect in relation to a single micronutrient, but moreover, because growth is uneven: at times of peak development such as infancy and childhood, growth phases may be rapid, and individuals develop at different rates. Yet, for the purposes of clinical research, growth is slow. Studies looking to measure a difference in somatic growth in response to a given intervention will require a sufficiently long period between baseline and endpoint as well as a large sample size to permit the estimation of group differences with a reasonable certainty [8]. Randomized controlled trials (RCT) are not always feasible for ethical reasons, and interpretations from cross-sectional studies are limited, since, by definition, they cannot describe the effect of an intervention and may be subject to bias [9]. Therefore, indicators other than height and, for example, height-for-age Z-scores, to indicate changes in the growth trajectory of an individual, must be considered.

This narrative review presents the physiological mechanisms by which iodine contributes to growth, including for both insufficient and excessive iodine intakes, and presents evidence from human studies that demonstrate these possible effects.

## 2. Thyroid Function and Growth

### 2.1. Iodine as a Component of Thyroid Hormone

TH synthesis is stimulated by the secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus, which in turn stimulates the anterior pituitary gland to synthesize and secrete thyrotropin, or thyroid-stimulating hormone (TSH). TSH acts directly on the thyroid gland to stimulate the synthesis of TH, completing the so-called hypothalamus–pituitary–thyroid (HPT) axis [10].

One of the principal steps in the synthesis of TH is the organification of iodine, that is, the iodination of tyrosine residues on the structure of the prohormone thyroglobulin, present in the colloid of thyroid follicular cells. The coupling of these residues forms triiodothyronine (T3) and thyroxine (T4), which are secreted from the thyroid cell following release from thyroglobulin. Circulating TH is usually bound to carrier proteins, including thyroxine-binding globulin, albumin and transthyretin [5]. Only approximately 0.2% of T3 and 0.02% of T4 are unbound in plasma [5] and it is these free, unbound hormones that act on the hypothalamus and anterior pituitary gland to inhibit the synthesis of further TH, in a negative feedback loop that regulates the HPT axis. Thus, TH status is maintained in a normal range for that individual.

The only known functional role of iodine in the body is for the formation of TH, and it is required at physiological doses from conception throughout life (Table 2), being

particularly critical periconceptually and during pregnancy and early infancy, as described later. Iodine enters the circulation as plasma inorganic iodide,  $I^-$ , and is cleared principally by the thyroid gland for hormone production, and kidney for excretion in urine. A healthy euthyroid adult would have approximately 15–20 mg iodine, of which 70–80% would be stored in the thyroid [11], and thyroidal iodine content has been shown to be positively correlated with TH concentrations [12]. However, thyroidal iodine stores will decrease when exposed to inadequate intakes or if not continually replenished during certain life stages, for example, in pregnancy, where the maternal iodine supply must account for maternal and fetal needs [13–16].

**Table 2.** Iodine intake recommendations during growth life stages.

	European Union Scientific Committee on Foods (2014, 2006)		US Institute of Medicine (2001)		World Health Organization (2004)	
	AI µg/Day	TUL	AI µg/Day	TUL	RI µg/Day	TUL
Periconception	150	500	150 <sup>c</sup>	1100	150 (adolescents and adults >13 y)	30 <sup>a</sup> (adolescents and adults >13 y)
Pregnant women	200	600	220	1100	250	40 <sup>a</sup>
Lactating women	200	600	290	1100	250	40 <sup>a</sup>
Infants and young children						
Individual level iodine intake recommendations						
0–6 mo <sup>1</sup>	ND	ND	110	ND	15 <sup>a</sup>	150 <sup>a</sup>
7–12 mo <sup>1</sup>	70	ND	130	ND	15 <sup>a</sup>	140 <sup>a</sup>
1–3 y <sup>1</sup>	90	200	65 <sup>b</sup> /90 <sup>c</sup>	200	6 <sup>a</sup> (2–5 y)	50 <sup>a</sup>
Population iodine intake recommendation						
0–59 months <sup>1</sup>					90	180
Older children and adolescents						
4–6 y	90	250	90 <sup>c</sup> (4–8 y)	300 (4–8 y)	6 <sup>a</sup> (2–5 y)	50 <sup>a</sup>
7–10 y	90	300	120 <sup>c</sup> (9–13 y)	600 (9–13 y)	4 <sup>a</sup> (6–12 y)	50 <sup>a</sup>
11–14 y	120	450				(7–12 y)
15–17 y	130	500	150 <sup>c</sup> (14–18 y)	900 (14–18 y)	150 (adolescents and adults >13 y)	30 <sup>a</sup> (adolescents and adults >13 y)

<sup>1</sup> Recommendations are age-relative and are not per source of iodine (i.e., breast milk, formula, complementary food) nor are based on whether the child is weaning or has already been weaned. Abbreviations: AI; adequate intake; mo, months; ND, not defined; RDA, recommended daily allowance; RI, recommended intake; TUL, tolerable upper level; y, years. <sup>a</sup> recommendation per kg bodyweight, <sup>b</sup> EAR, estimated average requirement; <sup>c</sup> RDA, recommended daily allowance. Sources: [17–20].

The principal sources of dietary iodine are seaweeds and seafoods [21], animal milk, particularly in countries where herds are fed with iodine-fortified feed or where the dairy industry permits iodine-based disinfectants [22,23], eggs [21], and iodized salt. Salt iodization is considered a public health success; increasing global efforts to iodize salt for human and animal consumption has led to the near elimination of previously widespread iodine deficiency leaving few countries still at risk [24]. It is a highly cost-effective intervention, at only USD 0.06 per capita per year or less [25], and reaches all population groups [26].

## 2.2. Thyroid Hormone and Growth

TH acts on almost every cell in the body, except for the adult brain and spleen. The key periods for growth across the life cycle—pregnancy, early infancy and lactation, childhood—are therefore crucial for ensuring optimal iodine intakes. During skeletal development and

linear bone growth, bone mass accumulates and bone mineralization increases until peak bone mass is achieved, usually by early adulthood [5].

Growth hormone (GH) and the insulin-like growth factors (IGFs) promote growth through action on the organs associated with key metabolic effects including the liver, skeletal muscle, and bone [27]. Through the somatotropic GH-IGF axis, GH promotes the synthesis and secretion of IGFs, which are proteins typically produced in the liver in response to GH stimulation [28]. IGFs, in turn, enhance cell proliferation and differentiation [29]. GH also stimulates the production of different growth factors (epidermal growth factor, nerve growth factor, and erythropoietin).

The physiological mechanisms linking iodine and growth arise through the important and intricate links between TH, GH, and the IGFs. TH influences the expression and action of GH [30,31], and the secretion of GH is dependent upon normal thyroid function [32,33]. Further, the synthesis of TH requires the presence of IGF-1 [34], and IGF-1 itself is necessary for the anabolic effect of T3 [33]. Additionally, GH accelerates the peripheral conversion of T4 to T3 [35]. During childhood, beginning from between six months and three years to puberty, the GH-IGF-1 axis and TH become more influential on growth, and at puberty, GH and IGF-1 concentrations increase significantly in both males and females [36].

Yet, some of the effects of TH on growth are direct and occur independently of the effects of GH. These include effects on bone and skeletal development [37,38]. This has been modelled in mice, where Kim and Mohan proposed that the increase in IGF-1 expression and bone growth during prepubertal and pubertal periods are mediated via TH- and GH-dependent mechanisms, respectively [37].

The skeleton is a target for TH action, and TH receptors have been identified in osteoblast cell lines and human bone samples [39], though the effect of TH on osteoclasts may be, rather, indirect [39]. Biochemical studies have shown that TH affects the expression of various bone markers in serum that reflect changes in both resorption and formation [39]. As in the thyroid gland itself, a delicate balance in bone exists between the inactive hormone T4 and its active metabolite, T3. This balance is facilitated by the D2 iodothyronine deiodinase enzyme in osteoblasts, and the inactivating iodothyronine deiodinase D3, which inactivates both T4 and T3 with the removal of a 5-iodine atom. D3 is present in all skeletal cell lines during development and until weaning [40,41]. It is thought that D3 is essential in limiting TH availability to the immature skeleton [41].

### *2.3. Mechanisms by which Suboptimal Iodine Intakes May Affect Growth*

#### *2.3.1. Iodine Deficiency and Hypothyroidism*

Hypothyroidism is the inadequate production of TH, and an inadequate iodine intake is the most common cause of hypothyroidism worldwide [4,42]. Hypothyroidism may be present at birth (congenital hypothyroidism) or arise in later life (acquired hypothyroidism). Criteria for the diagnosis of overt hypothyroidism are a high TSH and low T4, or normal T4 with a TSH greater than 10 mU/L; subclinical hypothyroidism is defined by high TSH and a normal T4. Symptoms of hypothyroidism include fatigue, cold intolerance, constipation, bradycardia, delayed reflexes, myxedema of the face or extremities, and goiter [4,42].

Sequelae of chronic hypothyroidism include other IDD (Table 1). In particular, iodine deficiency and hypothyroidism during key childhood growth phases, and until the point at which bone maturation and epiphyseal closure occurs, can lead to reduced and/or delayed growth, reduced linear bone growth velocity, and delayed bone maturation [14, 43]. In some cases, effects are irreversible, and can cause dwarfism, where the limbs are disproportionately short compared with the trunk.

Though each of the principal life stages demonstrates a critical need for iodine to support growth processes, evidence from across the literature is increasingly pointing towards the need for iodine sufficiency before a woman enters gestation [44–47]. Though much of the work in this area surrounds optimal neurodevelopment [44], it follows that growth processes may also be affected and it thus deserves mention here (Table 1).

In pregnancy, maternal iodine intakes and/or stores must be adequate to maintain a production of TH that is sufficient for both maternal and fetal needs. Yet, if iodine intakes before pregnancy are inadequate and iodine stores low, there is a risk that thyroid hormone synthesis will be insufficient for the needs of early pregnancy. The principal reasoning for this is the time needed to synthesize thyroid hormone after ingestion. Whilst iodine absorption from the gastrointestinal tract following ingestion is rapid [48], the synthesis of thyroid hormone and integration of iodine as iodinated tyrosines into stores may take up to several weeks [44,49]. Many women do not find out that they are pregnant until well within the first trimester, at which point supplement use may be too late to counteract the deleterious effects of a lack of iodine early in pregnancy [44–47]. Effects may even be seen in settings of mild-to-moderate iodine deficiency, which is today more often observed than severe deficiency, including in high-income countries with robust salt iodization schemes [50].

Finally, thyroid dysfunction has been associated with subfecundity, i.e., the ability to successfully conceive [51]. In a study in the US, a lower UIC ( $<50 \mu\text{g/g}$  creatinine) was associated with a 46% reduction in fecundity compared to women with UIC  $>100 \mu\text{g/g}$  creatinine [52]. In a large cohort study in Norway, iodine intakes of  $<100 \mu\text{g/day}$  were associated with increased subfecundity [47].

During pregnancy, the increased demand for iodine is potentiated by an increase in human chorionic gonadotropin (hCG) following oocyte fertilization, increased circulating estrogens that cause a progressive increase in thyroxine-binding globulin, and increased maternal renal excretion [53–55]. In early pregnancy, maternal T4 must cross the placenta until the fetus is able to organify iodide from the circulation at about week 16–20 [56]. Furthermore, the placenta likely protects the fetus from iodine deficiency. The expression of the sodium-iodide symporter (NIS) in placental syncytiotrophoblast cells is upregulated by hCG [57]. As intracellular iodide increases in these cells, iodide is transported from the maternal to the fetal circulation [57]. The placenta may also function as a storage organ for fetal iodine supply [58]. The optimal function of these mechanisms is most likely under conditions of euthyroidism, decreasing in functionality as iodine (from dietary intake and liberation of maternal stores) decreases. In severe iodine deficiency, when intakes are low and maternal stores depleted, these mechanisms may not be able to adequately protect the fetus, thereby elevating the risk of suboptimal growth and delayed development.

In our systematic review [59], results of meta-analyses support these hypotheses. In a pooled result from six randomized and non-randomized controlled trials, no effect of iodine supplementation was found on birthweight, though when results were stratified by maternal iodine status, supplementation of severely iodine-deficient pregnant women led to a 200 g greater birthweight compared to controls, whereas in the moderate-to-mild deficient group, supplementation had no effect.

In Peru, severely-iodine deficient pregnant women treated with intramuscular iodized oil gave birth to infants 4.7 cm longer compared with women who received a placebo [60]. In Algeria, mothers treated with oral iodized oil had infants with a greater birthweight than untreated women [61]. In Bangladesh, maternal iodine intakes were positively associated with infant birthweight and length, though interestingly only in males, in whom the mean weight increased by 70 g and length by 0.41 cm, after a  $500 \mu\text{g/L}$  increase in maternal UIC [62]. Spanish women with mildly insufficient iodine intakes in the third trimester were 13% less likely to have an infant small for gestational age than women with severe iodine deficiency [63], and in England, a trend for SGA or low-birthweight infants with iodine deficiency has been observed across several studies [64,65]. However, results are equivocal [66,67]. Our systematic review found no effect of iodine supplementation on infant length at birth [59]. In Papua New Guinea, when the children of mothers treated with iodized oil or placebo were followed at age 15, there was no difference in height [68]. This indicates confounding factors and the challenging nature of studies aiming to assess differences in somatic growth, and points to its multifactorial nature.



In early infancy, somatic growth is rapid, with an average of 25 cm length gained during the first 12 months [36]. Considering this, we might postulate that iodine deficiency has a greater impact on growth in infants and young children, when growth associated with TH is fastest [37]. Infants are at particular risk from inadequate intakes; neonatal iodine stores are scant [69,70] and a positive iodine balance is required from birth; infants require around 7 µg iodine/kg bodyweight at this time to replete thyroidal iodine stores in addition to daily iodine turnover [71]. During infancy, breastmilk iodine concentration (BMIC) determines the iodine status of exclusively breastfed infants, making sufficient iodine intakes also critical for lactating women [58].

A study in Morocco aptly demonstrates the importance of breastfeeding in promoting infant iodine repletion and healthy thyroid function [72]. In regions of moderate-to-severe iodine deficiency in Morocco, lactating women receiving 400 mg of oral iodized oil were able to provide sufficient iodine to their breastfed infants to achieve euthyroidism by 3 months of age, whereas direct supplementation to infants was less effective. The groups showed no difference in growth parameters, however. Yet, in Iranian infants aged 6 months, breast milk iodine concentration was positively associated with weight-for-length z-scores [73]. In China, the lowest mean values of height-for-age z-scores and weight-for-age z-scores in infants aged under 6 months were found when maternal UIC was well below requirements [74]. Furthermore, models calibrated on data from US lactating women predicted that a moderate iodine deficiency in these women would result in a ~30% decrease in T4 in their infants [75], underlining the critical role breast milk or properly iodized breast-milk-substitutes have on assuring iodine intakes in young infants.

Findings from a longitudinal study demonstrate the importance of IGF-1 on infant growth [76]. Wiley et al. followed an Indian birth cohort of  $n = 122$  infants at age two years, revealing a positive association between infant length and IGF-1 [76]. The authors did not measure the iodine status or thyroid function of the study population; however, further work in the same area of India suggested adequate iodine intakes in that population [77].

Studies in school-age children have demonstrated the relationship between iodine deficiency [78], or iodine repletion [79], and their influence on indirect biomarkers of growth, such as IGF-1 and their binding proteins. Pubertal children from a severely iodine-deficient area of Turkey had significantly lower IGF-1 and IGF-binding protein-3 (IGFBP-3) levels than counterparts living in an area of mild deficiency [80]. When iodized salt was introduced in a severely iodine-deficient area of Morocco, median IGF-1 concentrations improved in the 7–10-year-old school children living in households using the iodized salt [79,81]. The iodine repletion of school-age children using iodized oil in areas of moderate or mild iodine deficiency increased serum IGF-1 and IGFBP-3 compared to a placebo [82,83].

### 2.3.2. Excessive Iodine Intakes

There is less evidence that excessive iodine intakes may have sequelae on growth processes or outcomes, since physiological mechanisms exist that largely prevent adverse effects from excessive iodine exposure. The healthy thyroid is a highly flexible organ, capable of adapting to various levels of iodine. The WHO maximal tolerated upper level of iodine, safe for healthy, euthyroid persons is 1 mg iodine per day, equivalent to 17 µg/kg body weight [17], though most euthyroid adults, without underlying thyroid disease and living in iodine-sufficient areas, can tolerate a chronic excess iodine intake of up to 2 g/day without a clinical effect [84].

Following exposure to excessive iodine intake, the Wolff–Chaikoff effect protects the organism from excessive TH production. This mechanism is effectively a block in TH synthesis when plasma iodide concentrations exceed a critical level, and was elaborated by Wolff and Chaikoff in 1948 [85]. Once the plasma iodide concentration falls again, an “escape” from this block occurs. However, prolonged high iodine intakes may prevent an escape; indeed, this is the mechanism by which iodine is used prophylactically to protect the thyroid gland in the case of a nuclear accident [86]. However, unintended exposure

to iodine intakes beyond the critical level can lead to hypothyroidism and/or goiter in vulnerable individuals, particularly those with an underlying thyroid disorder. Effects usually disappear following a decrease in iodine intake [87].

This prompts the question: is a temporary cessation in the formation of TH deleterious during periods of intense growth, such as pregnancy or infancy? Though capable of iodide organification from gestational weeks 16 to 20, the developing fetal thyroid cannot escape from the Wolff–Chaikoff effect until about week 36 weeks [88]. Sequelae due to maternal–fetal excess iodine exposure include, in severe cases, the adverse formation of the thyroid gland during embryogenesis [89], fetal goiter that can obstruct the neonatal airway at delivery [90,91], or congenital hypothyroidism [88,92]. Even mildly excessive intakes may cause maternal hypothyroidism or isolated hypothyroxinaemia, thus reducing the availability of TH for growth processes. Iodine supplementation that is only started early in pregnancy in women having a low iodine intake and low stores periconceptually may also have the same effect [46]. Iodine-induced hypothyroid states may have the same effect on growth as hypothyroidism caused by iodine insufficiency (Part 2.c.i.). In some cases, the effects are reversible: maternal consumption of seaweed soup during and after pregnancy led to hypothyroidism in the infant; however, the interruption of breastfeeding and short-term therapy with synthetic TH (levothyroxine) corrected thyroid function and the infant had a normalized growth trajectory [93].

Excessive iodine intake increases the risk of subclinical hypothyroidism, where TSH is elevated yet T4 is normal. In an area of China exposed to high iodine concentrations in the drinking water, children aged 7 to 13 years showed a greater prevalence of subclinical hypothyroidism and other thyroid disorders compared with similar children living in an area with sufficient but not excessive iodine intakes (control children) [94]. Interestingly, however, the high-iodine children were, on average, 4 cm taller than the control children ( $p = 0.001$ ). This example perhaps illustrates the importance of iodine for growth, yet shows the delicate balance between low, optimal and elevated iodine intakes. It has previously been demonstrated in several life-stage groups, that an optimal iodine balance exists in a U-shaped curve [95–98]. Most cases of subclinical hypothyroidism revert to normal; however, between 1% and 5% of individuals will develop overt disease [99].

### 2.3.3. Hyperthyroidism, Thyrotoxicosis, and Graves' Disease

Unlike the link between hypothyroidism and an insufficient iodine intake, hyperthyroidism is usually due to autoimmunity rather than an excessive iodine intake. Hyperthyroidism is defined by elevated circulating THs: elevated T4 accompanied by a low or undetectable TSH. A subclinical diagnosis refers to a low TSH with normal T4 levels. Thyrotoxicosis refers to the clinical picture of excess circulating THs, irrespective of the source [100]. Finally, Graves' disease is an autoimmune disorder and the most common cause of hyperthyroidism [100–102]. Presenting symptoms of hyperthyroidism, including in children, include warm moist skin, diarrhea, tachycardia or cardiac arrhythmia, asthma or respiratory disease [100,102]. Goiter may be present due to the lymphocytic infiltration of the thyroid gland [42], and there may be unexpected weight loss or failure to gain weight, e.g., in childhood [103,104].

Graves' disease during pregnancy is associated with pregnancy loss and stillbirth, prematurity, low birth weight, and intrauterine growth restriction, as well as maternal complications such as hypertension and congestive heart failure. Risks are higher when the disease is uncontrolled, but persist even if under control [105,106]. Infants of mothers with Graves' disease may have a higher risk of neonatal thyrotoxicosis at birth, which can lead to significant morbidity and mortality if not treated [107].

If hyperthyroidism or Graves' disease in childhood is untreated, it can lead to negative growth sequelae. Accelerated linear growth and advanced bone age caused by hyperthyroidism [40,42,103] can cause the child to not attain full height potential due to the premature closure of the end of long bones (epiphyses) or premature closure of cranial plates [38,40]. In severe cases, craniosynostosis may result from premature fusion of the

skull sutures, which may also result in cognitive deficits [5]. If hyperthyroidism remains uncorrected, calcification and bone formation is increased, alongside enhanced bone resorption [39,108]. Bone mineral density is thus weakened with age [38], with increased porosity and decreased cortical thickness in cortical bone [39].

### 3. Other Micronutrients for Consideration

This review has described the effects that iodine may have on growth, via its critical role in thyroid function, with optimal thyroid function being the true facilitator for optimized growth trajectories. Nutrients rarely function alone in the human body, and it is therefore also important to note the other micronutrients crucial for optimal thyroid function.

Iron is a requirement for the heme-dependent thyroid peroxidase enzyme, that catalyzes the oxidation of iodide and the binding of iodine to the tyrosyl residues of thyroglobulin [109]. Selenium is critical for the selenoprotein iodothyronine deiodinase enzymes that catalyze the removal of iodide from T4 in the conversion of T4 to T3. Selenoproteins also have an important antioxidant role in the thyroid gland [110]. Zinc regulates both the synthesis and mechanism of action of THs. Zinc acts as a connector between T3 and its nuclear receptor in the hypothalamus to stimulate thyrotropin-releasing hormone synthesis, which, in turn, stimulates the synthesis of TSH and thereby regulates TH synthesis. Zinc is also involved in the activity of deiodinase selenoprotein enzymes and can modify the structures of the transcription factors involved in the synthesis of THs [111]. Vitamin A has an intricate and complex relationship with thyroid function and vitamin A status can influence iodine uptake by the thyroid, which is lessened in vitamin A deficiency. Vitamin A deficiency also impairs the synthesis of thyroglobulin, the glycoprotein structure on which THs are formed [112–114]. Finally, vitamin D, already associated with growth through its role in regulating bone metabolism and calcium and phosphorus homeostasis, may have other impacts on growth via its association with the GH-IGF-1 axis [115], which itself is associated with thyroid hormone, as reviewed above. Furthermore, through its significant role in immune system modulation, vitamin D may be implicated in the development of autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease; however, more research is required to substantiate this hypothesis [116].

### 4. Discussion

With the development of Universal Salt Iodization (USI) programs worldwide, there has been significant progress in reducing iodine deficiency disorders in recent decades. At the time of writing, the Iodine Global Network recorded 26 countries with a risk of insufficient iodine intakes, based on data from school-age children [24]. However, the parity of iodized salt programs within countries remains an issue [117], possibly putting part of the population at risk, particularly vulnerable groups such as pregnant and lactating women and young children, in whom somatic growth, and thus the requirement for iodine, is highest. Public health policy should continue to emphasize USI policy, or the iodization of salt in staple foods or other staple condiments, and assure adequate monitoring and surveillance, including sentinel surveys in vulnerable population groups to inform where iodized salt programs may not be as effective as assumed [118–120]. Since, if mild processing disorders linked to iodine deficiency may be increasing as reported, it follows that growth may too be affected.

On the other hand, 13 countries recorded a prevalence of excessive intakes, i.e., intakes higher than those required to prevent iodine deficiency [6]. Excessive intakes may be due to over-iodization or poor monitoring of USI, additive dietary factors, e.g., seaweed consumption, use of dietary supplements, or arising from environmental situations such as groundwater with a high iodine concentration [121]. Though perhaps not as critical as insufficient iodine intakes, as reviewed above, excessive intakes may also have negative long-term effects on growth.

This review has described several human studies reporting growth data in conjunction with iodine intakes, and underlined the public health importance of assuring sufficient



population iodine intakes throughout life, not just at periods associated with rapid growth such as pregnancy and infancy. These studies have used several anthropometric and biochemical markers to describe growth or growth changes, including height or length, birth outcomes such as birth weight, length or SGA, z-scores of height, weight and age, and circulating concentrations of IGF and IGFBP-3. Further potential indicators of growth include head circumference, body mass index, mid-upper arm circumference, and child growth rate. The indicators chosen will depend upon the study design. Several other micronutrients are also critical to consider when assessing the relationship of iodine to growth, including iron, selenium, zinc, and vitamins A and D, and studies should therefore also consider status of these micronutrients in the sample population.

**Funding:** This work received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The author declares no conflict of interest.

## References

1. Forhead, A.J.; Fowden, A.L. Thyroid Hormone Regulation of Metabolism. *Physiol. Rev.* **2014**, *94*, 355–382. [CrossRef]
2. Vanderpas, J.-B.; Moreno-Reyes, R. Historical aspects of iodine deficiency control. *Minerva Med.* **2017**, *108*, 124–135. [CrossRef] [PubMed]
3. De Onis, M.; Branca, F. Childhood stunting: A global perspective. *Matern. Child Nutr.* **2016**, *12* (Suppl. S1), 12–26. [CrossRef] [PubMed]
4. Delange, F. The disorders induced by iodine deficiency. *Thyroid* **1994**, *4*, 107–128. [CrossRef] [PubMed]
5. Wojcicka, A.; Bassett, J.H.D.; Williams, G.R. Mechanisms of action of thyroid hormones in the skeleton. *Biochim. Biophys. Acta Gen. Subj.* **2013**, *1830*, 3979–3986. [CrossRef]
6. World Health Organization; UNICEF; ICCIDD. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination: A Guide for Programme Managers*, 3rd ed.; WHO: Geneva, Switzerland, 2007; Available online: <https://apps.who.int/iris/handle/10665/43781> (accessed on 1 December 2022).
7. Hetzel, B.S. Iodine deficiency disorders (IDD) and their eradication. *Lancet* **1983**, *2*, 1126–1129. [CrossRef] [PubMed]
8. Eng, J. Sample size estimation: How many individuals should be studied? *Radiology* **2003**, *227*, 309–313. [CrossRef]
9. Hammer, G.P.; du Prel, J.-B.; Blettner, M. Avoiding bias in observational studies: Part 8 in a series of articles on evaluation of scientific publications. *Dtsch. Arztebl. Int.* **2009**, *106*, 664–668. [CrossRef] [PubMed]
10. Feldt-Rasmussen, U.; Effraimidis, G.; Klose, M. The hypothalamus-pituitary-thyroid (HPT)-axis and its role in physiology and pathophysiology of other hypothalamus-pituitary functions. *Mol. Cell. Endocrinol.* **2021**, *525*, 111173. [CrossRef]
11. Chung, H.R. Iodine and thyroid function. *Ann. Pediatr. Endocrinol. Metab.* **2014**, *19*, 8–12. [CrossRef]
12. Li, Z.-T.; Zhai, R.; Liu, H.-M.; Wang, M.; Pan, D.-M. Iodine concentration and content measured by dual-source computed tomography are correlated to thyroid hormone levels in euthyroid patients: A cross-sectional study in China. *BMC Med. Imaging* **2020**, *20*, 10. [CrossRef] [PubMed]
13. Glinoer, D. The regulation of thyroid function during normal pregnancy: Importance of the iodine nutrition status. *Best Pract. Res. Clin. Endocrinol. Metab.* **2004**, *18*, 133–152. [CrossRef] [PubMed]
14. Zimmermann, M.B.; Jooste, P.L.; Pandav, C.S. Iodine-deficiency disorders. *Lancet* **2008**, *372*, 1251–1262. [CrossRef] [PubMed]
15. Zimmermann, M.B.; Boelaert, K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol.* **2015**, *3*, 286–295. [CrossRef] [PubMed]
16. Zimmermann, M.B. Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: A review. *Am. J. Clin. Nutr.* **2009**, *89*, 668S–672S. [CrossRef]
17. World Health Organisation, Food and Agriculture Organisation of the United Nations. *Vitamin and Mineral Requirements in Human Nutrition*, 2nd ed.; WHO: Geneva, Switzerland, 2004.
18. European Food Safety Agency. Scientific Opinion on Dietary Reference Values for iodine. *EFSA J.* **2014**, *12*, 1–57. [CrossRef]
19. European Food Safety Agency. Tolerable upper intake level on vitamins and minerals. *Wei Sheng Yan Jiu J. Hyg. Res.* **2004**, *33*, 771–773.
20. Institute of Medicine (US) Panel on Micronutrients. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*; National Academies Press: Washington, DC, USA, 2001. [CrossRef]
21. Haldimann, M.; Alt, A.; Blanc, A.; Blondeau, K. Iodine content of food groups. *J. Food Compos. Anal.* **2005**, *18*, 461–471. [CrossRef]

22. Van Der Reijden, O.L.; Galetti, V.; Herter-Aeberli, I.; Zimmermann, M.B.; Zeder, C.; Krzystek, A.; Haldimann, M.; Barmaz, A.; Kreuzer, M.; Berard, J.; et al. Effects of feed iodine concentrations and milk processing on iodine concentrations of cows' milk and dairy products, and potential impact on iodine intake in Swiss adults. *Br. J. Nutr.* **2019**, *122*, 172–185. [\[CrossRef\]](#)
23. Flachowsky, G.; Franke, K.; Meyer, U.; Leiterer, M.; Schöne, F. Influencing factors on iodine content of cow milk. *Eur. J. Nutr.* **2014**, *53*, 351–365. [\[CrossRef\]](#)
24. Iodine Global Network. Iodine Global Network Scorecard 2021. 2021. Available online: [https://www.ign.org/cm\\_data/IGN\\_Global\\_Scorecard\\_2021\\_7\\_May\\_2021.pdf](https://www.ign.org/cm_data/IGN_Global_Scorecard_2021_7_May_2021.pdf) (accessed on 4 February 2023).
25. Mannar, V. Iodization Cost (via GiveWell.org). 2014. Available online: [https://www.givewell.org/international/technical/programs/salt-iodization#footnote154\\_1aoy6n4](https://www.givewell.org/international/technical/programs/salt-iodization#footnote154_1aoy6n4) (accessed on 28 March 2021).
26. Dold, S.; Zimmermann, M.B.; Jukic, T.; Kusic, Z.; Jia, Q.; Sang, Z.; Quirino, A.; San Luis, T.O.L.; Fingerhut, R.; Kupka, R.; et al. Universal salt iodization provides sufficient dietary iodine to achieve adequate iodine nutrition during the first 1000 days: A cross-sectional multicenter study. *J. Nutr.* **2018**, *148*, 587–598. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Ipsa, E.; Cruzat, V.F.; Kagize, J.N.; Yovich, J.L.; Keane, K.N. Growth Hormone and Insulin-Like Growth Factor Action in Reproductive Tissues. *Front. Endocrinol.* **2019**, *10*, 777. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Silva, J.R.V.; Figueiredo, J.R.; van den Hurk, R. Involvement of growth hormone (GH) and insulin-like growth factor (IGF) system in ovarian folliculogenesis. *Theriogenology* **2009**, *71*, 1193–1208. [\[CrossRef\]](#)
29. Hellström, A.; Ley, D.; Hansen-Pupp, I.; Hallberg, B.; Löfqvist, C.; van Marter, L.; an Weissenbruch, M.; Ramenghi, L.A.; Beardsall, K.; Dunger, D.; et al. Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. *Acta Paediatr.* **2016**, *105*, 576–586. [\[CrossRef\]](#)
30. Robson, H.; Siebler, T.; Shalet, S.M.; Williams, G.R. Interactions between, G.H.; IGF-I, glucocorticoids, and thyroid hormones during skeletal growth. *Pediatr. Res.* **2002**, *52*, 137–147. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Zimmermann, M.B. The role of iodine in human growth and development. *Semin. Cell Dev. Biol.* **2011**, *22*, 645–652. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Cabello, G.; Wrutniak, C. Thyroid hormone and growth: Relationships with growth hormone effects and regulation. *Reprod. Nutr. Dev.* **1989**, *29*, 387–402. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Laron, Z. Interactions between the thyroid hormones and the hormones of the growth hormone axis. *Pediatr. Endocrinol. Rev.* **2003**, *1* (Suppl. S2), 244–249, discussion 250.
34. Sellitti, D.F.; Suzuki, K. Intrinsic regulation of thyroid function by thyroglobulin. *Thyroid* **2014**, *24*, 625–638. [\[CrossRef\]](#)
35. Sato, T.; Suzuki, Y.; Taketani, T.; Ishiguro, K.; Masuyama, T. Enhanced Peripheral Conversion of Thyroxine to Triiodothyronine During hGH Therapy in GH Deficient Children. *J. Clin. Endocrinol. Metab.* **1977**, *45*, 324–329. [\[CrossRef\]](#)
36. Murray, P.G.; Clayton, P.E. Endocrine control of growth. *Am. J. Med. Genet. C Semin. Med. Genet.* **2013**, *163C*, 76–85. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Kim, H.-Y.; Mohan, S. Role and Mechanisms of Actions of Thyroid Hormone on the Skeletal Development. *Bone Res.* **2013**, *1*, 146–161. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Bassett, J.H.D.; Williams, G.R. Role of Thyroid Hormones in Skeletal Development and Bone Maintenance. *Endocr. Rev.* **2016**, *37*, 135–187. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Yen, P.M. Physiological and Molecular Basis of Thyroid Hormone Action. *Physiol. Rev.* **2001**, *81*, 1097–1142. [\[CrossRef\]](#)
40. Williams, G.R. Thyroid hormone actions in cartilage and bone. *Eur. Thyroid J.* **2013**, *2*, 3–13. [\[CrossRef\]](#)
41. Williams, A.J.; Robson, H.; Kester, M.H.A.; van Leeuwen, J.P.T.M.; Shalet, S.M.; Visser, T.J.; Williams, G.R. Iodothyronine deiodinase enzyme activities in bone. *Bone* **2008**, *43*, 126–134. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Hanley, P.; Lord, K.; Bauer, A.J. Thyroid Disorders in Children and Adolescents: A Review. *JAMA Pediatr.* **2016**, *170*, 1008–1019. [\[CrossRef\]](#)
43. Pearce, E.N. Iodine deficiency in children. *Endocr. Dev.* **2014**, *26*, 130–138. [\[CrossRef\]](#)
44. Hay, I.; Hynes, K.L.; Burgess, J.R. Mild-to-Moderate Gestational Iodine Deficiency Processing Disorder. *Nutrients* **2019**, *11*, 1974. [\[CrossRef\]](#)
45. Hynes, K.L.; Seal, J.A.; Otahal, P.; Oddy, W.H.; Burgess, J.R. Women Remain at Risk of Iodine Deficiency during Pregnancy: The Importance of Iodine Supplementation before Conception and Throughout Gestation. *Nutrients* **2019**, *11*, 172. [\[CrossRef\]](#)
46. Abel, M.H.; Korevaar, T.I.M.; Erlund, I.; Villanger, G.D.; Caspersen, I.H.; Arohonka, P.; Alexander, J.; Meltzer, H.M.; Brantsæter, A.L. Iodine Intake is Associated with Thyroid Function in Mild to Moderately Iodine Deficient Pregnant Women. *Thyroid* **2018**, *28*, 1359–1371. [\[CrossRef\]](#)
47. Abel, M.H.; Caspersen, I.H.; Sengpiel, V.; Jacobsson, B.; Meltzer, H.M.; Magnus, P.; Alexander, J.; Brantsæter, A.L. Insufficient maternal iodine intake is associated with subfecundity, reduced foetal growth, and adverse pregnancy outcomes in the Norwegian Mother, Father and Child Cohort Study. *BMC Med.* **2020**, *18*, 211. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Small, M.D.; Bezman, A.; Longarini, A.E.; Fennell, A.; Zamcheck, N. Absorption of Potassium Iodide from Gastro-Intestinal Tract. *Proc. Soc. Exp. Biol. Med.* **1961**, *106*, 450–452. [\[CrossRef\]](#)
49. Nussey, S.; Whitehead, S. Chapter 3—The Thyroid Gland. In *Endocrinology: An Integrated Approach*; BIOS Scientific Publishers: Oxford, UK, 2001; Available online: <https://www.ncbi.nlm.nih.gov/books/NBK28/> (accessed on 4 February 2023).

50. Andersson, M.; Hunziker, S.; Fingerhut, R.; Zimmermann, M.B.; Herter-Aeberli, I. Effectiveness of increased salt iodine concentration on iodine status: Trend analysis of cross-sectional national studies in Switzerland. *Eur. J. Nutr.* **2020**, *59*, 581–593. [\[CrossRef\]](#)
51. Krassas, G.E.; Poppe, K.; Glinioer, D. Thyroid Function and Human Reproductive Health. *Endocr. Rev.* **2010**, *31*, 702–755. [\[CrossRef\]](#)
52. Mills, J.L.; Buck Louis, G.M.; Kannan, K.; Weck, J.; Wan, Y.; Maisog, J.; Giannakou, A.; Wu, Q.; Sundaram, R. Delayed conception in women with low-urinary iodine concentrations: A population-based prospective cohort study. *Hum. Reprod.* **2018**, *33*, 426–433. [\[CrossRef\]](#)
53. Glinioer, D. The regulation of thyroid function in pregnancy: Pathways of endocrine adaptation from physiology to pathology. *Endocr. Rev.* **1997**, *18*, 404–433. [\[CrossRef\]](#)
54. Moleti, M.; Trimarchi, F.; Vermiglio, F. Thyroid Physiology in Pregnancy. *Endocr. Pract.* **2014**, *20*, 589–596. [\[CrossRef\]](#)
55. Davison, J.M.; Dunlop, W. Renal hemodynamics and tubular function normal human pregnancy. *Kidney Int.* **1980**, *18*, 152–161. [\[CrossRef\]](#)
56. Yarrington, C.; Pearce, E.N. Iodine and pregnancy. *J. Thyroid Res.* **2011**, *2011*, 934104. [\[CrossRef\]](#)
57. Richard, K.; Li, H.; Landers, K.; Patel, J.; Mortimer, R. Placental Transport of Thyroid Hormone and Iodide. In *Recent Advances in Research on the Human Placenta*; Zheng, J., Ed.; Intech: Rijeka, Croatia, 2012.
58. Burns, R.; O’Herlihy, C.; Smyth, P.P.A. The placenta as a compensatory iodine storage organ. *Thyroid* **2011**, *21*, 541–546. [\[CrossRef\]](#)
59. Farebrother, J.; Naude, C.E.; Nicol, L.; Sang, Z.; Yang, Z.; Jooste, P.L.; Andersson, M.; Zimmermann, M.B. Effects of iodised salt and iodine supplements on prenatal and postnatal growth: A systematic review. *Ann. Nutr. Metab.* **2017**, *9*, 1092. [\[CrossRef\]](#)
60. Pretell, E.A.; Torres, T.; Zenteno, V.; Cornejo, M. Prophylaxis of endemic goiter with iodized oil in rural Peru. *Adv. Exp. Med. Biol.* **1972**, *30*, 246–265. [\[PubMed\]](#)
61. Chaouki, M.L.; Benmiloud, M. Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. *Eur. J. Endocrinol.* **1994**, *130*, 547–551. [\[CrossRef\]](#)
62. Rydbeck, F.; Rahman, A.; Grandér, M.; Ekström, E.-C.; Vahter, M.; Kippler, M. Maternal Urinary Iodine Concentration up to 1.0 mg/L Is Positively Associated with Birth Weight, Length, and Head Circumference of Male Offspring. *J. Nutr.* **2014**, *144*, 1438–1444. [\[CrossRef\]](#)
63. Alvarez-Pedrerol, M.; Guxens, M.; Mendez, M.; Canet, Y.; Martorell, R.; Espada, M.; Plana, E.; Rebagliato, M.; Sunyer, J. Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring. *Eur. J. Endocrinol.* **2009**, *160*, 423–429. [\[CrossRef\]](#)
64. Farebrother, J.; Dalrymple, K.V.; White, S.L.; Gill, C.; Brockbank, A.; Lazarus, J.H.; Godfrey, K.M.; Poston, L.; Flynn, A. Iodine status of pregnant women with obesity from inner city populations in the United Kingdom. *Eur. J. Clin. Nutr.* **2021**, *75*, 801–808. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Snart, C.J.P.C.; Threapleton, D.E.; Keeble, C.; Taylor, E.; Waiblinger, D.; Reid, S.; Alwan, N.A.; Mason, D.; Azad, R.; Cade, J.E.; et al. Maternal iodine status, intrauterine growth, birth outcomes and congenital anomalies in a UK birth cohort. *BMC Med.* **2020**, *18*, 132. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Snart, C.J.P.; Keeble, C.; Taylor, E.; Cade, J.E.; Stewart, P.M.; Zimmermann, M.; Reid, S.; Threapleton, D.E.; Poston, L.; Myers, J.E.; et al. Maternal Iodine Status and Associations with Birth Outcomes in Three Major Cities in the United Kingdom. *Nutrients* **2019**, *11*, 441. [\[CrossRef\]](#)
67. Torlinska, B.; Bath, S.C.; Janjua, A.; Boelaert, K.; Chan, S.-Y. Iodine Status during Pregnancy in a Region of Mild-to-Moderate Iodine Deficiency is not Associated with Adverse Obstetric Outcomes; Results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Nutrients* **2018**, *10*, 291. [\[CrossRef\]](#) [\[PubMed\]](#)
68. Pharoah, P.O.; Connolly, K.J. Effects of maternal iodine supplementation during pregnancy. *Arch. Dis. Child.* **1991**, *66*, 145–147. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Segni, M. Disorders of the Thyroid Gland in Infancy. In *Disorders of the Thyroid Gland in Infancy, Childhood and Adolescence*; Feingold, K.R., Anawalt, B., Boyce, A., Chrousos, G., de Herder, W.W., Dhatariya, K., Hofland, J., Dungan, K., Hofland, J., et al., Eds.; Endotext: South Dartmouth, MA, USA, 2000.
70. Delange, F. Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and of its control. *Thyroid* **1998**, *8*, 1185–1192. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Zimmermann, M.B. Iodine deficiency. *Endocr. Rev.* **2009**, *30*, 376–408. [\[CrossRef\]](#)
72. Bouhouch, R.; Bouhouch, S.; Cherkaoui, M.; Aboussad, A.; Stinca, S.; Haldimann, M.; Andersson, M.; Zimmermann, M.B. Direct iodine supplementation of infants versus supplementation of their breastfeeding mothers: A double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol.* **2014**, *2*, 197–209. [\[CrossRef\]](#)
73. Nazeri, P.; Tahmasebinejad, Z.; Hedayati, M.; Mirmiran, P.; Azizi, F. Is breast milk iodine concentration an influential factor in growth- and obesity-related hormones and infants’ growth parameters? *Matern. Child Nutr.* **2021**, *17*, e13078. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Yang, J.; Zhu, L.; Li, X.; Zheng, H.; Wang, Z.; Hao, Z.; Liu, Y. Maternal iodine status during lactation and infant weight and length in Henan Province, China. *BMC Pregnancy Childbirth* **2017**, *17*, 383. [\[CrossRef\]](#)
75. Fisher, J.; Wang, J.; George, N.; Gearhart, J.; McLanahan, E. Dietary Iodine Sufficiency and Moderate Insufficiency in the Lactating Mother and Nursing Infant: A Computational Perspective. *PLoS ONE* **2016**, *11*, e0155169. [\[CrossRef\]](#)

76. Wiley, A.S.; Joshi, S.M.; Lubree, H.G.; Bhat, D.S.; Memane, N.S.; Raut, D.A.; Yajnik, C.S. IGF-I and IGFBP-3 concentrations at 2 years: Associations with anthropometry and milk consumption in an Indian cohort. *Eur. J. Clin. Nutr.* **2018**, *72*, 564–571. [\[CrossRef\]](#)
77. Lean, M.I.F.A.; Lean, M.E.J.; Yajnik, C.S.; Bhat, D.S.; Joshi, S.M.; Raut, D.A.; Lubree, H.G.; Combet, E. Iodine status during pregnancy in India and related neonatal and infant outcomes. *Public Health Nutr.* **2014**, *17*, 1353–1362. [\[CrossRef\]](#)
78. Wan Nazaimoon, W.M.; Osman, A.; Wu, L.L.; Khalid, B.A. Effects of iodine deficiency on insulin-like growth factor-I, insulin-like growth factor-binding protein-3 levels and height attainment in malnourished children. *Clin. Endocrinol.* **1996**, *45*, 79–83. [\[CrossRef\]](#)
79. Zimmermann, M.B.; Jooste, P.L.; Mabapa, N.S.; Mbhenyane, X.; Schoeman, S.; Biebinger, R.; Chaouki, N.; Bozo, M.; Grimci, L.; Bridson, J. Treatment of iodine deficiency in school-age children increases insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations and improves somatic growth. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 437–442. [\[CrossRef\]](#) [\[PubMed\]](#)
80. Alikashioglu, A.; Ozon, A.; Yordam, N. Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 levels in severe iodine deficiency. *Turk. J. Pediatr.* **2002**, *44*, 215–218.
81. Zimmermann, M.B.; Wegmueller, R.; Zeder, C.; Chaouki, N.; Biebinger, R.; Hurrell, R.F.; Windhab, E. Triple fortification of salt with microcapsules of iodine, iron, and vitamin, A. *Am. J. Clin. Nutr.* **2004**, *80*, 1283–1290. [\[CrossRef\]](#)
82. Zimmermann, M.B.; Jooste, P.L.; Mabapa, N.S.; Schoeman, S.; Biebinger, R.; Mushaphi, L.F.; Mbhenyane, X. Vitamin A supplementation in iodine-deficient African children decreases thyrotropin stimulation of the thyroid and reduces the goiter rate. *Am. J. Clin. Nutr.* **2007**, *86*, 1040–1044. [\[CrossRef\]](#)
83. Zimmermann, M.B.; Connolly, K.; Bozo, M.; Bridson, J.; Rohner, F.; Grimci, L. Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: A randomized, controlled, double-blind study. *Am. J. Clin. Nutr.* **2006**, *83*, 108–114. [\[CrossRef\]](#)
84. Bürgi, H. Iodine excess. *Best Pract. Res. Clin. Endocrinol. Metab.* **2010**, *24*, 107–115. [\[CrossRef\]](#)
85. Wolff, J.; Chaikoff, I.L. Plasma inorganic iodide as a homeostatic regulator of thyroid function. *J. Biol. Chem.* **1948**, *174*, 555–564. [\[CrossRef\]](#)
86. Franić, Z. Iodine prophylaxis and nuclear accidents. *Arch. Ind. Hyg. Toxicol.* **1999**, *50*, 223–233.
87. Markou, K.; Georgopoulos, N.; Kyriazopoulou, V.; Vagenakis, A.G. Iodine-Induced hypothyroidism. *Thyroid* **2001**, *11*, 501–510. [\[CrossRef\]](#)
88. Connelly, K.J.; Boston, B.A.; Pearce, E.N.; Sesser, D.; Snyder, D.; Braverman, L.E.; Pino, S.; LaFranchi, S.H. Congenital hypothyroidism caused by excess prenatal maternal iodine ingestion. *J. Pediatr.* **2012**, *161*, 760–762. [\[CrossRef\]](#)
89. Serrano-Nascimento, C.; Morillo-Bernal, J.; Rosa-Ribeiro, R.; Nunes, M.T.; Santisteban, P. Impaired Gene Expression Due to Iodine Excess in the Development and Differentiation of Endoderm and Thyroid Is Associated with Epigenetic Changes. *Thyroid* **2020**, *30*, 609–620. [\[CrossRef\]](#) [\[PubMed\]](#)
90. Overcash, R.T.; Marc-Aurele, K.L.; Hull, A.D.; Ramos, G.A. Maternal Iodine Exposure: A Case of Fetal Goiter and Neonatal Hearing Loss. *Pediatrics* **2016**, *137*, e20153722. [\[CrossRef\]](#) [\[PubMed\]](#)
91. Thomas, J.d.V.; Collett-Solberg, P.F. Perinatal goiter with increased iodine uptake and hypothyroidism due to excess maternal iodine ingestion. *Horm. Res.* **2009**, *72*, 344–347. [\[CrossRef\]](#)
92. Nishiyama, S.; Mikeda, T.; Okada, T.; Nakamura, K.; Kotani, T.; Hishinuma, A. Transient hypothyroidism or persistent hyperthyrotropinemia in neonates born to mothers with excessive iodine intake. *Thyroid* **2004**, *14*, 1077–1083. [\[CrossRef\]](#)
93. Hamby, T.; Kunnell, N.; Dallas, J.S.; Wilson, D.P. Maternal iodine excess: An uncommon cause of acquired neonatal hypothyroidism. *J. Pediatr. Endocrinol. Metab.* **2018**, *31*, 1061–1064. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Sang, Z.; Chen, W.; Shen, J.; Tan, L.; Zhao, N.; Liu, H.; Wen, S.; Wei, W.; Zhang, G.; Zhang, W. Long-Term Exposure to Excessive Iodine from Water Is Associated with Thyroid Dysfunction in Children. *J. Nutr.* **2013**, *143*, 2038–2043. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Zimmermann, M.B.; Aeberli, I.; Andersson, M.; Assey, V.; Yorg, J.A.J.J.; Jooste, P.; Jukić, T.; Kartono, D.; Kusić, Z.; Pretell, E.; et al. Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100–299 µg/L: A UNICEF/ICCIDD study group report. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 1271–1280. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Farebrother, J.; Zimmermann, M.B.; Assey, V.; Castro, M.C.; Cherkaoui, M.; Fingerhut, R.; Jia, Q.; Jukic, T.; Makokha, A.; San Luis, T.O.; et al. Thyroglobulin Is Markedly Elevated in 6- to 24-Month-Old Infants at Both Low and High Iodine Intakes and Suggests a Narrow Optimal Iodine Intake Range. *Thyroid* **2019**, *29*, 268–277. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Stinca, S.; Andersson, M.; Weibel, S.; Herter-Aeberli, I.; Fingerhut, R.; Gowachirapant, S.; Hess, S.Y.; Jaiswal, N.; Jukic, T.; Kusic, Z.; et al. Dried blood spot thyroglobulin as a biomarker of iodine status in pregnant women. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 23–32. [\[CrossRef\]](#)
98. Shi, X.; Han, C.; Li, C.; Mao, J.; Wang, W.; Xie, X.; Li, C.; Xu, B.; Meng, T.; Du, J.; et al. Optimal and Safe Upper Limits of Iodine Intake for Early Pregnancy in Iodine-Sufficient Regions: A Cross-Sectional Study of 7190 Pregnant Women in China. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 1630–1638. [\[CrossRef\]](#)
99. Cooper, D.S.; Biondi, B. Subclinical thyroid disease. *Lancet* **2012**, *379*, 1142–1154. [\[CrossRef\]](#) [\[PubMed\]](#)
100. De Leo, S.; Lee, S.Y.; Braverman, L.E. Hyperthyroidism. *Lancet* **2016**, *388*, 906–918. [\[CrossRef\]](#)
101. Brent, G.A. Graves' Disease. *N. Engl. J. Med.* **2008**, *358*, 2594–2605. [\[CrossRef\]](#) [\[PubMed\]](#)



102. Girgis, C.M.; Champion, B.L.; Wall, J.R. Current concepts in graves' disease. *Ther. Adv. Endocrinol. Metab.* **2011**, *2*, 135–144. [[CrossRef](#)]
103. Park, R.W.; Frasier, S.D. Hyperthyroidism Under 2 Years of Age: An Unusual Cause of Failure to Thrive. *Am. J. Dis. Child.* **1970**, *120*, 157–159. [[CrossRef](#)]
104. Boiro, D.; Diédhiou, D.; Niang, B.; Sow, D.; Mbodj, M.; Sarr, A.; Ndong, A.A.; Thiongane, A.; Guèye, M.; Thiam, L.; et al. Hyperthyroidism in children at the University Hospital in Dakar (Senegal). *Pan. Afr. Med. J.* **2017**, *28*, 10. [[CrossRef](#)] [[PubMed](#)]
105. Nguyen, C.T.; Sasso, E.B.; Barton, L.; Mestman, J.H. Graves' hyperthyroidism in pregnancy: A clinical review. *Clin. Diabetes Endocrinol.* **2018**, *4*, 28. [[CrossRef](#)]
106. Lee, S.Y.; Pearce, E.N. Assessment and treatment of thyroid disorders in pregnancy and the postpartum period. *Nat. Rev. Endocrinol.* **2022**, *18*, 158–171. [[CrossRef](#)]
107. Samuels, S.L.; Namoc, S.M.; Bauer, A.J. Neonatal Thyrotoxicosis. *Clin. Perinatol.* **2018**, *45*, 31–40. [[CrossRef](#)]
108. Mosekilde, L.; Eriksen, E.F.; Charles, P. Effects of thyroid hormones on bone and mineral metabolism. *Endocrinol. Metab. Clin. N. Am.* **1990**, *19*, 35–63. [[CrossRef](#)]
109. Zimmermann, M.B. The influence of iron status on iodine utilization and thyroid function. *Annu. Rev. Nutr.* **2006**, *26*, 367–389. [[CrossRef](#)] [[PubMed](#)]
110. Ventura, M.; Melo, M.; Carrilho, F. Selenium and Thyroid Disease: From Pathophysiology to Treatment. *Int. J. Endocrinol.* **2017**, *2017*, 1297658. [[CrossRef](#)] [[PubMed](#)]
111. Severo, J.S.; Morais, J.B.S.; de Freitas, T.E.C.; Andrade, A.L.P.; Feitosa, M.M.; Fontenelle, L.C.; de Oliveira, A.R.S.; Cruz, K.J.C.; do Nascimento Marreiro, D. The Role of Zinc in Thyroid Hormones Metabolism. *Int. Z. Vitam. Ernähr. J. Int. Vitaminol. Nutr.* **2019**, *89*, 80–88. [[CrossRef](#)] [[PubMed](#)]
112. Zimmermann, M.B.; Wegmüller, R.; Zeder, C.; Chaouki, N.; Torresani, T. The Effects of Vitamin A Deficiency and Vitamin A Supplementation on Thyroid Function in Goitrous Children. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 5441–5447. [[CrossRef](#)]
113. Oba, K.; Kimura, S. Effects of vitamin A deficiency on thyroid function and serum thyroxine levels in the rat. *J. Nutr. Sci. Vitaminol.* **1980**, *26*, 327–334. [[CrossRef](#)]
114. Ingenbleek, Y. Vitamin A-deficiency impairs the normal mannosylation, conformation and iodination of thyroglobulin: A new etiological approach to endemic goitre. *Exp. Suppl.* **1983**, *44*, 264–297. [[CrossRef](#)]
115. Esposito, S.; Leonardi, A.; Lanciotti, L.; Cofini, M.; Muzi, G.; Penta, L. Vitamin D and growth hormone in children: A review of the current scientific knowledge. *J. Transl. Med.* **2019**, *17*, 87. [[CrossRef](#)]
116. Kim, D. The role of vitamin D in thyroid diseases. *Int. J. Mol. Sci.* **2017**, *18*, 1949. [[CrossRef](#)]
117. Zimmermann, M.B.; Andersson, M. Global perspectives in endocrinology: Coverage of iodized salt programs and iodine status in 2020. *Eur. J. Endocrinol.* **2021**, *185*, R13–R21. [[CrossRef](#)]
118. Hynes, K.L.; Otahal, P.; Hay, I.; Burgess, J.R. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 1954–1962. [[CrossRef](#)]
119. Hynes, K.L.; Otahal, P.; Burgess, J.R.; Oddy, W.H.; Hay, I. Reduced Educational Outcomes Persist into Adolescence Following Mild Iodine Deficiency in Utero, Despite Adequacy in Childhood: 15-Year Follow-Up of the Gestational Iodine Cohort Investigating Auditory Processing Speed and Working Memory. *Nutrients* **2017**, *9*, 1354. [[CrossRef](#)] [[PubMed](#)]
120. Bath, S.C. Iodine supplementation in pregnancy in mildly deficient regions. *Lancet Diabetes Endocrinol.* **2017**, *5*, 840–841. [[CrossRef](#)]
121. Farebrother, J.; Zimmermann, M.B.; Andersson, M. Excess iodine intake: Sources, assessment, and effects on thyroid function. *Ann. N. Y. Acad. Sci.* **2019**, *1446*, 44–65. [[CrossRef](#)] [[PubMed](#)]

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