Iodine Deficiency: A Nutritional Crisis or A Matter of Speculation? The Perfect Discourse.

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Abstract: During pregnancy, an increase in dietary iodine intake arises due to physiologic adaptation, a phenomenon that is characterised by complex effects that increase metabolic demands and incite hormonal changes. The presence of iodine deficiency (ID) during critical stages of gestation is associated with neurodevelopmental deficits and poses as a risk factor to the development of postpartum depression that can disrupt early mother-infant interaction. A pertinent question is at what stage of pregnancy should pregnant women be advised to take iodine-containing supplements.

The narrative review aims to evaluate the recommended level of iodine supply of childbearing age, pregnant and lactating women in relation to foetal brain development and pursues to demonstrate the nutraceutical properties of seaweed as a complimentary supplement for maintaining iodine sufficiency. To achieve this, PICO was used for synthesising foreground research questions, and this was followed up by an electronic search of published data in Embase. As part of the search strategy the exclusion and inclusion criteria for eligible articles took place in Embase. To increase the variation in resources PubMed, Google Scholar, Annual Reviews and Semanticscholar were utilised.

Results indicate that the dietary iodine recommendations for pregnant and lactating women are ambiguous, as they fluctuate between 150-300 µg/d and interestingly, the reference urinary iodine concentration (UIC) value of 150 µg/L is not based on direct experimental evidence; this amount is simply the best estimate for ensuring optimal iodine intake. Further observations revealed that children exposed to severe ID are liable to a 12.45 IQ points loss using the Binet or Raven Scales compared to those in iodine sufficient areas (UIC >100 µg/g UI/Cr), were the use of iodine supplementation prior to and during pregnancy could result in an 8.7 IQ point recovery. Relatedly, seaweed supplementation markedly increased urinary iodine excretion from ~266µg/d (SD:155.8) in the control group to ~567µg/d (SD:177.8, $p<0.01$) post consumption. Importantly these results confirm the bioavailability of iodine in seaweed. Notably, cytoarchitectural development is not exclusive to in utero and exposure to postpartum ID is associated with behavioural disorders (ADHD), learning difficulties and subtle decrements in working memory and auditory processing speed.

Overall, a glut of complexities governing ID, emerging themes (dietary trends, metabolic syndrome, psycho-nutrition) and brief encounters (seaweed toxicity, processing and cooking methods) are discussed. In closing, a possible long-term indicator of iodine status is evaluated alongside the novel use of iodised food biofortification to tackle emerging micronutrient deficiencies.

Contents

Abbreviations: In order of appearance	
Iodine deficiency disorders (IDD)	Iodine Global Network (IGN)
Iodine deficiency (ID)	Recommended dietary allowance (RDA)
Universal salt iodisation (USI)	Recommended nutrient intake (RNI)
World Health Organisation (WHO)	Total goitre rate (TGR)
United Nations Children's Fund (UNICEF)	Iodine-creatinine ratio (I/Cr)
International Council for Control of Iodine Deficiency Disorders (ICCIDD)	Transient neonatal hyperthyrotropinemia (TNH)
Iodine (I)	Potassium iodate (KIO^3)
Sodium-Iodide symporter (NIS)	Cardiovascular diseases (CVD)
Recommended dietary intake (RDI)	Thyroid cancer (TC)
Iodide (I^-)	Congenital hypothyroidism (CH)
Potassium iodide (KI)	Antithyroperoxidase antibodies (anti-TPOAb)
Sodium iodide (NaI)	thyroid function tests (TFTs)
Thyroid hormone (TH)	Graves' disease (GD)
Tetraiodothyronine (T4: thyroxine)	TSH receptor antibody (TRAb)
Triiodothyronine (T3)	Intrauterine growth retardation (IUGR)
Zinc (Zn)	Anti-thyroid drugs (ATD)
Copper (Cu)	Propylthiouracil (PTU)
Selenium (Se)	2-mercapto-1-methyl-imidazole/Methimazole (MMI)
Sodium (Na)	Attention deficit disorder with hyperactivity (ADHD)
Iron (Fe)	Inter-quartile range (IQR)
Magnesium (Mg)	Bayley Scales of Infant Development (BSID)
Parathyroid hormone (PTH)	Organic anion-transporting polypeptide 1C1 (OATP1C1)
Internal jugular vein (IJV)	Carbimazole (CBZ)
Internal carotid artery (ICA)	Postpartum thyroiditis (PPT)
Thyroid hormone receptor(s) (TR)	Gestational iodine deficiency (GID)
Thyroglobulin (Tg)	Australian National Assessment Program Literacy and Numeracy (NAPLAN)
Rough endoplasmic reticulum (RER)	Comprehensive Evaluation of Language Fundamentals study (CELF-4)
Monoiodotyrosine (MIT)	Central Auditory Processing Disorder (CAPD)
Diiodityrosine (DIT)	Social-economic status (SES)
Thyroid peroxidase (TPO)	Unliganded thyroid hormone receptors (Apo-TR)
Thyroxine binding globulin (TBG)	Metabolic syndrome (MetS)
Thyroxine binding prealbumin (TBPA)	Ultra-high temperature (UHT)
Thyroxine binding albumin (TBA	Health care professionals (HCPs)
Hydrogen peroxide (H_2O_2)	B-cell lymphoma 2 proteins (Bcl2, Bcl-xL)
Thyrotropin releasing hormone (TRH)	Outer mitochondrial membrane (OMM)
Thyroid stimulating hormone (TSH)	Mitogen-Activated Protein Kinase (MAPK)
Thyroid stimulating hormone receptor (TSHR)	WD40 repeat domain (WD40)
Selenium-containing enzyme 5′-deiodinase type 2 (D2)	Caspase recruitment domain (CARD)
Brown adipose tissue (BAT)	Apoptotic protease activating factor-1 (Apaf-1)
Hypothalamic–pituitary–thyroid (HPT) axis	Inhibitors of apoptosis proteins (IAPs)
Selenium-containing enzyme 5′-deiodinase type 3 (D3)	Second mitochondrial activator of caspases (Smac/Diablo)
Selenium-containing enzyme 5′-deiodinase type 1 (D1)	Mitochondrial serine protease (Omi/ HtrA2)
Monocarboxylate transporter 8 (MCT8)	Septin gene protein (ARTS/ Sept4)
Retinoid X receptor (RXR)	Deoxyadenosine triphosphate (dATP/ATP)
Thyroid response element (TRE)	Papillary thyroid cancer (PTC)
Nuclear receptor co-repressor (NCoR)	γ-aminobutyric acid (GABA)
Silencing Mediator for Retinoid or Thyroid-hormone receptors (SMRT)	Chronic kidney disease (CKD)
Reverse triiodothyronine (rT3)	Estimated glomerular filtration rate (eGFR)
Urinary iodine concentrations (UIC)	National Health and Nutrition Examination Survey (NHANES)
Human chorionic gonadotropin (hCG)	Arsenic (As)
Intelligence quotient (IQ)	Cadmium (Cd)
Avon Longitudinal Study of Parents and Children (ALSPAC)	Lead (Pb)
Free thyroxine (fT4	Mercury (Hg)
Randomised controlled trials (RCT)	Maximum levels (MLs)
	Kashin Beck Disease (KBD)

1 - Introduction to Iodine Deficiency Disorders (IDDs)

In 1991 the World Health Assembly acknowledged the negative effects of iodine deficiency disorders (IDD) on public health and proceed with the goal of eliminating iodine deficiency (ID) worldwide. The goal was initially proposed in 1990 at the World Summit for Children at the United Nations.[1] However, it was not until 1993 that universal salt iodisation (USI) was employed as a prophylaxis for IDD by the World Health Organisation (WHO) and United Nations Children's Fund (UNICEF) following the International Conference on Nutrition in 1992.[1] To monitor their efforts, experts of WHO, UNICEF, and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) composed a manual "*Indicators for assessing Iodine Deficiency Disorders and their control through salt iodization*" to report on the progress of eliminating global ID.[1] The use of USI to combat ID showed tremendous success between 1993-2000, and as a result the manual was revised in 2001 and 2007 as more information was gathered on the identification, prevention and control of IDD.[1,2] In addition, monitoring the use of USI in homes, utilisation of biomarkers for diagnosing IDD and iodine (I) thresholds for pregnant and lactating women were subsequently added.[1,2]

The mention of iodine thresholds for pregnant and lactating women made above, serves as the main aim to a twofold aim literature review. A review which seeks to evaluate the recommended level of iodine supply of childbearing age, pregnant and lactating women in relation to foetal cognitive development and pursues to demonstrate the nutraceutical properties of seaweed as a complimentary supplement for maintaining iodine sufficiency.[3-5] Furthermore, the prevalence of IDD has drawn attention to whether ID is still a global problem because on a global scale approximately two billion individuals suffer from ID and approximately 50 million exhibit clinical symptoms.[6] Relatedly, it has been proposed that the full extent of the ID burden on foetal-maternal health is unclear due to infrequent and inadequate evaluation on ID; indicating that further research is required.[6,7] As will be shown in this review, ID is an emerging public health concern and it is imperative that governments, health organisations and the salt industry corroborate with the public to eliminate this burden.[1,6-8]

This introduction serves as a stratum for further examination of the current recommended iodine intake levels of the public, pregnant, and lactating women. The rationale behind this is: 1) diet, a significant decrease in individual iodine intake has been observed in vegan and vegetarian diets due to a decline in consumption of iodine rich foods, simultaneously similar observations have been noted in fast food diets.[9-12] And 2) Ravera *et al.*[13] notes that in addition to thyroid and breast tissue other extrathyroidal tissues such as epithelial cells from the salivary gland, stomach and intestines concentrate iodine as they express the sodium-iodide symporter (NIS).[13] Does this entail that the recommended dietary intake (RDI) of iodine set by WHO for the average person, pregnant and lactating women (100-250 µg/d)[6] requires a review? Based on such findings, the increased nutritional demand observed during pregnancy is unlikely to be met by ID diets or USI alone, therefore other complimentary supplements such as seaweed should be considered in providing essential nutritional properties that influence foetal-maternal health and pregnancy outcome.[14-19]

As part of the introduction, the following sections acquaint the reader with the mineral iodine, anatomy of the thyroid gland, physiological roles of thyroid hormones, re-emergence of ID, and the spectrum of ill-effects associated with the endocrinopathy (IDD).

1.1 - Iodine, essential trace element

Iodine or (I) as found on the periodic table is a non-metal element of high electronegativity that belongs to the group of halogens, elements of this group do not occur in the free state in nature but as diatomic molecules (iodine:I_2) when freed from their compounds.[20] Iodine is widely distributed in nature but uneven as most of it is found concentrated in the marine environment at levels between 50-60 µg/L of sea water.[20] Iodine exists in several ionic forms and this is dependent on its oxidation state.[20,21] For example, iodide (I^-) has an oxidation state of -1, this form is the most abundant in sea water where it is found forming salts such as potassium iodide (KI) or sodium iodide (NaI).[20,21] Oxidation states of +1, +3 form iodites (IO^-,IO^{-2}) whilst +5, +7 form iodates (IO^{-3},IO^{-4}); the latter is the most abundant in marine soils, where the iodine cycle in nature begins with phytoplankton assimilating the element and reducing it to iodide which is utilised by algae and transformed into iodine.[20-22] The cycle ends with the molecular evaporation of organic iodine compounds that are deposited to the terrestrial environment by rainfall.[20,21] Also, iodine cycling tends to be slow and incomplete, and this results in low levels of iodine being deposited to the ground water and soil in inadequate amounts.[22] Consequently, plants grown in iodine deficient regions tend to have iodine concentration as lows as 10 µg/kg per dry weight in comparison to ~1 mg/kg in plants from iodine replete soils.[22] It is no wonder that vertebrates that consume crops grown in iodine depleted soils tend to become iodine deficient and this is most common in inland and mountainous regions such as the Himalayas of India[23], areas prone to flooding and in some cases coastal regions; the U.K for example.[22,24]

Table 1. Koeings' analysis of various chemical elements found in the human body. Adapted from Jensen & Anderson[26].

Element	Percent	Element	Percent
Oxygen (O)	59.0	Potassium (K)	0.1
Carbon (C)	23.0	Sodium (Na)	0.1
Hydrogen (H)	9.0	Fluorine (F)	0.1
Calcium (Ca)	2.0	Silicon (Si)	0.1
Nitrogen (N)	2.5	Magnesium (Mg)	0.1
Phosphorus (P)	2.3	Iron (Fe)	0.1
Chlorine (Cl)	1.0	Iodine (I)	0.003
Sulfur (S)	0.2	Manganese (Mn)	trace

Table outlines some of the essential chemical elements which come in the following categories: **abundant elements** (O, C), these are important constituents of tissues; **semi-major elements** (Na, K), these are involved in the maintenance of osmotic pressure and membrane potential and lastly **trace elements** (I, Fe), which are components of specific tissues (brain, blood, thyroid) .[26,28]

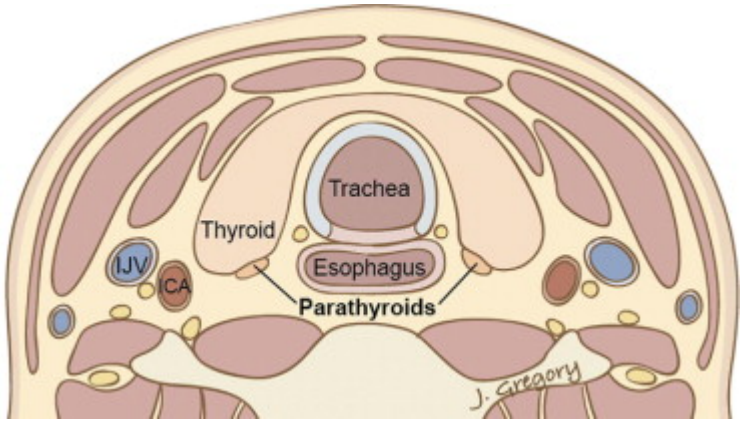
Furthermore, iodine is considered as one of the essential trace elements or micronutrient of the body despite its body percentage (Table 1). This is owed to its pivotal role during gestation and all stages of life there-after that involve the thyroid gland which utilises the mineral for the synthesis of thyroid hormones (TH), tetraiodothyronine (T4/thyroxine) and

triiodothyronine (T3).[25-27] Moreover, essential trace elements like iodine, zinc (Zn), copper (Cu) and selenium (Se) have other significant roles in the body such as being co-factors, constituents of enzyme active sites or as trace bioactive substances.[25-38] Therefore their depletion often results in clinical manifestations with various symptoms even though they account for only 0.02% of the total body weight.[25-28]

1.2 - Anatomy of the thyroid gland

Following the above, a brief overview of the anatomy and physiology of the thyroid gland is given alongside the inseparable parathyroid glands. The thyroid and parathyroid glands are positioned on the neck area (Figure 1). Their chief roles are in the regulation of body physiology, both are endocrine glands as they lack ducts and excrete their secretions directly into the blood stream.[29,30] Of interest, the thyroid gland serves as one of the largest endocrine glands as it weighs approximately 30g, but has been observed to be slightly heavier in women due to its capacity to enlarge during physiological adaptations such as pregnancy, puberty and goitre.[22,29] The gland exclusively produces thyroid hormones, T3 and T4, which are required in a wide spectrum of biochemical and metabolic pathways including brain maturation during gestation and homeostatic control of physiological mechanisms in vertebrates such as body growth, metabolism and calcitonin production for calcium homeostasis.[27,29,30] The parathyroid gland is also involved in calcium homeostasis through its production of the parathyroid hormone (PTH) that regulates calcium levels in the intestines, kidneys and skeletal system.[27,29] In embryology, both glands originate from the pharynx during gestation, but the distinction is that the thyroid gland arises from the diverticulum of the median ventral wall of the pharynx that is initially spherical and then becomes lobulated 7 weeks into gestation.[29] The parathyroid arises from the 3rd and 4th pharyngeal pouches where 2 to 6 superior and inferior parathyroid glands develop on each side.[29] In short, the cells from the pharyngeal wall that commit to the formation of the thyroid gland give rise to a specific lineage of cells called thyroid follicular cells or thyrocytes and these are responsible for the production and secretion of T3 and T4.[30]

Figure 1. Cross section of the neck outlining the anatomic location of both the thyroid and parathyroid glands. Credit, Policeni *et al.*[29]



The thyroid gland is located anterior to the trachea and oesophagus, a crescent shape encasing the trachea can be observed and this represents the right and left lobes. The parathyroid glands are located dorsal to the thyroid gland and the glands presented in this image are the superior parathyroid glands below these would be the inferior parathyroid glands.[29]

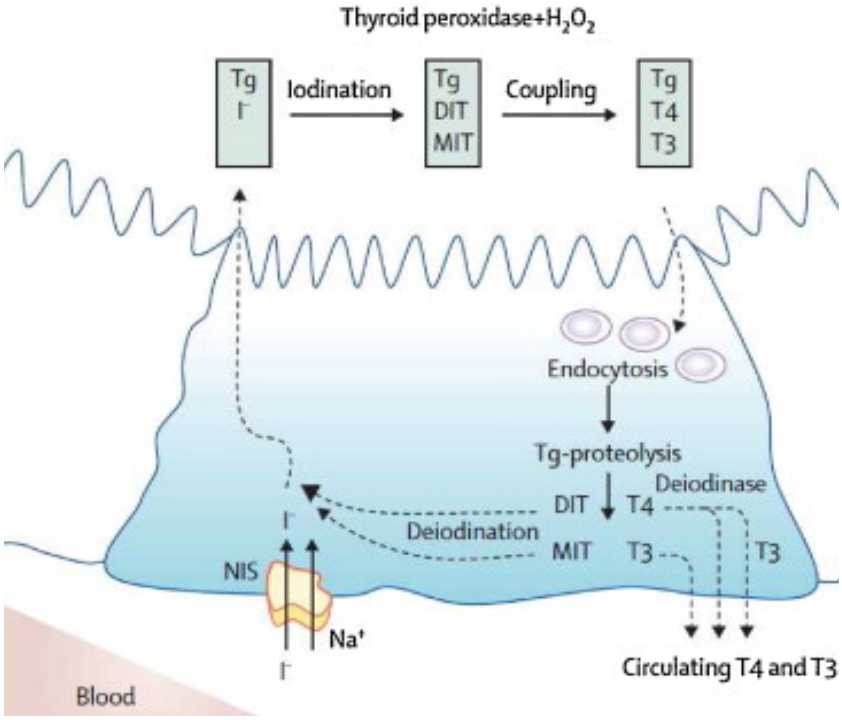
(IJV) Internal jugular vein, (ICA) Internal carotid artery

1.3 - Hormone Induction

The process by which TH (T4/T3) are synthesised (Figure 2) begins with several critical steps that results in their excretion and binding to thyroid hormone receptors (TR) in specific tissues leading to the initiation of gene transcription that triggers biological effects.[31,33] The process begins with iodide trapping to accumulate the micronutrient obtained from food sources during metabolism.[33] Next, is the uptake of iodide from the capillary into the follicular cell of the gland against a chemical and electrical gradient via the NIS protein; active transport is sustained by the ATPase dependent sodium-potassium (Na^+/K^+) pump.[31] Synthesis and secretion of the glycoprotein thyroglobulin (Tg) , a substrate for TH occurs next, and this starts on the rough endoplasmic reticulum (RER).[31,33] The process takes place within the follicular cell where the primary constituents are then shuttled to the Golgi apparatus, where a Tg molecule containing 140 tyrosine residues is produced in vesicles that transverse to the apical surface of the plasma membrane to be released in the follicular lumen.[31,33] Next, is the oxidation of iodide, from the follicular cell it must reach the apical surface of the plasma membrane to enter the follicular lumen via the sodium independent transporter (pendrin).[31] This results in instantaneous oxidation of iodide to iodine by iodine.[31] Afterwards, organification of Tg by iodination of its tyrosine residues occurs at position 3 to produce monoiodotyrosine (MIT) and at position 5 for diiodityrosine (DIT).[31-33] Iodination is proceeded by coupling reaction, whereby, two molecules of DIT conjugate to produce T4 and one MIT molecule couples with one molecule of DIT to form the T3; the reactions are catalysed by thyroid peroxidase (TPO).[31-33] The produced hormones (T4/T3), are kept in the thyroid follicles as colloid for several months depending on the body's needs.[31] Following secretion into the serum, T4 and T3 are present in two forms, bound or free; 99% of T4 and T3 circulate in bound form to several binding proteins such as thyroxine binding globulin

(TBG), thyroxine binding prealbumin (TBPA) and thyroxine binding albumin (TBA).[31] The binding proteins prevent urinary loss of the hormones and the remaining 1% of hormones found in the free form are biologically active.[31,32]

Figure 2. Synthesis and secretion of thyroid hormones. Credit, Trumpff *et al.*[63]



Schematic provides a detailed visual step-by-step process of thyroid hormone synthesis, secretion and iodine recycling within the thyrocyte as discussed above.

(Tg) Thyroglobulin, (I^-) Iodide, (Na^+) Sodium, (NIS) Sodium-Iodide symporter, (T4) Tetraiodothyronine, (T3) Triiodothyronine, (MIT) Monoiodotyrosine, (DIT) Diiodityrosine, (H_2O_2) Hydrogen peroxide

Regarding the mechanisms by which TH secretion is regulated and how the hormones play a role in the signalling of molecular cascades that result in gene transcription (Figure 3), an overview is given. Thyroid secretion is regulated by thyrotropin releasing hormone (TRH) of the hypothalamus and thyroid stimulating hormone (TSH) of the pituitary gland based on a feed-back mechanism that maintains normal T4 levels in the blood.[31-33] Low levels of T4 results in TSH secretion that acts on the TSH receptor (TSHR) present on the thyroid follicular cell basolateral membrane that is incorporated with NIS for iodide uptake thus beginning the steps for synthesis and secretion of T4 and T3.[31-33] On a molecular level T3 and T4 have TR isoforms α and β expressed in tissues (appendices), where they are involved in TH signalling.[32-34] Binding of T3 to specific TR isoforms (TRα/TRβ) results in expression of thyroid hormone-dependent genes and this is known as the genomic effect of TH because of their biological actions in the body such as cognition, development, growth and metabolic functions.[32-34] An example of how TH regulate metabolism is the activation of the T4 prohormone into the biological active form T3, by the selenium-containing enzyme 5′-

deiodinase type 2 (D2) that is essential in adaptive thermogenesis and is expressed in the hypothalamus, brown adipose tissue (BAT), white fat and skeletal muscle.[32,35] As for T4's interactions with TR, at higher concentrations T4 can trigger minimal biological effects by modifying gene transcription, this is due to T3's incomparable 10-fold affinity to TR than T4.[32-34] Simultaneously, T4 exhibits substantial nongenomic effects such as prompt D2 inactivation via ubiquitination of its lysine residues.[32-34] Additionally, secretion of T4 and T3 by the thyroid is significantly higher for T4 than T3 (molar ratio of 11:1, respectively), this means approximately 80% of T4 in contrast to 20% of T3 is excreted.[32-33] The rest of T3 comes from the peripheral deiodination (Figure 3) of the circulating prohormone T4, this action adds to the pool of circulating T3 and also has an immediate local effect.[32-34]

Figure 3. Nuclear action of thyroid hormone. Credit, Brent[33].

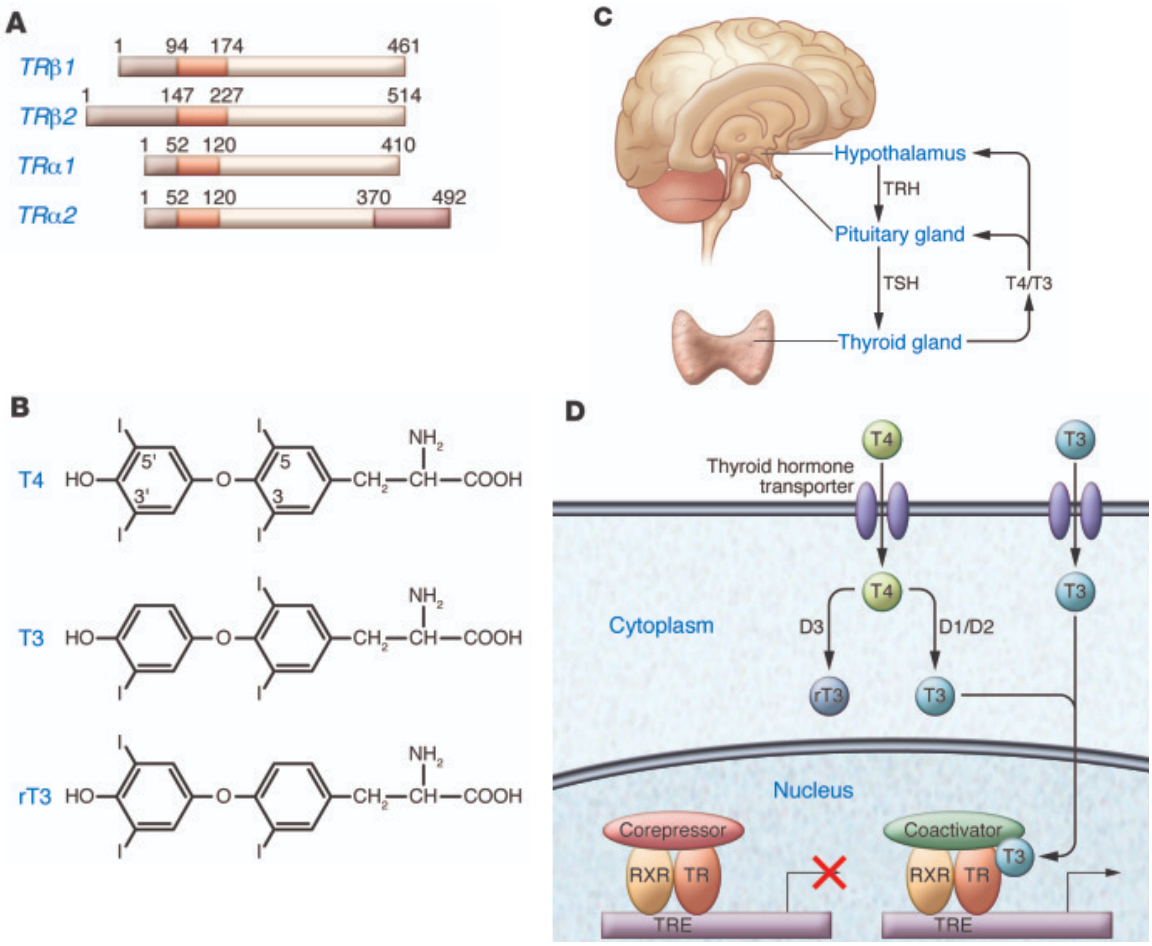


Diagram portrays key components necessary for thyroid hormone action.

(A) Represents the 2 major isoforms from the TR gene (TRβ/TRα); TRα1/TRα2 and TRβ1/TRβ2 which are target receptors for T3. **(B)** 3 types of thyroid hormones: T4, T3, and rT3; difference in moieties lays in specific iodination of tyrosine rings. **(C)** The hypothalamic–pituitary–thyroid (HPT) axis which maintains blood levels of T4 via the feed-back mechanism and is involved in metabolising circulating T4 in local tissues into T3 via membrane-bound D2. In addition, there is selenium-containing enzyme 5′-deiodinase 3 (D3) which converts T3 into inactive rT3 and D1 that converts T4 into T3. **(D)** An example of signal transduction displaying how a transporter such as MCT8 in the brain transports T4 and T3 into the cell. TH serve as ligands and if unliganded TR heterodimerizes with RXR and binds to a TRE plus a corepressor complex NCoR/SMRT causing gene expression to be repressed.[32-34] Binding of T3 to the ligand-binding domain leads to the modulation of the carboxyterminal helix 12 that prompts disruption of corepressor binding and recruitment of coactivator plus polymerase III, in order to initiate gene transcription.[32-34,36]

(MCT8) Monocarboxylate transporter 8, (RXR) Retinoid X receptor, (TRE) Thyroid response element, (NCoR) Nuclear receptor co-repressor, (SMRT) Silencing Mediator for Retinoid or Thyroid-hormone receptors, (rT3) Reverse triiodothyronine, (TR) Thyroid hormone receptor, (TSH) Thyroid stimulating hormone, (D1/D2/D3) Selenium-containing enzyme 5′-deiodinase type 1/2/3, (T4) Tetraiodothyronine, (T3) Triiodothyronine

1.4 - Development of Iodine Deficiency Disorders (IDD)

Iodine deficiency disorders (IDD) is a term that collectively defines the exhibition of clinical and subclinical symptoms of ID when dietary iodide requirements are not met.[31,22] Lack of the micronutrient often result in impaired TH synthesis that leads to the propagation of functional and developmental abnormalities that are preventable in a population by adequate dietary iodine intake.[31,37,22] This synopsis outlines some of the precursors that lead to the development of IDD, including the symptoms and the spectrum of ill-effects associated with the endocrinopathy (IDD) across different physiological groups (Table 2).[22,31,38] The proposed precursors responsible for IDD are: 1) inadequate dietary iodine intake from the consumption of foods grown in iodine depleted soils and often low consumption of seafood due to economic restraints.[31,37] And 2) inadequate iodine utilisation by the presences of goitrogens which are naturally occurring agents in foods such as cassava, cruciferous vegetables and millet.[31,37] For the goitrogens, when iodine supply is low they have the ability to interfere with iodine uptake if their consumption is increased and if prolonged this may result in goitre.[31,37] As a coping mechanism the thyroid will aid the body by releasing the hormones stored, but once stores are exhausted and T4 blood levels begin to decline the HPT axis intervenes by increasing TSH output to overstimulate the gland in order to increase iodide uptake and synthesise adequate amounts of TH.[31] If unresolved, as seen in areas with endemic ID the thyroid gland undergoes hypertrophy and hyperplasia of follicular cells that is characterised by the enlargement of the gland (goitre).[22,31] In addition, symptoms of ID such as extreme fatigue, decline in physical and mental processes, obesity, facial puffiness, constipation, and lethargy are exhibited.[27,31,37,38]

Table 2. Spectrum of ill-effects associated with IDD. Adapted from Li & Eastman[38].

Physiological groups	Health consequences of iodine deficiency
All ages	Goitre Hypothyroidism Increased susceptibility to nuclear radiation
Foetus	Spontaneous abortion Still birth Congenital anomalies Perinatal mortality
Neonate	Endemic hypothyroidism including mental deficiency with a mixture of mutism, spastic diplegia, squint, and short stature Infant mortality
Child and adolescent	Impaired cognitive function Delayed physical development Iodine-induced hyperthyroidism
Adults	Impaired cognitive function Iodine-induce hyperthyroidism

Table details an exhaustive list of complications that occur in all physiological groups as a result of ID.[22,38]

1.4.1 - Iodine Deficiency and Neurodevelopment

It is well acknowledged that median urinary iodine concentrations (UIC) between 100-199 µg/l in non-pregnant adults indicate that their iodine intake is sufficient.[8,22] This differs in pregnant and lactating adults as concentrations increase to 150-249 µg/l due to increased TH production, renal iodin loss and foetal iodine requirements.[8,22,24,41] The thyroid stores approximately 10-20 grams of iodine, of which the body taps into during the first few months of gestation for the synthesis of TH for the mother and child.[8,41] As the pregnancy progresses TH synthesis is further increased by 50%.[8.41] This is due to: 1) up regulated secretion of TSH via the HPT axis, 2) the presence of human chorionic gonadotropin (hCG) which binds and stimulate thyroidal TSH receptors and 3) elevated oestrogen levels that prompt an increase in TBG concentrations by 1.5-fold to match the increase in T3/T4 levels.[8,31,41] The increase in TH production indicate that they are critical for foetal development, specifically in neuronal migration, myelination, maturation, synaptic development and blood vessel supply; of which can be observed in a particular area of the brain, the hippocampus.[22,24,41] In contrast, optimum brain development in ID environments is often considered insufficient, therefore it is imperative that during pregnancy the mother's iodine intake stays repleted by iodine rich foods such as seafood (fish), bread and dairy products.[8,22,24] Consumption of the listed foods deters the presence of severe ID which is associated with irreversible congenital defects that have a deleterious effect on intelligence quotient (IQ).[22,24] For instance, an Avon Longitudinal Study of Parents and Children (ALSPAC) observed that the progeny of mothers with an iodine-to-creatinine ratio of less than 150 µg/g during pregnancy were likely to have scores in the lowest quartile (25%) for verbal IQ (odds ratio 1·58, 95% CI 1.09-2.30; p=0.02) and reading accuracy (1.69, 1.15-2.49; p=0.007) between the ages of 8 and 9.[8,40,42] Relatedly, a meta-analysis by Qian *et al.*[43] noted that children exposed to severe ID were liable to a 12.45 IQ points loss compared to those in iodine sufficient areas (UIC >100 µg/g iodine-to-creatine ratio).[41] The meta-analysis also suggested that the use iodine supplementation or USI prior to and during pregnancy could result in a 8.7 IQ point recovery.[41]

Furthermore, a prospective study by Korevaar *et al.*[44] on maternal thyroid function during early gestation noted an inverted U-shaped association between low child IQ, child grey matter and cortex volume and low and high maternal free thyroxine (fT4) concentrations.[5] In contrast, the study observed a loss of IQ points (1.4-3.8) instead of a gain[41,43], in mothers who received levothyroxine therapy during pregnancy for subclinical hypothyroidism.[44] Evidently, the status of the thyroid in terms of normal physiological function and adequate iodine supply during pregnancy is critical in neurodevelopment, yet the use of prophylaxis may not provide the desired outcomes. Regardless, Gernand *et al.*[7] cites two randomised controlled trials (RCT) that reported a strong and consistent link between maternal iodine supplementation prior to conception and a reduction in increased risk of foetal brain damage by severe ID. Interestingly, the effects of mild-low ID during gestation are less clear than those observed in severe ID situations.[7,22] Yet, it has been observed that untreated mild-low ID in pregnancy my lead to, cognitive delays in the offspring, 7 point reduction in IQ scores, subtle impairments of motor ability and difficulty in feeding of neonates with persistent lethargy in comparison to children of euthyroid mothers.[7,22,27,40,41]

1.4.2 - Re-emergence of ID

The accounts given above find their relevance here. This is because in recent years a global re-emergence in IDD has been taking place and this has once again captured the attention of health institutes and researchers.[4,6,23,24,39] Once again, the major concerns lay in dealing with the spectrum of ill-effects associated with ID and the devastating effects of preventable but irreversible cognitive impairment. The excerpts below provide some insights to this concern at home (UK).

Table 3 serves as a reference point for the adequate daily intake of iodine based on median UIC as recommended by WHO, ICCIDD, UNICEF and the Institute of Medicine for all age groups therefore anything below or above is usually considered insufficient or excessive.[38] Hence, it is likely that the resurgence of ID is linked to a decline in iodine intake; dietary or USI. For instance, in 2016 the Iodine Global Network (IGN) held a conference in London to address the role of iodine in pregnancy after concerns were raised on the presence of mild-to-moderate ID in the UK.[8,24,39,42] A country that is not only in the top ten of iodine deficient countries but also last updated its guidelines on iodine status in 1991 and is experiencing a decline in iodine intake.[8,24,40] In support, when commenting on the iodine status of Europe, Lazarus[39] noted that the UK's iodised salt coverage was approximately 5% compared to Switzerland (80%). This is suspected as there is no mandatory legalisation for the use of iodised salt and its availability in food stores is also low.[24,40] As a precaution to mitigate this trend, the IGN requested that the UK government should provide and determine the iodine status for the population and those most at risk, pregnant women.[8] Overall, a change in dietary habits in addition to the contributors cited above may also be a component to the re-emergence of ID.[9-12,39,66,75,107,124,132]

Table 3. Recommended iodine intake. Adapted from Li & Eastman[38].

Age or population group	Recommended iodine intake (µg/d)
WHO/UNICEF/ICCIDD RNI	
Children 0-5 years	90
Children 6-12 years	120
Children >12 years and adults	150
Pregnant women	250
Lactating women	250
Institute of Medicine RDA	
Infants 0-12 months	110-130
Children 1-8 years	90
Children 9-13 years	120
Children ≥14 year and adults	150
Pregnant women	220
Lactating women	290

Table provides values for the recommended iodine intake (µg/d) from WHO, ICCIDD UNICEF and the Institute of Medicine across different age groups. What is interesting is the marginal variations in daily I intake for all age groups as they differ between the recommending institutes.[38]

(RDA) Recommended dietary allowance, (RNI) Recommended nutrient intake

1.5 - Diagnosis and Iodine Deficiency Disorders

The diagnosis of the ill-effects associated with IDD is based on specific indicators for assessing ID.[22] The indicators often in use for assessing iodine status are: total goitre rate (TGR), urinary iodine concentration (UIC), neonatal thyroid-stimulating hormone (TSH) concentration, glycoprotein thyroglobulin (Tg).[6,22,38] Before proceeding, it is important to acknowledge that the Se containing enzyme, glutathione peroxidase can be utilised as diagnostic tool due to its ties (provides substrates) to the enzyme thyroperoxidase; involved in TH synthesis.[22]

1.5.1 - Total goitre rate (TGR)

An indicator that is associated with long term ID in certain geographical areas, and before the utilisation of the USI programme showed increased prevalence of goitre in the population.[1,3,4,6,39] The implementation of USI showed tremendous success in decrease of goitre prevalence but the accuracy of TGR has slowly declined as changes in goitre prevalence lag behind changes in iodine nutrition status and do not reflect the current iodine intake.[1,2,22,38] The assessment of goitre is done by palpation and ultrasonography.[22,45] Palpitation is based on a classification system by WHO were grade 0 denotes a thyroid gland that is not palpable or visible, grade 1 confirms the presence of goitre but the gland is not visibly enlarged and grade 2, goitre is clearly visible when the neck is in a neutral position.[22,45] Yet, neck palpation has been known to be notoriously imprecise when it comes to thyroid gland morphology and size determination, especially, in regions with mild ID.[22,45] As a safeguard, imaging via ultrasonography is used for diagnosis because it is non-invasive, efficient and achievable in remote areas that require portable equipment.[22,38,45]

1.5.2 - Urinary iodine concentration (UIC)

Approximately 90% of ingested iodine is excreted via micturition therefore, UIC serves as an excellent indicator for monitoring changes in dietary iodine intake after several days or weeks.[6,22,38] A diagnostic tool that uses urine samples to monitor ID has revamped the epidemiology and distribution of IDD; prevalent in developed countries, coastal regions and island states where goitre prevalence is low and ID was considered non-existent or to have been eliminated.[22,38] UIC is expressed in 3 ways: 1) as a concentration (µg/L) which is based on random collections of samples of a target group that is expressed as a median, 2) as iodine-creatinine excretion ratio (µg iodine/g creatinine) and 3) as 24-hour excretion (µg/day) from frequent samples collected in a day for an individual.[22] Moreover, UIC is useful in detecting excessive iodine intake analogous to inadequate dietary iodine intake, but UIC (µg/L) values can be misinterpreted as ID (<100 µg/L) because individual I consumption varies.[22] Therefore, the use of 24-hour collections (µg/day) are ideal for individuals.[22] Similar discrepancies can be observed in the iodine-creatinine ratio (I/Cr) spot samples because malnourished individuals tend to have low creatine concentration levels.[6,22] In summary, UIC is fundamentally required for estimating daily iodine intake for populations through this formula: urinary iodine (µg/L) x 0.0235 x body weight (kg) = daily iodine intake (~150 µg/d); based on a median UI of 100 µg/L and 92% iodine bioavailability.[6,22]

1.5.3 - Neonatal Thyroid Stimulating Hormone concentration (TSH)

Serum TSH is a useful indicator for ID because TSH concentrations are based on the level of circulating TH which is linked to iodine intake but the indicator falls short in older children and adults.[6,22,38] This is because even though ID causes elevation of serum TSH, the values stay within normal range and this makes this diagnostic tool an insensitive indicator of ID in adults.[22,38] Contrarily, neonatal TSH concentration is a more sensitive indicator because serum TSH concentration is inversely correlated to the serum free T4 concentration.[6,22] Infant thyroid contains less iodine but higher rates of iodine turnover due to low iodine and as result maintenance of high iodine turnover requires increased TSH stimulation.[6,22] As a rule elevated serum TSH concentrations (≥5 mIU/L) are observed in iodine deficient infants shortly after birth and this condition is termed transient neonate hypothyroidism or hyperthyrotropinemia (TNH); occurs at a stage where the developing brain is predominantly sensitive to ID.[22,46] However, limitations to the indicator include, day of sample collection post birth, assay methods and contamination by iodine sterilised antiseptics during delivery.[22,38] Together, they can alter the value and cause misinterpretation of the results.[22,38]

1.5.4 - Thyroglobulin (Tg)

Thyroglobulin (Tg), is a thyroid specific intrathyroidal protein that functions as an indicator of ID because the presence of Tg in circulation is normally <10 µg/L, but in endemic ID regions serum Tg is elevated due to increased thyroid cell mass and TSH stimulation.[6,22,47] The severity of ID is associated with increased levels of serum TG as measured by UIC.[22] To show the potential of Tg, study interventions using iodised oil and KI have shown that Tg levels decrease rapidly with iodine repletion and this has led to a proposition that Tg is a more sensitive indicator of iodine repletion than TSH or T4.[22] However, Koukkou *et al.*[48] noted that serum Tg concentration is a weak indicator[6] of iodine status during pregnancy as no change in serum Tg levels were observed during the three trimesters of pregnancy in a population that was ID. Such findings indicate that further studies are required to validate the results despite serum Tg being a useful indicator of long-term iodine status.[6] However, assays used to measure serum Tg can be problematic in remote areas because of venepuncture, centrifugation, and frozen sample transport, but the development of a new assay that uses dried blood spots from finger prick tests has simplified collection and transport.[22,49]

1.6 - Treatment of Iodine Deficient Disorders

Proceeding the above, the treatment for IDD after careful diagnosis is determined by the type of thyroid condition the individual presents from a broad list of conditions: hypothyroidism, hyperthyroidism, goitre, thyroid cancer and thyroiditis.[6.20,22,24,50] Different treatment options are available for each condition, but each condition is not limited to a single prophylaxis as they can be combined[52] for a synergistic effect and the type of treatments available are patient monitoring, pharmacological and non-pharmacological.[50] In terms of the pharmacological approach, the treatments available to the patient are based on the severity of the condition, medication tolerance and if the individual is pregnant or planning on getting pregnant.[5,50] The options available include radioactive iodine (RAI), chemotherapy, TH replacement drugs (levothyroxine-T4/liothyronine-T3).[5,50-52] From a non-pharmaceutical approach the prophylactic measures available for IDD include patient

monitoring, thyroidectomy and iodine supplementation by ISU which is complemented by dietary iodine intake.[1,8,22,24]

1.6.1 - Control and monitoring of Iodine Deficient Disorders

The use of USI in more than 120 countries[38] stands as the primary strategy against the prevention and sustainable elimination of ID and its ill-effects because it is regarded as a safe and cost-effective prophylactic that is consumed by humans and animals according to the internationally agreed recommended levels.[1,6,8,22] Two forms of iodine are used for salt iodisation in controlled conditions: potassium iodide (KI) and iodate (KIO^3).[1,22] Iodate is preferred due to its chemical stability for the production of iodised salt, a condiment that is available annually and consumed at a global scale regardless of social and economic status.[1,22] The daily requirement of iodine intake is between 150-290 µg for adults, pregnant and lactating women therefore, it is a necessity that the salt is adequately iodised at 15ppm to meet dietary requirements.[22,23,38,53] Edifying the previous remark, potential iodine loss can occur between point of production and consumption; in humid conditions salt absorbs moisture causing the iodate to dissolve and drip out of porous bags, leading to a 75% loss of iodine across nine months.[22] Moreover, WHO and other institutes recommend <5 g/day in salt consumption because >10-15 g/day is considered excessive and is associated with an increased risk in the development of cardiovascular diseases (CVD).[6,22,53] As demonstrated by its properties, USI stands as the most cost-effective vehicle for delivering iodine and improving iodine status in ID populations. Where this option is not available, oral KI supplements plus biofortification of food such as iodised oil (Lipiodol) and bread can be fortified with iodine to achieve the recommended intake (150-250 µg/d).[1,22,38,53]

Overall, it is well acknowledged that overcorrection of a previous state of ID through excess iodine intake (>600-1100 µg/day) can impair thyroid function and lead to the development of iodide goitre, iodine-induced hypothyroidism, hyperthyroidism (IIH) and thyroiditis, tachycardia and thyroid cancer (TC).[20,22,33,51,53] These conditions are rare[53] and severe cases occur in regions where the individual has been exposed to ID for several years prior to correction of ID.[20] Nevertheless, the risks associated with USI in correcting ID and the adverse ill-effects has been deemed minimal in comparison to the benefits granted by USI.[1,22] That is, the prevention of irreversible foetal brain damage, reduced prevalence of iodine-induced ill-effects, livestock health and reduced economic burden on medical and educational facilities.[1,22,31,38,,53] All of this can be achieved and permanently sustained through a framework (Figure 4), that is predicated on adequate quality assurance and monitoring of iodine supplementation that confirms adequate iodine intake and status.[1,22,53] Success of this framework depends on a long overdue dialogue between the salt industry, governments, health organisations and the public. The relevance of everything covered from the introduction to now serves as components or active parts which are the foundation of this review and can be returned to when unfamiliar with the terrain as dialogue matures.

In conclusion and returning to the aims of the review; to investigate the recommended level of iodine supply of childbearing age, pregnant and lactating women and the utilisation of seaweed as a complementary supplement for maintaining iodine sufficiency. Both are supported by the material discussed, and importantly, Figure 4 strengthens the rationale for revisiting dietary iodine intake policies. As a result, the following hypothesis has been synthesised: "*the success of USI in the decrease of goitre prevalence, an indicator for ID prior to the advent of USI has resulted in a reluctance of iodine status policy reform and eclipsed the importance of USI to the re-emerging IDDs; a key tenet of any government's public health agenda, in an era where the modern diets are seemingly ID*".

Figure 4. Series of steps involved in a national ID control programme. Credit, Andersson *et al.*[53]

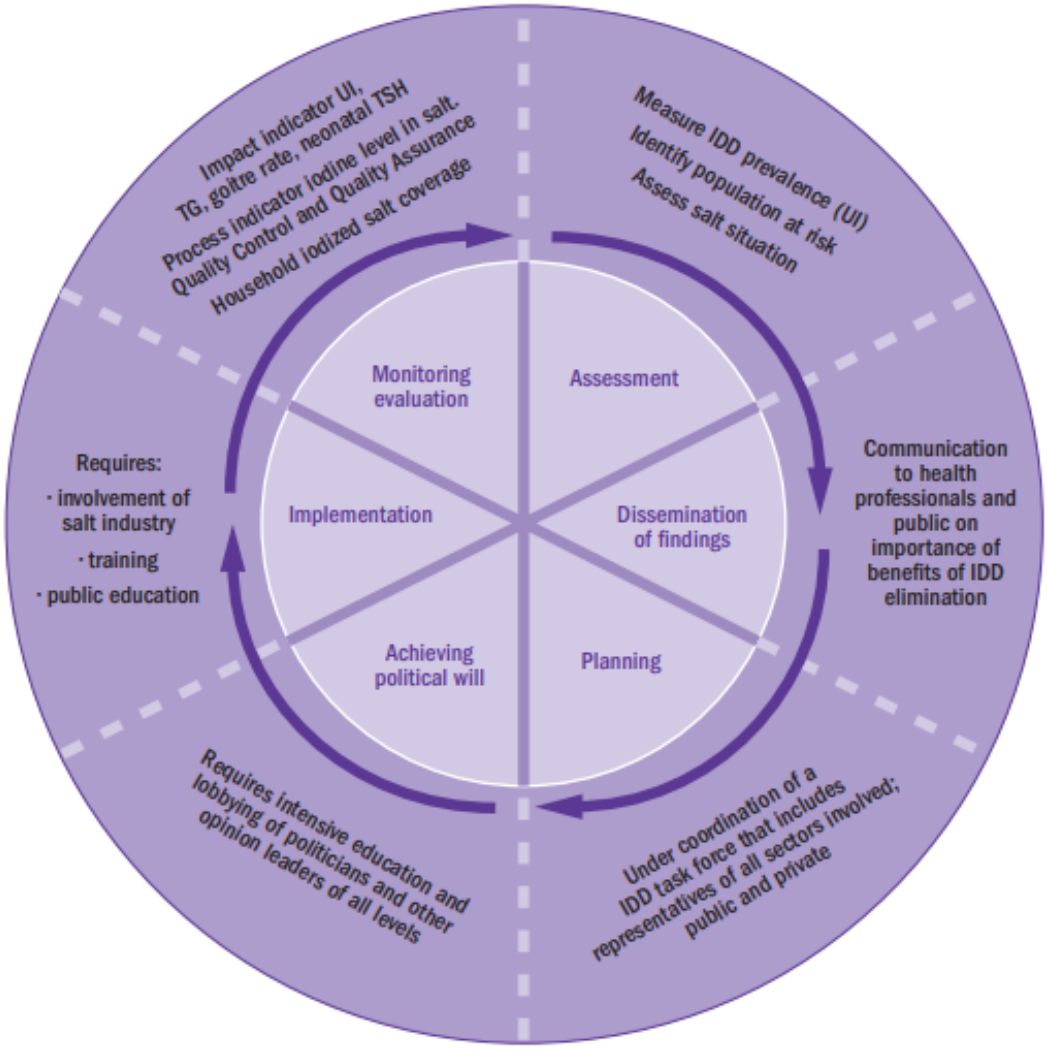


Diagram outlines the components required in the social process for successful implementation of a national IDD control programme. At the core are a series of steps and at the periphery of each step is a description of what that the step involves.[53] The initial step is situation assessment, followed by announcement of outcomes to health professionals, political authorities and the public and then formulation of an action plan, execution of the plan through politics and education and lastly the appraisal of its effect at population level.[1,22,23,53] Monitoring represents the "last phase", a critical step required for the sustainable elimination of IDD as a public health problem, but it often eclipsed by other components (implementation); evaluation of this stage dictates whether ID has been eliminated from the country.[22] Lastly, for a country to be declared iodine sufficient 8/10 of the programmatic indicators (appendices) must be met.[1,22,53]

2 - Overview of a Systematic review

A systematic or narrative review is synthesised from a collection of literature that is relevant to a specific topic and design, this helps to support the author's points of view and as a result the formulation of these articles is essential for understanding new concepts and ideas.[54,55] The competence of systematic reviews is predicated on a process that adheres to the prescribed steps depicted by Table 4, this ensures that the review is comprehensive, relevant and repeatable.[54,55] During this process, the quality of studies is evaluated and the relevant literature is critically appraised.[54] This aids in highlighting gaps in knowledge and insufficiencies in existing studies; an essential step as poor studies will not be able to provide answers to the effectiveness of practices but even worse they can be misleading.[54] Following the steps carefully increases the validity of the research and minimises publication bias as the relevant studies are selected and their results can be combined using a meta-analysis.[54] A meta-analysis is a research method that is utilised to produce analytical data from similar, independent studies via a software that uses statistical methods to summarise the results or the overall effect of the studies.[54,55]

This review is bereft of meta-analysis, and this is due to several reasons: in study design variation and lack of essential data from randomised control trials (control vs intervention) for synthesising forest plots. As a result, a narrative review with an objective to finding answers to the combined research query by data extraction of the available literature has been chosen. In addition, this comprehensive and analytical review seeks to compile the data from the extracted literature, augment it and present it in a manner that fortifies the review; in parallel to offering a glimpse on the evolution of the iodine status.

Table 4. Steps for undertaking a systematic Review. Adapted from Peat[54].

- Define outcome variables
- Identify intervention or exposure of interest
- Define search strategy and literature databases
- Define inclusion and exclusion criteria for studies
- Conduct research
- Review of studies by two independent observers
- Reach consensus about inclusion of studies
- Conduct review
- Pool data and conduct meta-analysis
- Submit and publish final review

2.1 - Methods and Search strategy

Prior to the undertaking of this systematic review, a background thematic literature review on iodine deficiency, maternal health and child development was carried to assess possible *caveats* to current knowledge. This was done to find what this review could add to that knowledge thus determining a niche where this review would be most valuable. Background literature was proceeded by formulating a study design using PICO[57] (Table 5) which followed the initial steps outlined in Table 4. To obtain relevant literature, an electronic search of published data was carried out using Embase. Embase was the primary search

database to retrieve articles due to its capabilities of providing published material from multiple sources including PubMed.

The exclusion and inclusion criteria took place in Embase, through the application of filters that were defined during the study design to make a broad question more specific and in turn retrieve the relevant literature. The results from Embase were checked to identify duplicates and critically appraised for their scientific merit to confirm their eligibility for the review; a process that is described in the study selection segment. In addition, articles retrieved were further appraised through the use of Semanticscholar, an academic search engine by the Allen Institute for AI which provides citation influence, velocity and acceleration of the article in relation to other publications that cite it.[58] Lastly, Semanticscholar, PubMed, Annual Reviews and Google Scholar (advanced search) was utilised to supplement the articles extracted from Embase, to increase the variation of contributions and bolster the critical analysis and discussion.

Table 5. Study design

	Population/Problem (P) Iodine deficient childbearing age women, pregnant and lactating women	Intervention (I) Seaweed	Comparison (C) N/A	Outcome (O) Averting maternal hypothyroidism prior to pre-conception Prevention of impaired neurodevelopment and other iodine induced ill-effects Preventing the influencing of iodine deficiency in the development of distal metabolic syndrome[56]
Concept	In patients with mild-severe iodine deficiency, which can result in impaired foetal cognitive development during pregnancy and other iodine induced ill-effects	Is the use of seaweed for supplementation effective in		
Synonyms	Lack of iodine Iodine deficiency	algae, seagrass, sea moss, kelp, dulse		
Broader terms	goitre, hypo-hyperthyroidism, congenital hypothyroidism, impaired neurological and physical development	*Chondrus crispus*		
Narrower terms		irish moss or carrageen moss		

2.2 - Study selection

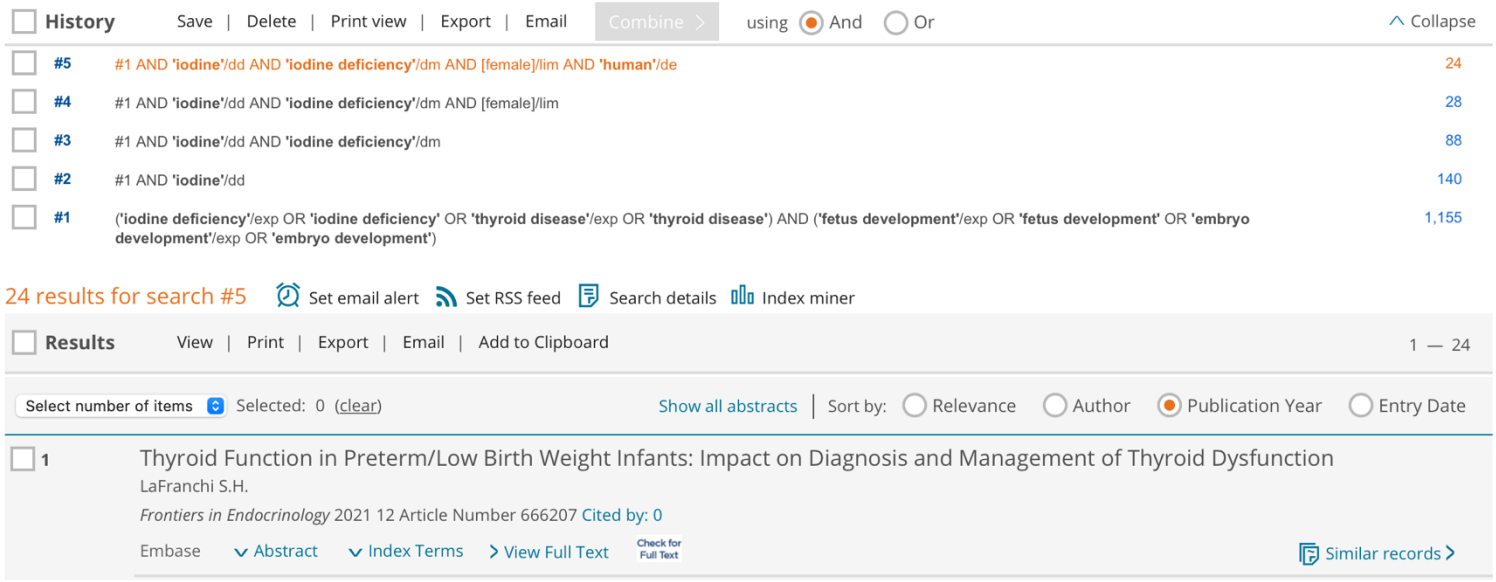
From the study design the definitive query entered into Embase was 'iodine deficiency and fetus development during pregnancy'; the formulation of this query was based on having a succinct question that encompasses ID, foetal development, and maternity. Broader queries yielded fewer results as the question became more specific. The initial search retrieved (*n*=186) studies and these underwent a study selection using the exclusion and inclusion criteria (Figure 5) by application of filters designed to specify the query and extract the relevant data required to address the objectives. The remaining articles (*n*=30) were reviewed and appraised for their eligibility to be used in the narrative review and after their appraisal. After the removal of duplicates plus random articles which did not address the query, the eligible articles for the review were reduced to 14. The articles were published between 2000-2019, therefore it was feasible to chronologically trace the progression of ID in the last 20 years and gather new insights on the association between ID in pregnancy and cognitive development, whilst tracking a change in the recommended level of I supply.

The second query entered into Embase database was 'seaweed for iodine supplementation', the search retrieved (*n*=32) studies compared to 9 articles when the query was made specific. The 32 studies underwent a study selection using the exclusion and inclusion criteria (Figure 5), that only focused on study type (human) to extract the relevant data. At the end (*n*=9) articles were retrieved and appraised for their eligibility for the review. Following the removal of duplicates plus articles which did not address the query only (*n*=5) studies were eligible. The synthesis of the initial query together with the second query forms a combined question that yields (*n*=19) articles open for arduous critiquing, plus aid in supporting the seaweed supplementation objective by critically analysing its benefits and drawbacks. Additionally, this synthesis initiates a dialogue on the dismissal of seaweed in certain publications[8,59] under the auspices that "*kelp and seaweed-based products, because of unacceptable variability in their iodine content, should be avoided"*. Sweeping statements made without further evidence or education on why, thus leaving little room for the public to make an informed choice. Of note, articles and supplements that did not meet the criteria but contain useful information were not discarded but used to bolster the review when needed.

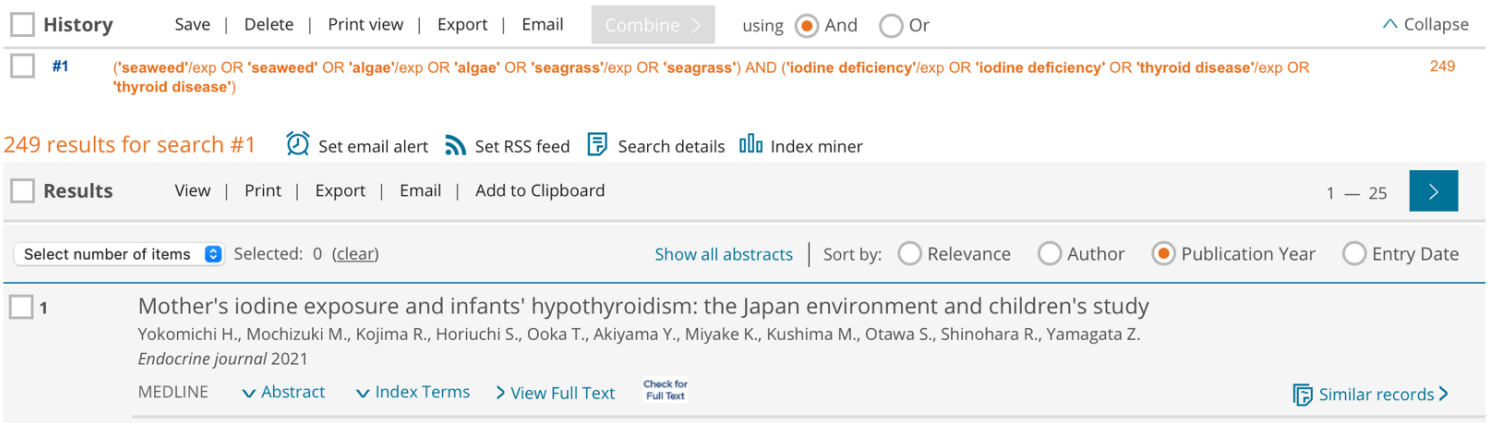
Revised study selection

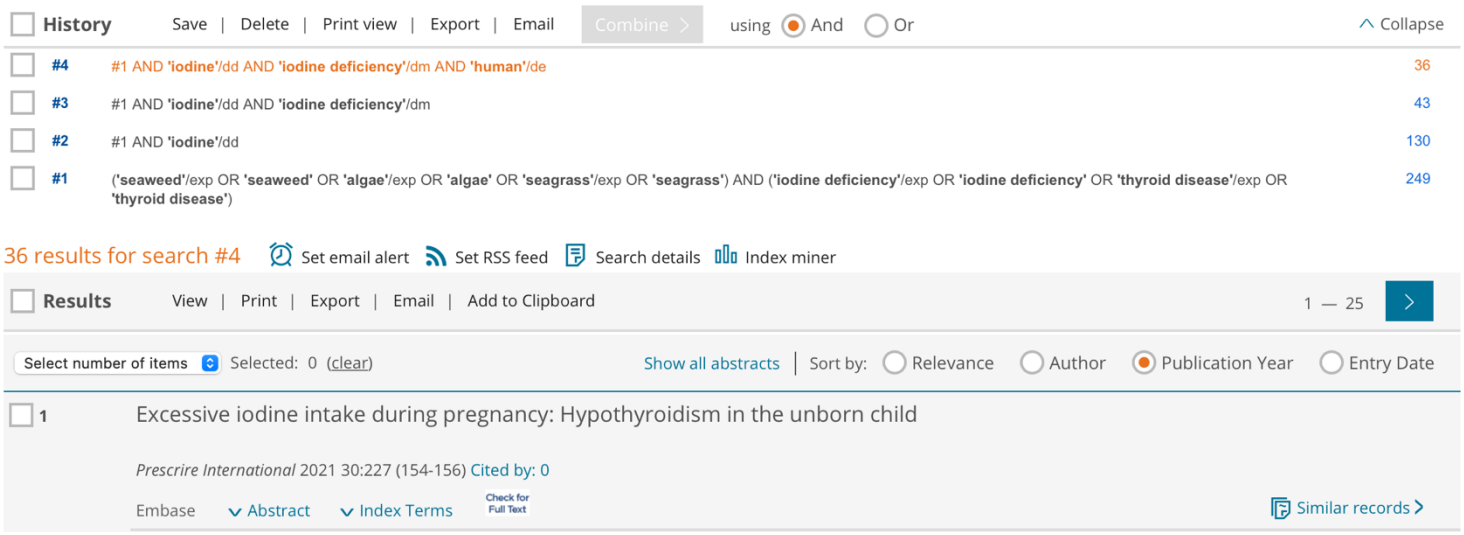
The use of full phrases, e.g., (iodine deficiency and fetus development during pregnancy) in literature search can result in omitting articles of value due to the specificity of the phrase. In order to rectify this, a comprehensive search strategy was carried out to return more hits. The query 'iodine deficiency and fetus development during pregnancy' was broken down to identify key concepts or words (iodine deficiency, foetal development, pregnancy).[147,148] This was followed up by identifying alternative terms for the key words (thyroid disorder, thyroid disease, embryo, *in-utero*, gestation, gravidity).[147,148] The reason for this is that use of keywords on their own allows room for articles that do not use your precise terms to be missed. In addition, the use of controlled vocabulary (e.g., Emtree for Embase) can also lead to articles to be missed if they have not been indexed in the database.[147] Once the alternative terms or free-text terms had been gathered, advanced search techniques (phrase searching, truncation, wild cards) were observed as they make the search more specific and efficient.[147,148] In this instance, the wild card was 'fetus' a word that is spelled in differently in two countries (America/Britain) but has the same meaning.

The next step was the search process in Embase using the identified free-text terms and controlled vocabulary terms. The following query was entered in the search field 'iodine deficiency OR thyroid disease AND fetus development (recommended Emtree term for pregnancy) OR embryo development'. The use of Boolean operators (OR. AND, NOT) where used to form search strings that combine both free-text and controlled vocabulary terms in order to broaden the search and capture all possible articles regardless of the term used in the article.[147,148] The utilisation of Boolean operator 'AND' was used to narrow the search and capture articles in which all concepts appear.[147] The result from search was 1,155 hits, compared to the 186 hits from the use of full phrases. Results retrieved (*n*=1,115; screenshot) then underwent a study selection using the exclusion and inclusion criteria (Figure 5) by application of filters designed to specify the query and extract the relevant data required to address the objectives. The remaining articles (*n*=24) were reviewed and appraised for their eligibility to be used in the narrative review. This included the removal of duplicates, supplements plus random articles which did not address the query, as a result 20 new records (appendices) were eligible for the review were.



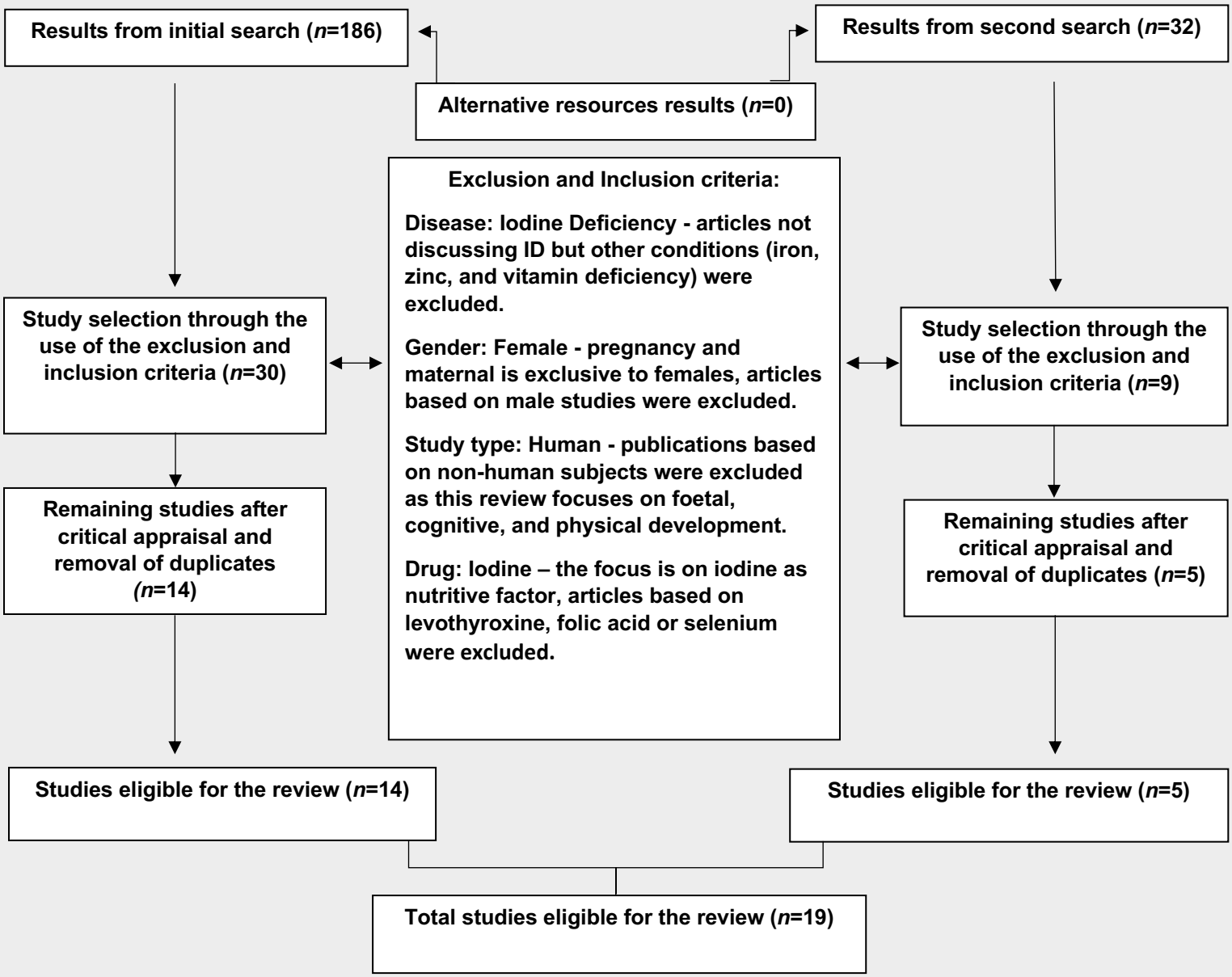
Like the first query, the second search query (seaweed for iodine supplementation) also required rectifying as it was not only 'sporadic' but the use of full phares in the literature search return few hits (*n*=32). The same method discussed above was applied to the query 'seaweed for iodine supplementation'. Key concepts (seaweed, iodine deficiency, thyroid disease) were identified and alternative terms for the key words (seagrass, algae, thyroid dysfunction, thyroid disorder,) were formulated.[147,148] Once the alternative terms or free-text terms had been gathered, advanced search techniques (phrase searching, truncation, wild cards) were observed as they make the search more specific and efficient.[147,148] Next, was the search process in Embase using the identified free-text terms and controlled vocabulary terms.[147,148] The following query was entered in the search field 'seaweed OR algae OR seagrass AND iodine deficiency OR thyroid disease'. Again, the use of Boolean operators (OR. AND, NOT) where used to form search strings that combine both free-text and controlled vocabulary terms in order to broaden the search and capture all possible articles regardless of the term used in the article.[147,148] The result from search was 249 hits, compared to the 32 hits from the use of full phrases. Results retrieved (*n*=249; screenshot) then underwent a study selection using the exclusion and inclusion criteria (Figure 5) by application of filters designed to specify the query and extract the relevant data required to address the objectives. The remaining articles (*n*=36) were reviewed and appraised for their eligibility to be used in the narrative review. This included the removal of duplicates, supplements plus random articles which did not address the query, as a result 22 new records (appendices) were eligible for the review.





Overall, the use of the search strategy involving the utilisation of search strings has proven to be a more robust approach in comparison to the first search strategy. This is clearly shown by the number of hits returned and the amount of ample material eligible for review once the literature appraisal has taken place. Importantly the new material found indicates that the original review, to extent, would have been different if those missed insights were included. On the same note, it is also important to justify why the change in dietary habits (vegetarianism or veganism) and the possible causes of iodine deficiency mentioned in the introduction were not included in the search strategy. Firstly, the change in dietary habits and its possible effect on iodine sufficiency in women as found in the background reading served as a strong drive to the main aim (reinvestigating the recommended level of iodine supply). To include it in the search would have only added more confusion as to what the aim is whilst simultaneously adding more literature to be analysed in a space of year. Fortunately, the decision paid off because the literature retrieved in the initial strategy already included this theme on dietary change and iodine deficiency and this is explicitly discussed in the results, discussion and linked back to the introduction. Secondly, the search strategy and results were done first before the material for the introduction was finalised, therefore it was the author's job to work backwards and find a way to link the concepts. The previous comment, to an extent, also covers why political or internal security influences were not included. The addition of these concepts or themes to the main aim would only aid in straying away from the two main objectives. Again, without being included in the search strategy the theme on iodine policies was already being discussed in the literature retrieved. As a result, this was important enough to be given a place in the results table and to be discussed in-depth in both the results and discussion sections and be linked back to the introduction to fulfil the objectives.

Figure 5. Flowchart illustrating the selection methodology for eligible studies.



Flow chart depicts the steps taken to acquire relevant articles for addressing the combined question mentioned above. The rationale behind the use of the filters is primarily due to the database being broad and unspecific as it provides numerous results based on the query. Therefore, their application serves to specify the articles retrieved based on the subject; the researcher does not determine the content of the information collected.[55] This feature is an exceptional tool for decreasing publication bias as it allows a fair representation of results and limit data "cherry picking". As a result, the application of each filter behaves as component of the query which reduces the broadness of the query and in turn provides a distillate of articles to be reviewed for their eligibility in the review. It is also important to note that only the first query had all the filters applied as per study design. This is largely due the amount of published data on the topic of iodine deficiency in comparison to the seaweed topic; a query which only had one filter applied (human study) to assess the efficacy of seaweed supplementation on iodine deficiency.

3 - Results and Critical Analysis

Table 6. Does the recommended level of iodine intake require re-evaluation?

Author	Recommended daily iodine intake. (µg/d)	Patho-physiological repercussions associated with low-high iodine status (gestation/postnatal)	Recommended therapeutic vector. (µg/d)	Endorsements and iodine status policy reform
Hetzel. (2000)	No comment	Hypothyroidism Congenital hypothyroidism. Delayed maturation of the cerebellum and greater neurone density in the cerebral hemispheres. A 13.5 IQ point difference between iodine sufficient and deficient groups.	Iodised salt and oil.	The need for a multidisciplinary approach, including assessment, communication, planning, political support, monitoring and evaluation of USI programme.
Glinoer. (2003)	150-200	Hypothyroidism and the goitrogenesis. Alterations in the child's psychoneuro-intellectual development. Average IQ loss of 13 points.	USI not considered to be the best choice for pregnant-lactating women or young children, due to the need to avoid salt abuse. Alternative supplement such as vitamin complexes containing iodine are suggested.	Systematic implementation of iodine prophylaxis for pregnant women.
Glinoer. (2004)	200–250	Enhanced thyroidal stimulation in both the mother and foetus. Presence of hypothyroxinaemia in pregnancy associated with 5–6 lower IQ points compared to children born to euthyroid mothers. Alterations in the child's psychoneuro-intellectual development: IQ loss of 13.5 points.	USI not considered to be the best choice for pregnant-lactating women or young children, due to the need to avoid salt abuse. Multivitamin pills containing appropriate mounts of iodine in order to supply the recommended dietary allowance of 200-250µg/d.	Development of iodine supplementation programme for the population by national public health authorities.
Lazarus. (2005)	No comment	Common cause of hyperthyroidism in pregnancy is Graves' disease (85–90%). Other complications that can arise during pregnancy include hyperemesis gravidarum, pre-eclampsia, tachycardia, congestive heart failure and thyroid storm and pregnancy-induced hypertension.	Anti-thyroid drugs: methimazole, carbimazole or propylthiouracil.	Use of preconception clinics and education to discuss the effects of hyperthyroidism on foetal-maternal health. Improvements in the ability to accurately assess thyroid function during gestation.
Ouzounian *et al.* (2007)	200	Hypothyroidism and infertility. The prevalence of clinical hypothyroidism in the general	L-thyroxine: 2-2.4 µg/kg/d. Sea salt, seafood, fish.	Screening of IDD becomes systematic as soon as the diagnosis of pregnancy is confirmed.

		population of reproductive age is estimated between 3-5%. Hypothyroid patients often exhibited menstrual irregularities three times higher than that of control population. The most dominate cycle disorders presented alongside hypothyroidism were oligo- or amenorrhea and menorrhagia.	Tablet of potassium iodide (KI).	
Morreale de Escobar *et al.* (2007)	250-300	Maternal hypothyroxinaemia and foetal brain development. Observation in aborted foetuses from an area of China where severe ID and congenital hypothyroidism showed poorly differentiated cerebral cortices. Additionally, cortex nerve cells consisted mostly of undifferentiated neuroblasts.	Levothyroxine: 2-2.4 µg/kg/d Universal salt iodisation. Iodine supplements: such as vitamin-mineral mixtures that contain KI, or KI tablets.	Advised iodine supplementation at onset of pregnancy or prior to conception to meet needs just as folate supplements are extensively promoted.
Williamson *et al.* (2012)	250	Only 16% understood the role of iodine in brain development. Only 34% of the population had received any information on iodine during gestation and 11% of the cohort received sufficient information to modify diet to achieve adequate level of iodine.	Iodine rich foods (milk, vegetables, and seafood) as there is no iodine prophylaxis in the UK.	It is crucial that women of childbearing age receive effective recommendations on iodine intake during pregnancy.
Zimmermann (2012)	220-290	Maternal and foetal hypo-hyperthyroidism. Neurological development (congenital hypothyroidism). In contrast to severely iodine-deficient children, there was an increase of 12 IQ points in children born more than 3.5 years after iodine prophylaxis was introduced.	Salt iodisation. Iodised oil. KI or KIO^3.	Regional and national public health programmes should focus on effective and sustained iodine prophylaxis of pregnant women and infants.
Trumpff *et al.*, (2013)	250	Hypothyroxinaemia cognitive and psychomotor deficits. Isolated hypothyroxinaemia has been detected in 4-10% of pregnant women. Progeny of women exposed to hypothyroxinaemia at 12 weeks of gestation had significantly lower scores at the motor scale of Bayley Scales of Infant Development (BSID).	Iodine supplementation.	Periodic monitoring and adjustment of salt iodide concentrations is needed for pregnant women.
Vandana *et al.*, 2014	250	Hypo-hyperthyroidism. Thyroid peroxidase antibodies (TPOAbs) presence is a marker for an increased risk of	Levothyroxine (LT4). Methimazole (MMI) and Carbimazole (CBZ). Dietary iodine supplementation.	Suggestions for trimester specific TFT reference values for all TFTs, especially TSH and fT4.

		infertility, miscarriage and preterm delivery. The presence of TPO antibodies at 32 weeks into gestation has been observed to result in significant IQ decrement.		Concerns raised over the use of anti-thyroid drugs due to their side effects. A need for early recognition of foetal-maternal hypo-hyperthyroidism.
Granfors *et al.* (2015)	150-249	Negative impact on motor and cognitive functions in the progeny born to mothers with mild to moderate iodine deficiency. A 9-year follow-up on the offspring from the study revealed an association between reduced educational outcomes and mild iodine deficiency.	Iodised salt Formulas containing 150 µg/d to meet dietary iodine intake.	Swedish health authorities need to establish and implement a policy plan for regular national iodine nutrition monitoring to ensure optimal iodine status of the whole population.
Tingi *et al.* (2016)	No comment	Overt hypothyroidism, hyperthyroidism, and thyroiditis. Hypothyroidism and goitre are the most common incidences for mothers with severe maternal iodine deficiency. Other complications that can manifest are hypertension and pre-eclampsia, placental abruption, premature, neonatal mortality and gestational diabetes. Adverse implications on the foetus: stillbirth, miscarriage and neonatal mortality.	Levothyroxine. Propylthiouracil. Methimazole and Carbimazole.	Pre-conception counselling on the pros and cons of anti-thyroid drug treatment during pregnancy due to anti-thyroid drug-induced congenital defects.
Hynes *et al.* 2017	≥150	Reduction in working memory and auditory processing speed for children born to iodine deficient mothers. Children born to mothers with a UIC below 150 µg/L had lowered educational performance in literacy than in numeracy compared to children born to euthyroid mothers (≥150 µg/L).	Fortification of bread with iodised salt.	Public health action is required to eliminate this preventable condition and ensure that no more children are prevented from reaching their full cognitive potential.
Eastman *et al.* (2019)	150-249	Gestational iodine deficiency. Participants from regions of China inflicted with iodine reported intellectual damage in children exposed to severe iodine deficiency (average IQ decrement 12.45 points). Women exposed to less severe degrees of iodine deficiency during gestation are more likely to give birth to infants with varying, but subtle or mild degrees of neurocognitive impairment.	Iodine supplementation is most effective.	Timing, safety, and the efficacy of prophylactic iodine supplementation for pregnant and lactating women needs to be established. Call for investigators to agree on systemic screening of IDD, standardisation of testing instruments and procedures for IQ and psychomotor tests for valid comparisons.

The following sections present the results from the literature extraction in a chronological manner (2000-2020). Quantitative and qualitative data extracted from each article is presented above by Table 6 which works as directory that outlines the recommended daily iodine intake, patho-physiological repercussions associated with low-high iodine status (gestation/postnatal), recommended therapeutic vector and whether the suggested preventative measures coerce a policy reform on population iodine status. The reasons behind the data being presented in this fashion is: 1) this structure allows the dialogue on the recommended iodine intake to be built up from the early literature to the current literature on the subject in cross referencing manner; the new literature is indelibly marked by ideas of the old. 2) allows the trace of a change in iodine requirements for the at-risk group (women of childbearing age, pregnant and lactating women). And 3) to see if USI has maintained the same rank it had when it was implemented[1] as a therapeutic vector for IDD as alternatives become available; this should help bolster the argument for adopting seaweed for maintaining iodine sufficiency. Furthermore, the following sections report and acknowledge other conditions from the spectrum of ill-effects associated with the endocrinopathy (IDD). This is done from a two-patient approach (mother and infant), where foetal cognitive and psychomotor development is the main theme that is discussed to provide a distillate of the effects of both severe and mild-moderate ID. The previously mentioned theme is complexed with other themes such as changes in dietary trends and iodine deficiency plus iodine policy reform, which don't stand on their own but are interweaved into the main dialogue. Lastly, the results from the first query are preceded by the results of the second query which report on the efficacy of seaweed supplementation in order to provide comprehensive review.

*From the report "*It's quite puzzling that in certain years (2005 – 2010 and 2015 - 2020) Graves's disease has not been mentioned in any literature while it remained one of the causes of hypothyroidism due to difficulties in anti-thyroid therapy"*. It is puzzling to the author too that this comment has been made because early in the results (2000 – 2005), the literature discusses iatrogenic foetal hypothyroidism due to the commencement of anti-thyroid drugs (ATD) in 3rd trimester. This results in foetal hypothyroidism that is associated with transplacental passage of ATD prescribed to the mother to combat hyperthyroidism (Graves' Disease). To show that this is not "*evidence of the sporadicity of themes being extracted from each timeframe?*", the following section (2010 – 2015) complements the previous years by richly discussing ATD-induced congenital defects as a result of combating maternal hyperthyroidism. In the same section alternatives to the main ATD (propylthiouracil) are given (methimazole/carbimazole) and it is suggested that in the preconception counselling on hyperthyroidism the pros and cons of ATD treatment during pregnancy should be discussed. In the same section the side-effects of 2-mercapto-1-methyl-imidazole (MMI), an alternative ATD are discussed as the drug is associated with behavioural defects. To come full circle, the final section (2015 – 2020) supplements the previous years by noting the difficulties of ATD therapy and induction of foetal hypothyroidism. In each section cross references are made to show these connections between different investigators at different times and this is signified by extra citations for a complete understanding of those connections.

3.1- Iodine status of 2000 - 2005

Beginning this dialogue is the work by Hetzel[60], which investigated the prevalence of cretinism [appears as congenital hypothyroidism (CH) from here on] and its association with higher rates of goitre (~30%) in a population; an observation which prompted whether ID was a significant causative factor in CH. Trying to find a link between ID and CH, reference is made to a double-blind controlled trial on the prevention of CH with iodised oil (injection) in Papua New Guinea, the therapeutic vector was observed to be more effective at preventing CH prior conception than after.[60] The enquiry is further developed by detailing the effects of ID on brain development in model species; reduction in brain weight and DNA, that is characterised by delayed maturation of the cerebellum and greater neurone density in the cerebral hemispheres (motor and visual areas).[60] Such delays in brain development were more significant in maternal sheep that received thyroidectomy as neuroblast multiplication that is known to occur 40-80 days during development began to take place 70 days into gestation.[60,61] From such findings, it is suggested that the occurrence of such effects in humans may be lead to the pathogenesis of CH.[60] In addition, it was observed that effects of maternal thyroidectomy on brain maturation could be further amplified by foetal thyroidectomy.[60] A procedure that further increased the reduction of TH available to the offspring after enduring limited placental transfer of maternal T4; a key component in brain development.[5,60,62-65]

Shifting the focus to neuropsychological development, Hetzel[60] refers to a meta-analysis that revealed a 13.5 IQ point decrement between the control and ID group with similar social and cultural background. In favour of the previous statement and a decade later, Glinoer[66,67] stated that alterations in the child's psychoneuro-intellectual development were associated with a 13.5 point in IQ loss. The previous statement was further reinforced by subsequent investigators[66-68] that found a 12-13.5 IQ point reduction in children subject to chronic ID. As a precaution, the use of USI as a preventative measure to IDD is promoted, a statement that is largely supported by most investigators in their publications.[63,65-67,69] Simultaneously, Hetzel[60] notes that the USI programme is losing its value, and the propositions put forward for this are: a decrease in assessment, communication, planning, political support, monitoring and evaluation.[22,23,53] Components which are outlined and supported by the IDD control framework (Figure 4). The enquiry is concluded by stating that USI is one element of the IDD control programme that requires a multidisciplinary approach to function in order to prevent cognitive defects that impairs school children from reaching their full cognitive potential and a reduced quality of life.[60,64]

Moving on, the previous article[60] in similarity to Lazarus[72], does not clarify what constitutes as iodine deficiency or sufficiency for pregnant and lactating women as there is no comment on dietary allowances. In contrast, the next article by Glinoer[66] states that 150 µg/d in adults and an increase to 200 µg/d in pregnant and lactating women is considered sufficient. The marked increase in dietary iodine intake during pregnancy is attributed to what is called a "physiologic adaptation".[66] A phenomenon that is characterised by complex effects that increase metabolic demands and incite hormonal changes, surge in TBG levels due to elevated oestrogen concentrations plus maternal thyroid gland stimulation from increasing serum levels of hCG.[8,31,41,66] The phenomenon is well supported and these actions can either be temporary or may persist until term, nonetheless, they have a profound effect on the maternal thyroid during pregnancy.[62-64,66] One of the effects, is a brief increase in fT4 concentrations caused by hCG-induced stimulation on the thyroid in the 1st trimester that progressively decreases as the pregnancy progresses.[8,31,41] However, low levels of hCG concentration in early gestation are often associated with a risk of hypothyroxinaemia.[66]

In addition, the presence of maternal hypothyroxinaemia[71] (normal TSH value with fT4 concentrations in the lower 2.5th - 5th percentile of the reference range: 4.0-10 mIU/L) to women with severe ID during gestation adds more strain on TH synthesis during critical periods of brain development.[66,71] The consequences of this manifestation is often irreversible brain damage with psychoneuro-intellectual deficits.[60,66-69,71] Therefore, it is suggested that the association between severe ID (in this case <25 µg/d) and a high prevalence of CH (5-15%) in the offspring from severely ID regions has its origins in the 1st trimester, where insults continue into the 2nd trimester with cerebellar abnormalities continuing after parturition.[66-69] Similar to Hetzel[60], it is suspected that the average 13 point in IQ loss may be attributed to impaired cognitive and psychomotor development but could potential be prevented by maintaining iodine sufficiency prior to conception.[66,68] On top, Glinoer[66] suggests that impaired neurodevelopment can be corrected with a therapeutic vector given prior to the 2nd trimester; a confounding view that is in opposition to investigators that think it may be too late.[60,69,72,73]

Interestingly, the re-emergence of IDD is acknowledged by the author[66], and this results in suggesting that iodine prophylaxis should be introduced systematically prior to conception in hopes that mothers enter pregnancy in a euthyroid manner.[3,4,24,39] Success of the programme is dependent on the medical community and public health officials.[66] As for the amount of iodine to be consumed, Glinoer[66] is reluctant on an estimate and states that this is a matter of personal appreciation in conjunction with how long the individual has been deprived of adequate iodine intake. A drawback, as definitive estimates in pregnancy would help those at risk because the use of qualitative terms (mild, moderate, or severe) to describe a problem with a specific cut off range (150 µg/d) invites room for confusion.

In connection with the previous article, the next article[67], further comments on the physiologic adaptation of the thyroid gland by describing how a restricted iodine intake as low as 70 µg/d up-regulates the iodide trapping mechanism thereby causing a ~50% increase in iodine intake. In accordance, Morreale de Escobar *et al.*[69] notes a 50% increase in the daily T4 requirements that is imposed upon the thyroid soon after conception; indicating more iodine is required. This possibility is in conceptual agreement as physiological processes such as reduced NIS activity (adaptive), increased renal iodine loss from increased glomerular filtration rate by hyperoestrogenism, foetal transplacental acquisition of maternal iodine and TH can lead to a depletion in both iodine and TH stores.[8,22,24,62,63,69.] Consequently, all can induce relative ID during gestation.

Furthermore, if the nutritional status of the individual remains unchanged during pregnancy as seen in regions with severe ID (Africa and Asia;<25 µg/d).[67] Patho-physiological repercussions in pregnant women can be further amplified by Se deficiency and thiocyanate excess leading to a combination of severe ID and hypothyroidism that is associated with a decline in fertility and increased prevalence of spontaneous abortions.[25,66,31,67] Ouzounian *et al.*[62] complements the previous statement by noting an association between infertility and antithyroperoxidase antibodies (anti-TPOAb); the presence of TPOAb was significantly more frequent in infertile individuals, and more particularly in the group whose origin of infertility was endometriosis.[5,67]

With regards to cognitive and psychomotor development, reference is made to the authors previous work[66] on severe ID and a loss of ~13 IQ points.[60,67,68] In addition, the abnormalities associated with severe ID and cognitive and psychomotor development have been observed at a lesser extent in children of European countries with moderate-mild ID; minor brain damage associated with transient neonatal hypothyroidism may occur in the perinatal period.[67] A stage where the developing brain is predominantly sensitive to ID.[67] Persisting

with neurointellectual deficits, reference is made on cases in the 1970s, where the offspring (4-7 years old) of mothers (~3%) from Rhode Island (US) who had hypothyroxinaemia during gestation displayed a 5-6 point reduction in mean IQ points in contrast to those born to euthyroid mothers.[67] Furthermore, 19% of children born to untreated hypothyroid mothers had IQ scores below 86, in contrast to 5%, for children from the control group.[67] On the other side of the spectrum, a decrease in intellectual and school performances has been observed in pregnant woman with mild and asymptomatic hypothyroidism.[62,67] Findings indicate that subtle impairments can occur across the spectrum of mild to severe ID.

Attentively, the author[67] appreciates the geographical variations in iodine intake across countries and as result mild-moderate ID is subject to vary from one place to another. This is followed up by promoting the use of iodine supplements such as iodised salt, KI drops, and iodised oil as effective therapeutic vectors.[1,22,60,66,67] Especially in regions with severe ID that often result in CH.[60,67] Developing the previous statement, the findings on the reduced efficacy of delayed iodine supplementation[60] receive some sustenance from a study conducted in two regions of Denmark.[67] In that study, pregnant women without iodine supplementation had a median iodine excretion level of 62 μg/g (I/Cr) in Copenhagen, in comparison to 33 μg/g (I/Cr) in Jutland.[67] The women received iodine supplementation during pregnancy, but to their surprise the iodine prophylaxis was not sufficient enough to ameliorate the differences, this was attributed to the iodine supplement being entirely taken up by the maternal-foetal ID thyroid glands.[67] The previous comment is reinforced by describing a "lag period", a phase that is inevitable and equivalent to a trimester before the benefits of iodine supplementation can be observed during pregnancy due to a prolonged iodine restriction prior to conception.[67] In support, a time-lag between the commencement of iodine supplementation (USI) and the amelioration of clinically diagnosed IDD (goitre) has been observed.[22,37] In contrast to the previous article[66], what is considered as significant ID (<100 μg/d) during pregnancy is explicitly outlined and a recommendation of iodine intake (200-250 μg/d) for pregnant and lactating women is given; an estimate that is largely agreed upon.[62,63,67,68]

In the last article[72] the focus is shifted on to the possible repercussions of hyperthyroidism during pregnancy, a different outlook to the previous articles which concentrate on hypothyroidism. From onset, the findings on pregnancy and physiological adaptation receive further complements by noting the effects of pregnancy on thyroid economy.[66,67,72] For instance, placental secretion of hCG; a glycoprotein hormone that shares a common α subunit with TSH but has a unique β subunit for conferring specificity is able to stimulate TSH receptors of thyroid tissue.[5,8,31,41,72,65] The impact of this action on thyroid function are similar to those already described above and for physiologic changes not previously mentioned, the list below provides a succinct overview of the changes.[5,62-64,72]

List of the physiologic changes in pregnancy that influence thyroid function tests (TFTs). Adapted from Lazarus[72].

Physiologic change	**Thyroid function test change**
↑ Thyroid binding globulin	↑ Serum total T4 and T3 concentration
First trimester hCG elevation	↑ Free T4 and ↓TSH
↑ Plasma volume	↑ T4 and T3 pool size
↑ Type III 5-deiodinase (inner-ring deiodination) due to increased placental mass	↑ T4 and T3 degradation (resulting in requirement for increased hormone production)
Thyroid enlargement (in some women)	↑ Serum thyroglobulin

↑ Iodine clearance	↓ Hormone production in iodine-deficient areas
(hCG) Human chorionic gonadotropin, (TSH) Thyroid stimulating hormone, (T4) Tetraiodothyronine, (T3) Triiodothyronine	

Continuing onwards and before proceeding into the foetal-maternal complications associated with hyperthyroidism. The Lazarus[72] notes that the main cause of the disorder in pregnant women (0.2%), is the auto-immune disorder Graves' disease (GD; 85–90%).[5,64,72] Also, a "spill over" of hCG onto TSH receptors that lead to the suppression of TSH and elevated hCG levels (20-50%) has been indicted for transient gestational hyperthyroidism and thyrotoxicosis in the 1st trimester.[5,64,72] Moreover, the symptoms observed in hyperthyroidism: cardiac systolic flow murmurs, tachycardia, sweating, dyspnoea, vomiting and nausea are known to occur in normal pregnancy in the absence of hyperthyroidism.[72] Therefore, to prevent misdiagnosis, sensitive assays (circulating TH [fT4/T3]and TSH) are used to confirm diagnosis.[72]

Proceeding into the patho-physiological repercussions, Lazarus[72] points to the alterations pregnancy has on the immune system for the preservation of the foetal-maternal allograft in order to prevent its rejection despite displaying paternal histocompatibility antigens.[72] To further clarify the previous remark, physiologic adaptation is brought back into the fray by focusing on the effects of elevated oestrogen levels that contribute to the decline of autoantibody levels seen in pregnant women with autoimmune thyroid disease; TSH receptor antibody (TRAb).[72] TRAb, a gold standard diagnostic tool for GD declines with the progression of gestation in parallel to anti-thyroid peroxidase antibody (anti-TPOAb).[72,74] As a precaution the presence of TRAb is evaluated 36 weeks into pregnancy; positive test indicates a high risk of neonatal hyperthyroidism due to the transplacental passage of maternal antibody.[72,74] Vandana *et al.*[64] match the previous comment by stating that TRAb presence is rare during gestation (1%), but increased levels suggest the presence of hyperthyroidism. Subsequently, the maternal complications associated with hyperthyroidism include placenta abruption, miscarriage, pre-eclampsia and preterm delivery.[5,72] In accord, similar complications were observed in hypothyroid individuals and similar to TRAb, to some degree, the presence of anti-TPOAb antibodies was associated with an increased risk of infertility, miscarriage and preterm delivery.[62,64,67,72,75] Furthermore, pregnancy-induced hypertension, congestive heart failure and thyroid storm are likely to occur in women with poorly controlled hyperthyroidism.[72,75,76] From a foetal aspect, the manifestation of neonatal hyperthyroidism is often synchronous with intrauterine growth retardation (IUGR) .[62,72,77]

With respect to neuro-psychomotor development, the article[72] does not elucidate any IQ decrement associated with hyperthyroidism but focuses on the complications that may arise if gestational hyperthyroidism is poorly managed. For instance, the foetus is at risk of developing hypothyroidism due to the presence of maternal TRAb or the commencement of anti-thyroid drugs (ATD) in 3rd trimester; iatrogenic foetal hypothyroidism.[72] In accordance with Batra[78], foetal hypothyroidism is associated with transplacental passage of ATD prescribed to the mother. In trying to prevent excessive iodine exposure, indirect gestational hypothyroidism can be induced. In cross reference, Lazarus[72] with other investigators on the effects of gestational hypothyroidism and impaired neurointellectual deficits.[8,40,42,66-68] In summary, the use of preconception clinics is suggested for women with maternal GD in order for them to better understand the effects of the disorder on foetal-maternal health.[72]

The suggested route is through education in conjunction with evaluation of patient thyroid status (euthyroid prior to conception to reduce risk of miscarriage).[72] In contrast to the previous articles[60,66,67] there is no mention of USI as therapeutic vector, as this sort of thyroid de-arrangement requires medication (propylthiouracil; PTU) and modifications in the ability to accurately assess thyroid function during gestation in order to alleviate complications.[5,64,72]

3.2 - Iodine status of 2005 - 2010

The dialogue resumes by returning to hypothyroidism and maternal complications. Specifically, infertility and how the severity of untreated maternal hypothyroidism can lead to impaired brain development.[60,62,66,67] In coherence with the previous section, the physiologic adaptation observed in pregnancy is acknowledged.[62] Simultaneously, it is also proposed that the exact role of TH on female reproductive function requires further attention regardless of the association between clinical hypothyroidism and the patient being susceptible to cycle and ovulation disorders.[5,62] In support, reference is made to a study that observed 171 patients with frank hypothyroidism (TSH>5 mIU/l ± T4 and T3 lowered) and 214 control patients.[62] Results showed that 23.4% of hypothyroid patients exhibited menstrual irregularities, in comparison to the control population (8.4 %); most common disorder was oligomenorrhea (42.5%).[62] The connection between subclinical hypothyroidism (TSH>4 mIU/l with normal concentrations fT4/T3) and infertility is further discussed by noting a retrospective Finnish study that analysed 335 files of infertile women.[62] Results indicated that 4% of the women had elevated TSH (between ~5.7-32 mIU/l).[62] Incidence of high TSH was 6.3% in anovulatory patients and cycle disturbances (oligo- or amenorrhea) were observed in 67% of women with elevated TSH compared to 34% of the patients with normal TSH.[62,79] In support, observations in a subclinical hypothyroidism group (*n*=80; 57.5%) that displayed menstrual dysfunction, oligomenorrhea was the most prevalent (28.2%), followed by menorrhagia (17.39%).[79] Additionally, Ouzounian *et al.*[62] in parallel to Acharya *et al.*[79] comments on the presence of anti-TPOAb in hypothyroidism as a contributing factor to repetitive miscarriages and cycle disturbances.[5,64,72] A view that has been discussed and agreed upon, but is upbraided because the mechanisms behind the maternal complications is yet to be elucidated.[5,64,65,67,80]

The argument is further developed by shifting the attention to the possible foetal-maternal consequences that can occur: pregnancy-induced hypertension, preeclampsia, premature birth and transient gestational hyperthyroidism or hyperemesis gravidarum; poorly managed can develop into iatrogenic foetal hypothyroidism.[5,62,64,72,78] Furthermore, it is put forward that a decrease in TH production during the 1st trimester may result in a low birth weight, spastic motor deficit and more or less severe neurological alterations.[62,63,65,68-70,73] The previous remark is reinforced by a retrospective study on IQ decrement which observed 62 patients (7-9 years old) born to mothers with asymptomatic hypothyroidism against a control group (124).[62] Results from neuropsychological tests indicated a 4 point decrease in IQ scores compared to the control group, plus 15% of the candidates had an IQ below 85, a 10% difference from the control group (5%).[62,67] Moreover, the same study assessed the benefit of hormone replacement therapy (L-thyroxine) and outlined that children born to mothers who did not receive L-thyroxine had a 7 point decrease in IQ scores plus 19% of them had an IQ below 85 in contrast to the control group.[62] Through cross referencing, the IQ decrement noted by Ouzounian *et al.*[62] varies by 6-9 IQ points against the ~13 IQ points associated with severe ID.[60,66,67] This is attributed to different development scales being used in the studies and more importantly how severely ID the patients were in the study as there is no remark.[62] Shedding some light on the previous commnet, the general association

between ID and reduced cognitive performance (IQ of 10-13 points) seen in different studies is difficult to clarify because the studies include patients with moderate-severe ID.[62]

With regard to prevention of ID during pregnancy, sea salt and seafood is recommended in addition to a tablet of KI to maintain the recommended daily iodine intake of 200 µg; an estimate that fluctuates between investigators.[62,66-69,75] Expectedly, the diagnosis of hypothyroidism during pregnancy requires rapid treatment with L-thyroxine at a dose between 2-2.4 µg/kg/d each morning.[62,64,69] Additionally, a plea is made for thyroid function evaluation for all women including those with a history of thyroid disorders (life time acquired or hereditary) prior to conception because systematic screening[64,66] is something that the scientific literature has not yet reached a consensus on.[62,64,66] Seven years later, Vandana *et al.*[64] reiterates the aforementioned statement by quoting Leslie De Groot (Endocrine Society): "*No agreement regarding necessary screening of all new pregnant women for thyroid status could be reached by the society*".

Proceeding into the next article, Morreale de Escobar *et al.*[69] focuses on neurodevelopment from the 1st trimester into mid-gestation. Two periods where the developing foetal brain relies heavily on maternal iodine and TH acquisition as the cerebral cortex requires maternal T4 for production of T3; required for nuclear receptor-binding and biological effectiveness.[31-34,62-64,69] As an example, the presence of mild and transient hypothyroxinaemia is associated with the malformation of cortical development by interrupting the migration of radial neurons, which settle permanently in heterotopic locations in opposition to their 'assigned' layer within the cortex and hippocampus during corticogenesis.[22,60,65,69,73] Furthermore, behavioural defects have been observed in rat dams treated with 2-mercapto-1-methyl-imidazole (MMI).[69] A goitrogen that induces transient and mild maternal hormone deficiency that leads to alterations in radial neuronal migration; behaviour alterations included responding to an acoustic stimulus with 'wild runs' followed by clonic-tonic seizures in the progeny of MMI treated dams in comparison to the control group.[69,82] In affiliation, Ouzounian *et al.*[62] notes behavioural alterations associated with moderate ID and the prevalence of attention deficit disorder with hyperactivity (ADHD) in 69% of the children born to ID mothers.[5,65] From the evidence, it is inferential that the offspring of ID mothers are not only at risk of landing anywhere on the spectrum of IDD but also on the autism and ADHD spectrum.

Leading into brain development, a discussion is put forward on the presence of thyroid hormone receptors (TR) on the foetal brain and these are considered to mediate cyclic AMP-independent biological effects of TSH, such as posing as a growth factor for brain development.[31,33,69,83] Furthermore, the presence of TR support the proposition that the cytoarchitecture events that require TH have their origin prior to mid-gestation because of the presence of TR in the cerebral cortex between 3.8-9 weeks postconceptional age that increase in concentration by at least 10-fold by 18 weeks into gestation.[63,69,70,83] Additionally, the study by Morreale de Escobar *et al.*[69] reveals that the occupation of TR by T3 was ~25-30% and that the levels of T3 increased in the cerebral cortex between 13-20 weeks post conception to resemble levels seen in adults. Clearly, TH are involved in development of the cerebral cortex during the 1st trimester of gestation.[69,73,83] Desirous on developing the previous statements. The effects of ID on brain development are evaluated as observations regarding the neuropathology are observed mainly in adults with CH and this makes it difficult to discern between the alterations that occur during early maternal hypothyroxinaemia and life-long exposure to clinical hypothyroidism.[69] Persisting with brain development, a study on CH individuals of the Andean regions noted atrophy of the cerebral cortex and subcortical structures of the pons and mesencephalon, accompanied by dilation of the basal cisterns, lateral ventricles and the folded surfaces of the cerebral cortex (sulci).[69,84] In addition, a reference is made to a study on aborted foetuses from a region in

China prone to severe ID and CH; foetuses were acquired at the 4th, 5th, 6th, 7th and 8th months of gestation.[69] Foetuses acquired at 4th and 5th month displayed inadequate cytoarchitectural development.[60,66,69] Whilst foetuses from the 6th and 8th month had reduced brain weight, delayed neuroblast multiplication of cortex nerve cells and poorly differentiated cerebral cortices as only 3 layers were distinguishable in comparison to the standard 6-layered cortex.[60,61,66,69,84] Inspection of foetuses obtained 8 months into gestation revealed well differentiated cerebral cortices with identifiable granular cells, pyramidal cells plus neuroblasts but no myelination of the axons was observed.[69,70,73]

In closing and in coherence with several investigators, the use of USI is endorsed in addition to iodine supplements in the form of vitamin–mineral complexes that contain KI to be used as a prophylaxis to ID.[60,22,66,67,69] The supplements should be used prior to pregnancy or upon conception to meet the increased iodine demands (250-300µg/d.[69] And just as folate supplements are extensively promoted from the onset of conception without the diagnosis of folate deficiency similar attention should be granted to iodine.[69]

3.3 - Iodine status of 2010 - 2015

In connection with previous article[69], the dialogue on giving attention to the importance of iodine sufficiency during pregnancy is sustained by Williamson *et al.*[81] through a study that brings iodine awareness to the public. In a cross-sectional study that took place between August 2011 and February 2012, involving 831 women aged 32±5 years, with different levels of education: school or college level (33%), graduate level (46%) and postgraduate level (21%).[81] Of which, 34% were pregnant at the start and 66% became pregnant 36 months into the study.[81] The participants were subject to a questionnaire based on the following: demographic and lifestyle data, awareness in dietary recommendations for pregnancy, knowledge on the role of dietary iodine in pregnancy and dietary habits or changes made during pregnancy involving intake of iodine rich foods.[81] Results revealed that 95% of the participants were well informed on dietary and lifestyle changes associated with pregnancy.[81] 89% of the respondents found guidelines easy to adhere to, with 78% of the group noting that they “closely” followed the recommendations (7 points likert scale, mode 6, inter-quartile range-IQR 2).[81] Interestingly, 40% were unaware about the effects of excess vitamin A consumption and 25% had insufficient knowledge on limiting oily fish consumption to 2 portions per week during pregnancy.[81,85] The previous remark remains a topic of discussion due to the complexity of the guidelines that are thought to misrepresent the nutritional capacity of fish.[81,85,86]

The topic on dietary awareness during pregnancy is further developed by shifting the focus onto iodine, in relation to other nutrients (Table 7).[81] Interestingly, compared to other nutrients, 66% of the participants had no knowledge of iodine requirement during pregnancy with 89% asserting that they had insufficient information on how to achieve the recommended daily intake (confidence level “not confident at all”, mode 1 on a 7 points likert scale, IQR 2).[81] Furthermore, only 16% understood the role of iodine in brain development and 174 µg/d (IQR 104) was the estimated median dietary iodine intake of the group with 79% below the recommended 250 µg/d.[81,87] Intriguingly, the majority of participants (54%) identified dark green vegetables, table salt (22%) and milk (10%) as major sources of iodine rich foods.[42,87,81]

Table 7. Nutritional recommendations and awareness among mothers in the UK. Adapted from Williamson *et al.*[81]

	Had received information (any)	Had received sufficient information to modify diet to achieve adequate level
Folic acid	100%	90%
Iron	96%	73%
Iodine	34%	11%
Vitamin A	76%	47%
Vitamin D	80%	45%
Calcium	88%	60%

Based on the data extrapolated from the study, the table shows how other nutritive factors in comparison to iodine receive more attention during pregnancy.

From the results, Table 7 showcases how iodine awareness in the public is still at the fringes compared to other nutrients; of interest, folic acid that is highly promoted (100%) from the onset of conception in comparison to the 34% I receives.[69,81] Williamson *et al.*[81] add to the previous remark by stating that the findings bring into focus why effective recommendations should be provided in women of childbearing age, especially in a country that has no iodine prophylaxis.[8,24,40,81]

The previous article[81] sets the stage for returning to the subject of the patho-physiological repercussions associated with ID, as the severity of consequences has been attributed to the timing of iodine supplementation during pregnancy.[65,68,73] In favour of the previous supposition, observations have shown that early iodine supplementation prior to conception or during pregnancy progressively reduces and eliminates new cases of CH, including a reduction in perinatal infant mortality rates and increases birth weight alongside a 10-20% increase in IQ score.[63,68,70,75] Due to a use of different methods, testing instruments and procedures for IQ and psychomotor tests by investigators, the previous statement is reproached.[65,68] Other investigators argue that commencement of iodine supplementation during pregnancy maybe too late and in some instances no significant changes in IQ decrement is reported.[62,68-70,72,73] In affiliation, it is suggested that the previous remarks may be attributed to the inevitable lag period during pregnancy where the benefits of iodine supplementation take approximately a trimester to take effect.[22,37,67] Therefore it is best that iodine supplementation be commenced before conception so that the mothers enter pregnancy in a euthyroid manner to better prevent foetal neurological alterations.[65,67,68,70,72]

Persisting on the subject of neurological alterations, the impacts of mild-moderate ID on cognitive function are re-examined by noting ID resurgence in industrialised countries.[3,23,66,68] The ID mention is in the form of maternal hypothyroxinaemia which is associated with defects in cytoarchitecture development, but the degree of the effects remain uncertain.[63,65,68,69,70] In accord to the previous account, is it debated that limited data exist between the long term effects of mild-moderate ID and the degree of cerebral alterations that occur during gestation as most observations regarding the neuropathology is well studied between severe ID and CH.[5,65,68,69,73,75] In an attempt to elucidate the limited observations surrounding mil-moderate ID, 6 controlled studies on iodine supplementation during pregnancy were conducted in regions of Europe with mild-moderate iodine deficiency.[68] Results indicated that iodine supplementation was effective on the grounds of decreasing

maternal thyroid gland size and TSH levels back to normal, but the impact on maternal and new born total or free TH concentrations was not clear.[68] Of interest, no observations were reported on child development or the potential adverse effects of mild-moderate ID during gestation.[68] Clarifying the previous extract, Zimmermann[68] states that it can be inferred that the objective of the study design often leads to the extraction of the relevant data. And simultaneously, cohort studies are known to be difficult to follow up and consequently any tangible evidence to be acquired on postnatal neurological development is lost.[68,70,75]

As for psychoneuro-intellectual development and the use of prophylaxis to prevent or ameliorate the manifestations associated with ID, the focus is turned on severe ID and endemic CH.[68] As a reference, a randomised Peruvian trial involving women of childbearing age from a region of severe ID with a 1-3% in CH rate, iodised oil injections were administered to the treatment group prior to conception or during pregnancy; control group did not receive an injection.[68] In a follow up, a subsample of the children between 1 and 4 years of age, cognitive development scores were performed but no significant statistical difference in cognitive outcomes were observed.[68] In a reanalysis of cognitive testing, children were divided in two groups: iodine deficient or sufficient based on their UIC and T4 levels; results indicated a significantly higher IQ score in the iodine sufficient group in contrast to the iodine deficient group, respectively (85.6 ± 13.9 vs. 74.4 ± 4.8).[68] Interestingly, similar results (IQ below 85) were observed from the use of a different therapeutic vector, L-thyroxine.[62,68] Furthermore, two villages in Ecuador known for severe intellectual disability and a prevalence of CH (~8%) underwent a study, one village received iodine treatment in the form of iodised oil injection and the other served as an ID control group.[68] The study population included pregnant women, women of childbearing age and children with an estimated 90% iodine coverage in the region.[68] A follow up was conducted on the village that received the therapeutic vector for ≈20 years to measure the effects on the offspring.[68] Results showed no CH individuals were born from the treated group, and two years into the use of the prophylaxis, the mean developmental IQ in infancy was not significantly changed between villages.[68]

Overall, Zimmermann[68] notes that in regions affected by ID, the most cost-effective therapeutic vector for improving maternal and infant health is salt iodisation and in some regions the use of USI is limited to short term use.[1,22,62] In affiliation, the limitations of iodised salt as the ideal therapeutic vector can be observed mainly during gestation and breastfeeding where it is considered a necessity to limit salt intake as excess intake is associated with the development of CVD.[6,22,53,66,67] As alternatives to USI, the use of iodised oil at a dose of 200-400 mg iodine/year and the use of KI or KIO^3 in the form of drops or tablets[22,62,69] in order to achieve a daily iodine intake of 250 µg/d is suggested.[22,62,69,65,68] This is done with hopes of fostering euthyroidism prior to conception, during gestation and after parturition if breastfeeding. In addition to the recommendations, a plea is made for future research to focus on development of novel biomarkers for individual iodine status and RCTs based on presence of mild-moderate ID in order to assess long-term clinical outcomes such as post-partum thyroid dysfunction, maternal goitre, and infant development.[68] The benefit resides in the addition of information to a subject (mild-moderate ID) with a paucity in human based evidence.

In relation to the previous articles[68,81], Trumpff *et al.*[63] strengthens the dialogue on ID as a public health issue by acknowledging its resurgence in Europe; a region that saw a decline in countries affected with ID go from 23 to 14 in 2003.[3,23,39] Relatedly, a precipitous reappearance of ID can be seen in the UK; a previously iodine sufficient country.[24,39,40] However, the resurgence of ID has been largely concentrated on the consequences of mild-moderate ID during pregnancy, as it is believed to be a feature in the development of

maternal hypothyroxinaemia.[63,66-69,71] This has been observed in apparently iodine sufficient regions of Eastern and Western Europe, where UIC below 150 µg/d has been detected in 50-92% of pregnant women in addition to the occurrence of hypothyroxinaemia at 4-10%.[63] In accordance with several investigators, the physiologic adaptation concept is fortified by recognising the metabolic and hormonal demands imposed on the thyroid gland during gestation by noting a 30-100% increase in T4/T3 concentrations by the start of the 2nd trimester.[62,63,66,67,72] Furthermore, the presence of nuclear T3 receptors on the foetal brain can be identified during early gestation and between 10-16 weeks there is 10-fold increase[68,65,83] in T3 receptors which serve as binding sites for T3 derived from sufficient maternal T4, by type 2 and 3 iodothyronine deiodinase.[31-34,63,65,68,83] Additionally, insufficient maternal T3 and T4 transfer before 12-14 weeks of gestation is associated with defects in the cytoarchitecture[63,70] of the brain as the foetus is reliant on the mother's storage for brain development through genomic and non-genomic actions in glial cells and neurons.[32-34,63,67-70,89] The previous remarks are edified by noting that the lack of TH during the critical periods of gestation has impressionable effects on neural differentiation and migration, axon myelination, synaptogenesis and neurotransmission; as a rule the degree of aberrations increases with the severity in ID.[63,67,68,73]

Alas, the true impacts of the neurological impairments mentioned above to the foetus remain undetermined until early childhood where cognitive and psychomotor tests can be used to quantify the degree of the damage to the offspring's development.[5,63,65,68,75] For instance, a study on maternal hypothyroxinaemia and psychoneuro-intellectual development assessed 220 infants from pregnant women at 12 weeks of gestation using Bayley Scales of Infant Development (BSID).[63] Results revealed that this group had significantly lower scores in motor function at 10 months in contrast to infants from euthyroid mothers.[63,73] Interestingly, no observable differences were noted when hypothyroxinaemia occurred 32 weeks into gestation.[63] The previous statement does not only support the efficacy of early iodine supplementation but may also sustain the link between insufficient maternal hormone acquisition and irreversible brain damage that occurs in the 1st trimester.[60,62-67,75] In attempt to address a research request by Zimmermann[68] on infant development and mild-moderate ID. A study evaluated the impact of mild to severe hypothyroxinaemia during gestation and verbal and non-verbal development in 18 and 30-month-old infants.[63] Observations on mild hypothyroxinaemia revealed expressive language delay at 18 and 30 months of age whilst severe hypothyroxinaemia was seen as a risk factor to expressive language delay at 18 and 30 months and across age; again, the presence of hypothyroxinaemia 12 weeks into pregnancy may affect cognitive development.[63,72,73] Desirous in complementing the previous statements, a brief discussion on neonatal hyperthyrotropinemia and cognitive and psychomotor development is provided by a retrospective study that revealed suboptimal neuromotor function at 18 months from the 102 preterm infants with TSH values exceeding 4.3 mU/L.[63] In affiliation, Cuestas *et al.*[46] using Parents' Evaluation of Developmental Status (PEDS) reported significantly higher developmental delay in TNH in normal-term infants with TSH ≥10 mU/L. Evidently, these findings support the supposition that both transient or prolonged neonatal and maternal thyroid gland dysfunction has the capacity to adversely affect intellectual or psychomotor development in early childhood.[46,63,64,69,82]

All in all, no specific therapeutic vector is recommended for the prevention of ID as the article focuses on the efficacy of iodine supplementation on cognitive and psychomotor development in relation to mild-moderate maternal ID.[63] For example, a Spanish study using KI (300 µg/d) as a therapeutic vector from the first trimester until the end of term, found that the infants (aged 3-18months) of the cohort that received iodine supplementation had significantly higher motor scores on the BSID than the control group.[63]

In another Spanish study, the Brunet-Lezine scale was used to measure the IQ score of older infants (18 months) born to mothers diagnosed with hypothyroxinaemia during the first 12-14 weeks of gestation who received KI (200 µg/d) at the start of the study.[63,72,73] Results showed no significant deference in IQ scores between the supplemented and non-supplemented hypothyroxinaemic group.[63] These studies provide some tangible evidence on the association between mild-moderate ID and altered neurodevelopment but the evidence is deemed "weak".[63] This is understandable, by analysis, the aforementioned examples use different testing instruments and procedures for IQ and psychomotor tests because no standard procedure has been reached by investigators.[63,65] The dialogue is concluded by recommending 200-250 µg/d of iodine intake during pregnancy and a request is made for periodic monitoring and adjustment of salt iodide concentrations during pregnancy.[1,22,53,62-64,67,68]

The article by Vandana *et al.*[64] serves as a perfect medium for summarising this chapter as the focus is turned towards recommendations, treatment, and the side effects on foetal and maternal health that manifest during pregnancy or after parturition. Again, the effects of the physiologic adaptation that occur during pregnancy are recognised.[64,66,67] These include increased serum levels of TH, thyroid size, excess fatigue[6,22,27], yet attention should be paid to the enumerated effects as they are similar to common symptoms that occur during normal pregnancy and these should not be misinterpreted for thyroid disorders.[66,22,27,69,64,72] Moving on, special attention is given to T4 levels that rise exponentially 6-12 weeks into pregnancy and peak by mid-gestation, this demand has been attributed to deliverance of TH to foetal neuronal cells during a critical period of cytoarchitecture development.[63-70] In addition, the role of T3 and T4 in the maturation of foetal brain cells is fortified by the presence of the transfer proteins, organic anion-transporting polypeptide 1C1 (OATP1C1) and MCT8 which relay T3/T4 across the blood-brain barrier into glia and neuronal cells.[31-34,63,64,71,90] Consequently, a rise in T4 during pregnancy draws attention to a decrease in serum TSH, a sensitive diagnostic tool for thyroid status that is transiently suppressed by hCG during gestation.[64] For the health of the foetus and mother, trimester-specific TFT reference values for all TFTs, especially TSH and fT4 are called for.[5,22,64,72] The previous comment is added to by proposing TSH trimester-specific values for 1st trimester (0.1–2.5 mIU/L), 2nd trimester (0.2–3.0 mIU/L) and 3rd trimester (0.3–3.0 mIU/L).[64] Interestingly, Vandana *et al.*[64] declare that these values are suggested knowing that several factors: ethnicity, multiple pregnancies and subclinical hyperthyroidism are known to affect TSH levels during pregnancy.[63,64,91,92]

Turning to gestational and postpartum manifestations. Thyroid dysfunctions are described as the second most common endocrine disorders affecting women of child-bearing age and maternal hypothyroidism, due to ID, is the most common dysfunction that is associated with placental abruption, foetal loss and IQ decrement.[5,63,64,72,93,94] Furthermore, hypothyroidism is known to occur in iodine sufficient regions due to autoimmune thyroiditis and cases of overt hypothyroidism in pregnancy are reported to be around 0.2% whilst 2.3% cases are seen in subclinical hypothyroidism.[22,64] In aid, observations have been made between pregnant women with subclinical hypothyroidism (50-60%) and the presence of autoimmune thyroid disease (positive thyroglobulin antibodies and or TPOAbs) in iodine sufficient areas.[5,62,64,72,79] Subsequently, the recommended therapeutic vector for maternal hypothyroidism is L-thyroxine, the dose given should maintain TSH levels at 2.5 mIU/L in the 1st trimester but not exceed 3.0 mIU/L in the 2nd or 3rd trimester and after parturition dose reduction should be considered.[5,62,64,69] In affiliation with Ouzounian *et al.*[62], no mandatory universal routine screening has been agreed upon, a drawback that puts subclinical hypothyroidism patients at risk.[64] To put this into context and to show why this area requires immediate attention, reference is made to a study (*n*=305) that showed that, out of 2.2% spontaneous abortions, 71.4% occurred in the hypothyroid group in contrast to the euthyroid group (28.5%).[64,95]

In relation to the above, the other common maternal thyroid dysfunction discussed is hyperthyroidism, which can manifest as an auto-immune (GD) or non-autoimmune (thyrotoxicosis) disorder.[5,64,72,74] Of interest, subclinical hyperthyroidism is prevalent in ID regions where incidence rates increase with age and 1.7% of pregnant women are affected.[64] No adverse outcomes have been observed but the suspected long term effects include CVD, osteoporosis and overt thyrotoxicosis or thyroid failure.[5,64,72] The preferred prophylaxis for hyperthyroidism is the anti-thyroid drug ATD, propylthiouracil [78], but alternatives such as MMI and carbimazole (CBZ) can be prescribed and the dose given is dependent on the severity of hyperthyroidism, the supply of iodine and the size of the thyroid gland.[5,63,64,78,97] Patients diagnosed with hyperthyroidism prior to conception are given MMI and upon conception it is advised that MMI be replaced for PTU at a dose between 100-300 mg/d split 3 times across the day.[64,97] Both drugs are teratogenic agents but MMI in contrast to PTU is associated with aplasia cutis, a congenital defect.[5,64,72,98] In addition, the teratogenic effects of MMI are associated with the induction of MMI embryopathies such as choanal atresia, omphalomesenteric tract anomalies and oesophageal atresia whereas PTU is associated with neck and face region malformations and urinary tract anomalies.[5,64,72,98] The incidence rate of the previously enumerated cases is deemed rare, therefore PTU, among clinicians remains the preferred prophylaxis.[5,65] Nonetheless, oral and written prescription advice should be given on the side effects (pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, pancreatitis and hypoglycaemia) in conjunction with the preconception counselling on hyperthyroidism.[5,64,72,98]

Moreover, following parturition, transient manifestations of postpartum thyroiditis (PPT), thyrotoxicosis, and postpartum GD are known to occur 3-6 months after delivery and remit spontaneously.[5,64,72] Additionally, rare cases of thyroid storm and thyrotoxic heart failure due to severe hyperthyroidism can manifest during gestation or after birth.[5,72] Symptoms include delirium or coma, tachycardia, tremor, nausea, diarrhoea and dehydration.[64] Likewise, the aforementioned extracts by Vandana *et al.*[64] are reproached by studies[62,65,80] that question the mechanisms by which the maternal and reproductive repercussions manifest. With that said, it safer to have preventative measures in place than to wait until these manifestations present themselves. As a preventive measure, 150-200 µg/d of iodine intake is recommended to deter ID during pregnancy and in pregnant or lactating women, a daily dose of 250 µg/d of iodine is suggested.[64,68,81,87]

3.4 - Iodine status of 2015 - 2020

In connection with previous section, the examination of population iodine status begins with a Swedish cross-sectional study that supports the re-emergence of ID in the form of mild-moderate ID across Europe.[62,67,68,75] A region that was suspected to be ID sufficient for decades but is now lagging behind as iodine nutrition surveys on pregnant women from these regions suggest that two-thirds of the examined populations are ID.[23,24,39,75] As an example, a study (*n*=459) by Granfors *et al.*[75] was synthesised to evaluate iodine nutrition during pregnancy in Sweden. A country that is considered to have adequate iodine intake, but the results revealed a median UIC of 98 µg/L (interquartile range 57-148 µg/L) for the participants.[75] By consensus, a UIC value below 150µg/L indicates that the majority of the population were iodine deficient during pregnancy.[63-65,75] Faithfully, the results lead to a debate on the potential consequences of milder forms of ID, but as the clarity on the mechanisms which the maternal and reproductive repercussions occur remain obscure the authors[75] do not fully commit to a cause and effect relationship.[5,62,65,67,68] However, an acknowledgement is given to studies that have observed improved motor and cognitive

function in infants born to euthyroid mothers in contrast to infants born to mothers with mild-moderate ID.[63,64,67,68,73,75]

Desirous on finding the attributes that have contributed to the median UIC of 98 µg/L observed in pregnant women, Granfors *et al.*[75] deviate from the previous studies by critiquing the contents of their study. For instance, the use of single spot UIC for a large cohort due to large intra-individual variations in spot UIC which can be misinterpreted for ID.[6,22,75] The former statement is further developed by condemning the use of single spot UIC as an individual marker of ID[22] and critiquing the adoption of median UIC of school-aged girls as a surrogate for monitoring I status of pregnant women.[22,65,75] An erroneous approach as dietary iodine intake of school-aged children (6-12 years old) differ tremendously to that of pregnant and lactating women (Table 3).[38,65,70,75] From such findings, it is suggested that a nationwide survey on iodine status is required for monitoring ID in pregnant women in order to prevent the misinterpretation between mild, moderate and severe ID in the general population.[75] In addition, an enquiry is made on the scarcity of evidence regarding iodine status during pregnancy in Sweden.[75] This reluctance in assessing population iodine status is attributed to the use of nationwide iodine prophylaxis with USI that was established by 1936 and was maintained for decades.[75] Until prompted by the potential consequences of milder forms of ID, it seems that the attention of investigators was elsewhere.

Shifting the focus to gestational and post parturition development, the increased risk in expressive language delay and reduced educational outcomes is recognised for infants born to mothers with mild-moderate ID.[68-70,75] Yet, the benefits of iodine supplementation on infant and childhood development due to a lack of RCT's are questioned as more evidence is required on their post parturition benefits.[60,63,68-70,75] In summary, Granfors *et al.*[75], examines Sweden's lack of information on the public's iodine status and in agreement with several investigators appeals to public health authorities to establish and employ a policy plan aimed at monitoring iodine status to ensure optimal iodine intake of the whole population.[60,63,67,68] The previous commented is complemented by recommending targeted interventions to increase iodine intake by consumption of dairy products, fish and seafood in the Swedish pregnant population.[75] A population that has seen a decline in iodine exposure go from 200 µg/day in 1999 to 126 µg/day in 2010, in a country where USI exists but iodine fortification of edible salt is voluntary.[8,24,42,75]

The previous article subjoins with the next[5] by acting as a foundation for constructing a brief dialogue on the importance of TH in early gestation, where the foetal thyroid gland reaches maturity between 10-12 weeks and begins manufacturing T4/T3 but remains inactive until 16-20 weeks of gestation.[65,67,68,73,99] This critical period can be defined as the end of the 1st and start of the 2nd trimester.[5] A phase where the foetus is dependent on maternal TH for cytoarchitecture development and the lack of iodine or the presence of maternal thyroid dysfunction is associated with significant maternal and foetal aberrations.[5,62-65,72,75,79] By default, the development of the well documented foetal-maternal complications is strongly associated with severe ID.[60,66-69] But Tingi *et al.*[5], draws attention to the emergence of mild-moderate ID and its effects amongst pregnant and childbearing age women of developed countries. The given example is the iodine status of the UK because of the longitudinal AVON study.[24,39,42,73,75] The study proposed new evidence on the association between mild-moderate maternal ID and reduced cognitive abilities.[5] Infants born to mothers with an iodine-to-creatinine ratio of less than 150 µg/g during pregnancy were likely to have scores in the lowest quartile (25%) for verbal IQ and reading accuracy between the ages of 8 and 9.[5,8,40,42] Despite these encouraging observations, the efficacy of iodine supplementation to pregnant women of mild-moderate ID regions is criticised.[5,62,67,68] Again, this is attributed to different methodologies used by investigators and the lack of data on the long-term effects

of iodine supplementation on thyroid function and neurodevelopment after child birth.[5,63,65,70,73,75] Equally, the previous comment is contested by evidence that has observed better outcomes when iodine supplementation is dispensed prior to conception.[65,67,68,70,72]

In procession, iodine supplementation is recommended as preventative vector and consumption of oily fish during pregnancy is proposed due to its association with improved infant cognitive development which is partially attributed to the omega-3 fatty acid content of oily fish and the iodine content it offers for optimum thyroid function.[5,8,24,62,100] Additionally, Tingi *et al.*[5] makes note of a RCT that took place in a moderate-severe ID Moroccan population. The study revealed that direct administration of 400 mg of iodised oil to the mother instead of 100 mg to the nursing infant was more effective in preventing infant thyroid hypofunction.[60,65,68] The dialogue is further developed by acknowledging the use of pharmacological therapeutic vectors such as l-thyroxine for overt hypothyroidism and for overt hyperthyroidism, PTU is recommended.[5,63,72,78,98] Likewise, the use of ATD for treatment of thyroid dysfunction is suggested in conjunction with preconception counselling on the pros and cons of ATD treatment during pregnancy due to ATD-induced congenital defects.[5,64,72,97,98] For prophylaxis, the use of USI as therapeutic vector for ID is not mentioned, but intriguingly, kelp supplements are discouraged.[5,8,59] This is attributed to variable and occasionally excessive iodine content.[5,8,59] In closing, it is noted that the euthyroid status of the individual is not only attributed to the availability of iodine but complicated by Se deficiency.[25,66,67,75] A poorly recognised liaison that is a component of Se containing biomolecules required for TH synthesis.[5,33-35] In support, the supplementation of selenomethionine to euthyroid pregnant women with TPOAb positivity proved beneficial by reducing TPOAb levels during gestation and in the diminishing of post-partum thyroid dysfunction and hypothyroidism.[5,101,102] Similar to the mechanisms involved in thyroid function, further research is required.

Complementing the above, the next study[70] adds weight to the relationship between neurocognitive impairment and mild ID in the form of gestational iodine deficiency (GID) and questions whether altered cytoarchitecture development as a result of prolonged exposure to GID can be ameliorated by an iodine replete environment during childhood.[63-66,68,72,73,89] The study consisted of 226 participants that experienced a period of mild ID during gestation.[70] The investigation was to assess whether there is a connection between mild GID and reductions in literacy outcomes in the offspring at 9 years old until adolescence.[70] The cohort was divided into two groups, iodine sufficient and iodine deficient by specific UIC cut of points ≥150 μg/L and <150 μg/L, respectively.[63-65,70] The assessment for neurocognitive impairment and mild GID where based on these two groups.[70] To measure the educational outcomes the scales used were the Australian National Assessment Program Literacy and Numeracy (NAPLAN) study for literacy and numeracy, Comprehensive Evaluation of Language Fundamentals (CELF-4) study for diagnosing language disorders between 5–21 years of age plus the Central Auditory Processing Disorder (CAPD) study.[70] Methods and materials which vary from the psychomotor tests previously discussed.[63,65,68] The purpose of CELF-4 was to determine the association between GID and specific delays in language development that may be linked to deficits in NAPLAN literacy outcomes.[70] The CAPD was used to find a link between mild GID and deficits in hearing such as auditory processing disorder.[70]

Remarkable results were obtained, as the offspring from the ID group (<150 μg/L) displayed persistent reductions in spelling from Year 3 (10%, −41.4 points (95% C>I −65.1 to −17.6, $p = 0.001$) to Year 9 (5.6%, −31.6 (−57.0 to −6.2, $p = 0.015$) in contrast to children of euthyroid mothers.[70] Similar disadvantages in educational outcomes have been observed in the offspring born to mild-moderate ID mothers.[60,63,72,73] In addition, there is a possibility that

mild GID may not only impact working memory but also auditory processing speed, thereby adding insult to injury.[70] Further enquiry into the results showed that children (9 years old) born to mothers with a UIC below 150 µg/L had lowered educational performance in literacy than in numeracy compared to children born to euthyroid mothers (≥150 µg/L).[70] The previous comment is strengthened by an Italian study that reported defective cognitive function in verbal abilities in the offspring (6-12 years old) born to mothers exposed to mild GID during gestation.[70] This referenced study is complemented by Norwegian study that observed expressive language delay in 3 year olds born to GID mothers (<160 µg/d).[63,70,75] Paying attention to age, the previous accounts on defective cognitive function in verbal development have been observed much earlier in 18-30 month old infants born to mothers with mild hypothyroxinaemia during gestation.[63,72,73] This extends to lowered scores in verbal IQ and reading accuracy in 8-9 year olds born to mothers with low UI/Cr (<150 µg/g) during pregnancy.[8,40,42] These findings provide considerable evidence on the impact of mild GID and impaired neurocognitive development observed in childhood, but once again the investigators[70] debate whether the deleterious impacts of *in utero* ID are long-lasting and if they can be ameliorated by iodine sufficiency in childhood.[63-66,68,69,73,75] A self-refuting claim, as this is deemed unpunctual for correcting early gestation cytoarchitecture damage.[66,69,72,73]

Sequentially, the results for the NAPLAN assessment showed that the difference in spelling between the iodine deficient and sufficient groups from year 3 to year 9 decreased in scale.[70] However, they remained significantly different as schooling progressed because spelling outcomes in years 3, 5, 7 and 9 were 10.0%, 6.6%, 6.1% and 5.6%; lower in the I deficient group.[70] Additionally, grammar and reading assessments revealed significant differences that declined and remained steady into year 9 as school progressed.[70] Between year 3 to year 9 a 6.5% difference in grammar difference declined to 2.8% and a 7.1% difference in reading declined to 2.5% by Year 7.[70] No significant differences were noted for the NAPLAN writing and numeracy outcomes and likewise, no specific language disorders were apparent for the participants of the CELF-4 study but the offspring of ID mothers exhibited reduced performance in the expressive language index (ELI) which incorporates the formulated sentence (FS) sub-test.[63,70,72,73] As well, the CAPD assessment revealed no hearing impairments amongst the participants.[70] Following the previous remark, Hynes *et al.*[70] commented on what the results may demonstrate and that was, uncorrected mild GID can have deleterious irreversible impacts on specific elements of cytoarchitecture development that are resistant to change in childhood regardless of iodine supplementation.[22,60,61,63-68,73] Instances are on record for learning difficulties and incomplete myelination of the corpus callosum, the damage initiated during gestation is resistant to change after birth and persists into adolescence.[70,103,104] Furthermore, some of the impacts (reduced working memory and processing speed) in the study are believed to persist into adolescence despite the offspring of the ID deficient mother growing up in an iodine replete environment. The previous is observed with the adolescent receiving formal education for more than a decade, indicating that outcomes are independent of biological or social-economic status (SES) factors which are known to impact learning.[1,22,53,70]

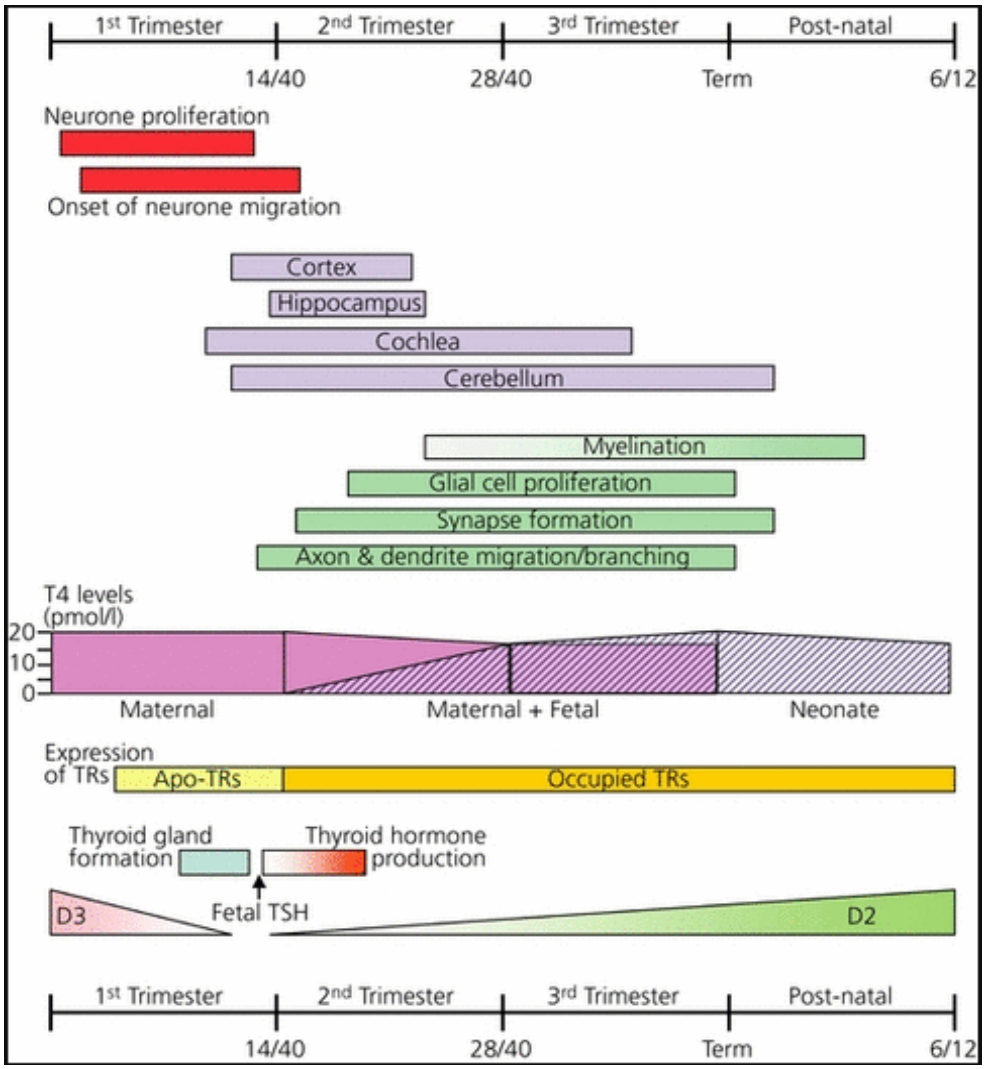
Correspondingly, the findings of Hynes *et al.*[70] appeal to public health authorities to address the levels of optimal iodine intake for not only the public, but pregnant and lactating women. This is because despite the use of therapeutic vectors such as iodised bread or recommended supplements most women enter pregnancy in an ID manner.[22,63,65,67,68] In addition, postpartum iodine nutrition must receive the same attention as gestational iodine status as brain development is not exclusive to in utero as further development occurs in early childhood onwards.[5,62-68,70,75]

The last article[65] concluding the results is an inquisitive body of work that investigates the premises behind 1) the hazards of using school-age based spot UIC for the qualitative categorisation of ID in pregnant women, 2) the association between impaired neurocognitive development and mild-moderate ID and 3), the efficacy of gestational and postnatal iodine supplementation.[60-64,66-70,72-81] Eastman *et al.*[65] finds the use of UIC as a proxy measure of dietary iodine intake unacceptable, as iodine intake vary tremendously between school-aged children and pregnant women.[38,70,75] The previous remark is followed by a request for spot UIC to be replaced by novel instruments, precise measurements and definitions of GID as 150 µg/L UIC remains the only standard value for determining iodine sufficiency or deficiency.[65,70,75] The previous request is coupled with an appeal to investigators to agree on testing instruments and calibration of processes and procedures for IQ and psychomotor tests, so that valid comparisons can be made on neurocognitive outcomes and GID.[65,70]

Continuing on, the effects of mild-moderate ID on neurocognitive development during gestation are brought into focus by acknowledging the detrimental effects associated with severe ID; especially, IQ decrement which has also been linked to mild-moderate ID.[22,60,62,63,65,68] The former is developed by offering a rebuttal on the effects of mild-moderate ID on neurocognitive impairment because the findings have not been universal.[62,65,67,68,75] According to Eastman *et al.*[65], this is down to, 1) the erroneous use of spot UIC for classifying the severity of maternal ID, coupled with the inability to determine the degree of ID during gestation and 2) the underlying mechanisms by which the patho-physiological repercussions occur remain unclear.[5,70,75,80,101] The last remark is devoted to the mechanisms associated with neurodevelopment defects, a structure which is believed to be mediated by iodine, therefore the lack of TH to receptive neural tissues during cytoarchitecture development result in complications.[60,65,68] The previous statement is reproached due to limited evidence on TH transport across the placenta, the inability to quantify foetal TH levels or to demonstrate their action on the foetus.[65] The previous remark is a strong one. To an astute observer, the already discussed presence of transfer proteins (OATP1C1/MCT8) that relay maternal T3/T4 across the foetal blood-brain barrier into glia and neuronal cells indicate an exchange of TH at a stage where the foetal thyroid gland remains inactive until 16-20 weeks of gestation.[31,34,65,67,68,71,90,99] Returning to mechanism function, the earlier remark is supplemented by acknowledging the contribution of other nutrients such as iron and Se to a complex mechanism.[32-35,65,75] Plus what has been transcribed about the mechanism in humans is extrapolated from animal studies[60,61,69] thus additional evidence in humans is required.[60,61,69,65,75]

Adding to the above, the dialogue matures by examining the effects of mild-moderate ID on neurocognitive impairment by offering excerpts from studies done in China on subjects living in persisting ID regions.[65] Through the use of Hiskey-Nebraska tests and Griffiths Mental Development Scales, subjects from ID regions exhibited reduced neuromotor and intellectual development across a broad spectrum of severity.[5,63-65,73] Further observations in supposedly ID sufficient individuals showed subtle but detectable auditory impairements.[39,65,70,75] Adding to the broad spectrum of ill-effects linked to mild-moderate ID, reports in developed countries have reported behavioural disorders (ADHD) in the offspring born to mothers exposed to GID.[65,69,70] In the worst case scenario, children born to mothers exposed to chronic ID were reported to have an IQ point reduction of ~12.45.[66-68] This is comparison to children born to mothers exposed to less severe degrees of ID who exhibited subtle neurocognitive impairment in the form of learning difficulties and reduced IQ.[60,63,65,70] From the accounts presented above, to state that the lack of iodine has a cause-and-effect relationship between the possible repercussions of ID is a gross misinterpretation of the data. In order to exemplify this Eastman *et al.*[65] provides a schematic (Figure 6) to show that the lack of iodine in the cytoarchitecture processes may have overarching detrimental effects.

Figure 6. Nexus between thyroid hormone action and foetal cytoarchitecture development. Credit, Eastman *et al.*[65]



In the 1st trimester of gestation, early neuronal proliferation and migration[22,24,41] are presumably dependent on transplacental transfer of maternal iodine and TH.[22,24,41,62,63,69] During this complex of processes, inactivating D3 enzyme expression falls as foetal thyroid gland forms and matures between 10-20 weeks.[5,65,99] By the end of the 1st trimester, the HPT axis is fully developed and prompts the secretion of TSH that results in foetal TH production, increased expression of activating D2 enzymes and increased occupation of TR as the brain develops.[8,31-35,65,69] Proceeding into the 2nd trimester, further neurodevelopmental processes occur and these are dependent on both maternal and foetal T4 production and action.[5,31-34,63-65] The cytoarchitecture processes instigated in the 1st trimester continue in to the 3rd trimester until term as the brain matures and carry on post-parturition, where they are dependent on the infant's T4 production which is regulated by iodine from lactation and external food sources.[8,22,38,62,65,81]

(D2) Type 2 iodothyronine deiodinase enzyme, (D3) Type 3 iodothyronine deiodinase enzyme, (Apo-TR) unliganded thyroid hormone receptors, (TSH) Thyroid-stimulating hormone, (TH) Thyroid hormone, (HPT) hypothalamic–pituitary–thyroid axis

In closing, Eastman *et al.*[65] contributes to the debate on the effectiveness of iodine supplementation during pregnancy and lactation by conforming that supplementation commenced before conception is the most effective route to preventing foetal neurological damage.[5,62,63,66-70,75] The sound advice is cognisant of the lag period, where the benefits of iodine supplementation can be seen a month later after prolonged iodine restriction.[22,37,65,67] As for how much iodine should be supplemented during pregnancy and lactation, the proposed increase in intake of iodine from 150 to 250 µg/d as a result of physiologic adaptation is acknowledged.[63-67] Yet, the role of the reference UIC value in this suggestion is queried.[62,65-67,72] The query is followed up by stating that the reference UIC value of 150 µg/L theoretically represents an RDI of ~250 µg/d.[65] Subsequently, its use is not based on direct experimental evidence and the instruction to supplement that amount is simply the best estimate for ensuring optimal iodine intake in pregnancy.[65] Upon reflection, it begs to wonder if there has ever been a substantiate effort to have a look at the scientific background that brought about these guidelines over the years. Mindful of how iodine requirements vary across different populations, and as a matter of personal appreciation depending on how long the individual has been deprived of adequate iodine intake.[65-67] An estimate is not offered, but reference to 150-249 µg/d is made for maintaining iodine sufficicency.[65] However, the benefits of iodine supplementation on physical and biochemical outcomes in pregnant women exposed to mild-moderate GID are reinforced by referencing the use of KI as a supplement (100 µg/d) to prevent the manifestation of maternal goitre and a rise in serum Tg and TSH levels.[22,65-67,72] Eastman *et al.*[65], attributes the efficacy of prophylactic iodine to timing and states that the commencement of iodine supplementation prior to gestation is critical as adequate thyroidal iodine stores are required during interim periods of GID in the 1st trimester where morning sickness may interfere with iodine intake.[5,62,63,66-70,73,105] The dialogue is sealed by drawing attention the potential risks of excess iodine supplementation during pregnancy as the foetal thyroid gland is relatively more avid for iodine than the maternal thyroid.[5,22,33,65,72,106] The advice on iodine supplementation, irrespective of the proposed recommendations is that “more is not better” and excessive intake should be avoided until the possible repercussions have been adequately investigated.[5,22,65]

List of key themes identified from all timeframes	
Iodine status of 2000 - 2005	An average of 13.5 in IQ decrement associated with iodine deficiency. Resurgence of iodine deficiency. Iatrogenic foetal hypothyroidism due to the use of anti-thyroid drugs to combat Graves' Disease. Rejection of universal salt iodisation. Endorsement for the evaluation of population iodine status and systematic implementation of iodine prophylaxis for pregnant women. Reluctance in determining iodine intake levels for pregnant women.
Iodine status of 2005 - 2010	Associations between hypothyroidism and infertility. Observations of cytoarchitecture development from foetuses born to mothers with gestation iodine deficiency. Endorsement for iodine supplementation at onset of pregnancy or prior to conception is heavily recommended. Fluctuating iodine intake values determined at 200-300 µg/d. Universal salt iodisation and levothyroxine commonly recommended as therapeutic vector for iodine deficiency
Iodine status of 2010 - 2015	An association between a change in dietary trends and iodine deficiency. Cognitive and psychomotor deficits associated with hypothyroidism. Side-effects of anti-thyroid drugs on foetal-maternal health include behavioural defects on top of inducing foetal hypothyroidism. Debate on the possible repercussions associated with mild-moderate. Endorsement of effective and sustained iodine prophylaxis for pregnant women and infants.
Iodine status of 2015 - 2020	Resurgence of iodine deficiency. Cognitive and psychomotor deficits associated with hypothyroidism also include decrements in working memory, auditory processing speed and lowered educational performance. Debate on the degree of neurocognitive impairment associated with varying degrees of hypothyroidism (mild, moderate and severe). Fluctuating iodine intake values determined at 150-246 µg/d. Difficulties of anti-thyroid therapy and induction of foetal hypothyroidism. Call for investigators to agree on systemic screening of IDD, standardisation of testing instruments and procedures for IQ and psychomotor test. Endorsement of regular national iodine nutrition monitoring to ensure optimal iodine status.

3.5 - Seaweed, a complementary supplement for Iodine Deficiency

Table 8. Is seaweed a useful complementary supplement?

Author	References	Experimental Model	Study Type	Findings
Redway *et al.* (2018)	108	The impact of the food matrix of 3 iodine rich foods (fish, milk and seaweed) was explored for iodine bioavailability.	Human; randomised cross-over trial	All 3 foods used in the study were equally offered as dietary options for increasing iodine intake despite the iodine excretion variability of seaweed amongst participants.
Combet *et al.* (2014)	109	The potential of seaweed as a prophylactic for ID was investigated through a series of trials. A cross-over iodine bioavailability trial using seaweed capsule Napiers Hebridean Seagreens (NaHS) or a potassium iodide (KI) supplement, impact of seaweed supplementation and a review on the safety and acceptability of seaweed supplementation.	Human; randomised cross-over trial, Cross-sectional study	Seaweed supplementation was shown to increase iodine status from insufficient (<55 µg/d) to sufficient (239 µg/d). And the variation of iodine bioavailability between the two interventions was linked to seaweed matrix, incomplete urine collections and variability within and between participants.
Teas *et al.* (2007)	111	A low-iodine-containing (95 µg/g) seaweed (*Alaria esculenta*) was used to investigate the efficacy of seaweed supplementation and the effects of companion foods: seaweed and soy on thyroid function due to their iodine content and goitrogenic effect. Iodine is primitively a potent antioxidant that can provide cell membrane and mammary tissue protection by inducing apoptotic and antiproliferative actions.	Human; randomised cross-over trial	Seaweed supplementation markedly increased urinary iodine excretion from ~266 µg/d (SD: 155.8) in the control to ~567 µg/d (SD: 177.8, $p<0.01$) post consumption. Additionally, no significant change in thyroid function (T3, T4, fT4 index or TSH) after consumption of both seaweed and/or soy.
Mišurcová *et al.* (2011)	110	The principal aim of the analysis was to outline the nutraceutical properties of seaweed alongside its ability to provide an abundance of essential minerals required for physiological functions.	Qualitative	The essential elements found in seaweed play a role as structural components in various catalytic metalloenzymes by serving as cofactors. More so the bioactive compounds found in seaweed have therapeutic effects beyond basic nutrition, however the utilisation of these compounds for maintaining normal

				physiological functions is closely linked to the individual's sex, age and health.
Bouga *et al.* (2018)	107	In a country (UK) were there is a lack of mandatory fortification programmes this review examines dietary choices, iodine awareness and public health strategies in order to effectively increase iodine intake address ID at home and worldwide.	Qualitative	67% of midwives did not discuss the role of iodine in antenatal care, whilst 20% mentioned its role in foetal development and only 10% were aware of the increase in iodine intake during pregnancy. Dietary choices are complexed by other drivers such as taste, familial preferences, perceived health benefits as well as social economic status, age and sex; factors that influence adequate iodine intake. Importantly, nutritional experts must contribute to this diet-related challenge by working in unison with the public and HCPs; their absence is likely to blunt the efficacy of any given strategy.

At home ID has been described as the low-hanging fruit of public health and on top, the UK holds a place in the top ten list of countries with the lowest iodine status globally.[107] The previous has been attributed to a lack of an iodine based prophylaxis and a policy revision that clearly specifies the RDI of iodine.[39,40,42,81,107,108] Altogether this has led the UK to become an ideal terrain for interventions involving seaweed (algae) as a prophylactic for ID.[107-109] The former serves as an ideal strata for presenting the results of the second query which aims to complement and complete this review by displaying the benefits of seaweed as a complementary supplement for ID. The suggestion for using seaweed as a supplement belongs to a plethora of nutraceutical properties.[15,16,110,112] And just as important, the "armchair" solutions offered in the first results analysis (2000 – 2020) on this subject have done little to engage and educate the public on how, when and which item can be used if the individual considers seaweed as part of their diet. The previous remarks are edified by the fact that seaweed consumption has been revitalised and one of the contenders spearheading this phenomenon is social media.[113,114] A place where the product has been labelled a "superfood"; foods which are alibis for nutritionally deficient diets. Of concern, is safety and the material presented below is not to foist the interests of the author but to present the pleiotropic properties of seaweed with the goal to improve health and health equity in the UK and worldwide.[107,111,114]

On the grounds of seeking other avenues of increasing dietary iodine intake, a recent pilot study on iodine bioavailability explored the impact of the food matrix of 3 iodine rich foods (fish, milk and seaweed).[109-111] The randomised cross-over trial consisted of 11 participants that completed each of the 3 study arms and all subjects were required to adopt a low I diet outside of the study until completion.[108] To monitor the iodine levels after each meal, urine

samples collected at specific time intervals: pre-feed baseline urine collection (−12–0) and post prandial urine collection (0–1; 1–2; 2–3; 3–5; 5–8; 8–12; 12–24 and 24–36 hours) were used.[108] Feeding was marked by 0.[108] To observe the differences in amount of iodine excreted between the 3 arms, analysis of variance (ANOVA) was used and the cumulated amounts of iodine excreted following consumption (36 hours) for fish and milk were 86% (SD:17%) and 87% (SD:39%), respectively.[108] By comparison, only 60% (SD:16%) of the iodine consumed in seaweed was excreted and this difference was attributed to high variability within and between participants.[108,109,111] Simultaneously, observations showed that statistically, there was no significant difference in the sum of iodine excreted in urine between the 3 study arms.[108] Nevertheless, all 3 foods used in the study were equally offered as dietary options for increasing iodine intake despite the iodine excretion variability of seaweed amongst participants; a key finding that may reflect the difference in the food matrix of the 3 tests foods.[108] Further research is warranted to elucidate the specific mechanisms governing iodine bioavailability.[108]

Supplementing the previous vignette, a comprehensive study[109] on the potential of seaweeds as prophylactics for ID investigated the safety and acceptability of seaweed supplementation through a series of trials. The first trial consisted of healthy self-reporting ID (<55 µg/d) women (*n*=22) who partook in a cross-over iodine bioavailability study that randomly allocated a treatment of either a seaweed capsule Napiers Hebridean Seagreens (NaHS) or a KI supplement.[108,109,111] In contrast to Redway *et al.*[108], dosage for the supplement was 0.5 g/d for NaHS (equivalent iodine content 356 µg/d x 2) and 712 µg/d for KI.[109] In addition, consumption of iodine rich foods was to be avoided until study completion, and for analysis 24 hour urine samples (0-2; 2-5; 5-8; 8-20; 20-24h) were collected.[109] Results indicated that peak iodine excretion was significantly ($p<0.001$) higher for individuals ingesting the KI supplement (421 µg/d, IQR 328-526) in comparison to the seaweed supplement (239 µg/d, IQR 199-352).[109] Similar to Redway *et al.*[108], the bioavailability of seaweed (33%, IQR 28-46) after ingestion was low compared to that of the KI supplement (59%, IQR 46-74).[109] However, seaweed supplementation was shown to increase iodine status from insufficient (<55 µg/d) to sufficient (239 µg/d), and the variation of iodine bioavailability between the two interventions was linked to seaweed matrix, incomplete urine collections and variability within and between participants.[108-111] Interestingly, high iodine excretion was observed in iodine sufficient participants who consumed the KI supplement, and the idea is, individuals with iodine replete stores excrete excess amounts through micuration.[109,111]

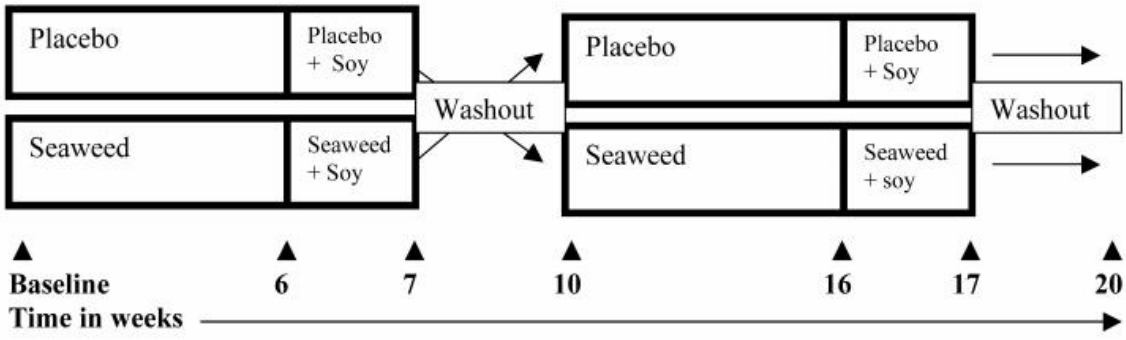
The bioavailability study was followed up by a review on the impact of seaweed supplementation on median UIC via a 2-week supplementation trial involving healthy females (*n*=42) of childbearing age (18-50 years old).[109] All candidates self-reported low iodine consumption as the median UIC for the population was below the cut-off value (100 µg/l) for iodine sufficiency at 78 µg/l (IQR 39-114).[109] Subsequently, the group was sorted into iodine sufficient (>140 µg/d) or insufficient (<140 µg/d) based on the investigators recommended value (140 µg/d).[109] In contrast to the bioavailability study, the dose of NaHS was changed to 0·5g/d (356 µg/d), and 24 hour urine and fasting venous blood samples were collected for analysis.[109] Supplementation results indicated significant ($p<0.001$) median UIC increase from 78 to 140 µg/l (IQR 103-194).[109] Interestingly, both groups displayed significant increase in the amount of iodine excreted; insufficient group from 93 (IQR 60-109) to 262 (IQR 198-301) µg/d and sufficient group from 138 (IQR 73-157) to 214 (IQR 75-343) µg/d.[109] The previous finding is in opposition to the notion that excess iodine is often excreted in iodine replete individuals, therefore the mechanisms governing iodine bioavailability are brought into question because there seems to be a complex relationship between the gastrointestinal environment and the food ingested.[108,115] With regard to thyroid

function, observations showed no significant change in the concentrations of T3, T4, fT3 and fT4 or Tg, but there was a significant increase in TSH concentrations, from a median 1.5 (IQR 1.2–2.2) to 2.1 (IQR 1.3–2.9) mIU/l.[109,111] TSH increase was significant in both the iodine sufficient (p=0.006) and deficient (p=0.027) groups, but more pronounced in individuals with habitual iodine intake, and the increase maybe associated with iodine induced hypothyroidism seen in those with replete I stores.[22,62,72,109] No change in TH concentrations were observed.[109,111]

Adding to the above, participants (*n*=63) of the same study answered a questionnaire on the acceptability of the seaweed supplement after consumption.[107,109,111] Most candidates (67%) held a positive view on the supplement, and 71% favoured consuming the item in capsule form rather than as a whole food (19%) or ingredient (33%).[109] The positive reviews were linked to flavour enhancement[107,108], nutritional properties and health benefits.[15,16,107-110,112] Although, 7% of the group disliked the seaweed as a supplement on the basis of taste (75%) and the rest did not comment.[109]

The above-mentioned studies do well in displaying the potential of seaweeds as a supplement capable of improving iodine status and due to their rich sporadic iodine content, low-level or intermittent supplementation has been put forward as the best way to maintain iodine sufficiency.[15,107-109,111,114] As an example, a study by Teas *et al.*[111] which used a low-iodine-containing (95 µg/g) seaweed (*Alaria esculenta*) to investigate the effects of companion foods: seaweed and soy on thyroid function due to their iodine content and goitrogenic effect, attest to this.[31,37] In the double-blinded randomised cross over study, 25 healthy postmenopausal women were supplemented 475 µg/d of iodine for 7 weeks and in each treatment arm a soy protein isolate supplement at 67.5 g/d was given for a week (total of 2 weeks).[111] Participants of study (Figure 7), received 10 capsules (5 g/d) of placebo (maltodextrose) or seaweed, and for analysis 48 hour urine and blood samples were collected a total of 7 times.[111] In between the crossover a 3 week wash-out period was undertaken.[111]

Figure 7. Randomized, placebo-controlled crossover design. Credit, Teas *et al.*[111]



▲ Depicts mandatory clinic visit for 48-hour urine and blood sample collection.

Results indicated no significant change in thyroid function (T3, T4, fT4 index or TSH) after consumption of both seaweed and/or soy, but a subtle increase in serum TSH levels was observed for seaweed alone (2.19 IU/mL) plus seaweed and soy (1.94 IU/mL) in comparison to the control (1.69 IU/mL).[71,109,111] However, the values remained within normal range with no physiological implications.[109,111] Additionally, seaweed supplementation markedly increased urinary iodine excretion from ~266 µg/d (SD: 155.8) in the control to ~567 µg/d (SD: 177.8, $p<0.01$) post consumption.[109,111] Standardisation of UIC for creatine content (I/Cr) revealed an increase in iodine excretion from ~291 µg/g-I/Cr to ~587 µg/g-I/Cr, respectively.[111] In contrast to previous study[109], participants of this study display iodine sufficiency from the onset of the study until the end, but more importantly these results confirm the bioavailability of iodine in seaweed.[107-111] Moreover, the iodine replete participants did not experience significant changes in thyroid function during soy consumption.[111] In support, the notion that iodine status may be compounded by consumption of cruciferous vegetables or soya products is repudiated due to a paucity in human based evidence.[31,37,107,111] In favour of intermittent supplementation through appropriate medical supervision, the study is summarised by acknowledging that safety and social acceptability plays an important role in preventing possible harms that may come with dietary changes.[107,109,111] Consequently, further studies with bigger populations are required to excavate the effects of long-term seaweed exposure on thyroid function.[107,111]

The remaining studies[107,110] complement the remarks made above by drawing attention to the use of seaweeds as nutraceuticals due to their bioactive compounds and enquire on the level of iodine awareness and knowledge between healthcare professionals and the public.[15,16,81,110,112] Developing the initial remark, comments on how the essential elements found in seaweed play a role as structural components in various catalytic metalloenzymes by serving as cofactors.[25,26,28,75,116] The enzymes require constant mineral replenishment as the essential fatty acid content (omega-3 and 6) provided by seaweeds compete for the same metabolic enzymes to maintain a balanced ratio of the ensuing eicosanoids.[15,110,112,117,118] From a dietary perspective, fatty acids are essential in brain and retina development during and after pregnancy.[110,117,118] They are also associated with alleviating depression plus chronic metabolic syndrome (MetS); their efficacy is predicated on a balanced ratio of consumption (omega 6:3, ~2.5:1 and ~4:1).[15,110-112,118] Seaweeds have been shown to exhibit this low ratio in contrast to the amount consumed in developed Western countries, ~20:1; a ratio associated with chronic inflammatory diseases.[15,112] The accounts provided by Mišurcová *et al.*[110] briefly demonstrate how bioactive compiunds found in seaweed have therapeutic effects beyond basic nutrition.[15,109,111,112,117,118] Teas *et al.*[111] attests to this by noting that, iodine is primitively a potent antioxidant. An antioxidant that can provide cell membrane and mammary tissue protection by inducing apoptotic and antiproliferative actions via iodinated lipids called iodolactones.[15,110,112,118] Interestingly, these effects have yet to be demonstrated by KI used in supplementation studies.[111]

Offering a balanced view on the use of seaweeds, Mišurcová *et al.*[110] returns to the subject of bioavailability by noting that the utilisation of these compounds for maintaining normal physiological functions is closely linked to the individual's sex, age and health. Furthermore, the level of macroelements concentrated in seaweed tissue is low and although an excellent source of trace elements, the mineral composition varies amongst species (11-6118 µg/g of dried seaweed) due to exogenous and endogenous factors.[15,107,109-112] These factors include pH, age and living cycle of the seaweed, element affinity and salinity.[110] The extent to which the nutrients concentrated in seaweeds are made available to the human body also rests on diet composition.[110] This is because the presence of nutrient or non-nutrient (phytates) components plus nutrient synergistic or antagonistic interactions, are capable of reducing mineral absorption.[110] Finally, food preparation or cooking has a major effect on the final

mineral content available for utilisation as the type of cooking results in nutrient reduction and loss of water-soluble minerals.[15,110,113,114]

Concluding this dialogue is an article by Bouga *et al.*[107], which examines dietary choices, iodine awareness and public health strategies in order to effectively address ID at home and worldwide. Dietary choices serve as the foundation of adequate iodine intake and at home (UK) the choices are fish, dairy products, seafood or seaweed.[8,62,81,107] Dairy products are the principal sources of dietary iodine, but seasonality and farming practices are known to affect iodine concentration in milk as summer milk has lower iodine concentration in contrast to winter milk.[40,107] Further reductions in the iodine content is owed to ultra-high temperature (UHT) processing of milk that leads to a further ~30% reduction in iodine in contrast to unprocessed conventional milk.[107] Returning to dietary choices, it is important to note that dietary choices are complexed by other drivers such as taste, familial preferences, perceived health benefits as well as social economic status, age and sex.[107,09,110] Factors that influence adequate iodine intake.[107,109,110]

The dialogue is expanded by weaving the vignette above with the disparity of iodine awareness between health care professionals (HCPs) and pregnant women in order to explain how knowledge can potentially be a cost-effective way of increasing iodine intake.[81,107] Bouga *et al.*[107] attributes the low level of iodine awareness between mothers and HCPs to low public health and media coverage. The former is given support by referencing a web-based survey (*n*=476) that showed 46% of midwives correctly identified seafood and dairy products (23%) as a source of dietary iodine.[107] Expectant mothers receive dietary guidelines from community midwives during their first antenatal care appointment (~12th week of pregnancy), but the survey found that 67% of midwives did not discuss the role of iodine in antenatal care, as 20% mentioned its role in foetal development.[107] Whilst only 10% were aware of the increase in iodine intake during pregnancy.[107] In addition, 60% of the participants (obstetricians and midwives) recognised that supplementation is beneficial to pregnant and childbearing aged women, but 75% reported to rarely or never prescribing iodine based supplements.[107] The findings are put down as “not surprising” due to nutrition not being a significant part of HCPs repertoire or curriculum.[107] Furthermore, education and personal interest in nutrition for both parties (HCP’s and women) can determine the discussion of iodine awareness during visits.[107] Encouragingly, a strong interest in further education was expressed by HCPs once they became aware of the significance of iodine during and post pregnancy.[107]

It is evident that both HCPs and expectant mothers must work in unison to achieve a level ground of awareness on these issues, and in order to draw more public attention to this area several causes for why they should get involved in the discourse are noted. For instance, a UK based cross-sectional survey (*n*=1026) demonstrated that 55% of the participants misidentified salt (21%) and vegetables (54%) as iodine-rich foods, whilst 9% of the women correctly identified milk as a source of iodine.[81,107] However, 87% of the participants were eager to augment their dietary behaviour once they received information on the significance of iodine for foetal development.[107] This was displayed by a change in attitude towards supplementation; 41% of pregnant women did not consider them as necessary, but after receiving dietary information the value fell to 18.5%.[107] Complementing the importance of education. There is a notion that poor knowledge did not improve with the inception of mandatory iodine fortification, and this can be seen in Iran, where ID is still persistent in childbearing age women with low iodine awareness.[107,119] Simultaneously, limited data exists on the effectiveness of educative programmes to influence an increase of iodine intake as more focus is given to the success, harm and benefits of supplements or USI.[107] This orientation requires re-evaluation. Nonetheless, the call for implementing public health

strategies and educative programmes is reiterated because the burden associated with ID is not limited to intellectual impairment but stems into social and economic facilities.[1,22,53,60,68,70,72,81,107] In closing, and persistent on improving maternal, perinatal and population iodine status, Bouga *et al.*[107] urges diet and nutritional experts to contribute to this diet-related challenge by working in unison with the public and HCPs. Their absence is likely to blunt the efficacy of any given strategy.[107]

4 - Discussion

In this review, the nexus between iodine status and impaired foetal-maternal health was examined alongside the efficacy of seaweed as a complimentary supplement for maintaining iodine sufficiency. Both objectives have been met and the data retrieved not only supports the presumptions outlined in the hypothesis but offers novel insights to the sympathetic connections between nutrition and politics. The remainder of the dialogue aims to discuss some insights gathered from the analysis of results. Secondarily, present a glut of complexities governing ID, explore emerging themes (dietary trends, MetS, psycho-nutrition), and further comment on brief encounters (seaweed toxicity, processing and cooking methods) in order to show why the public's appetite for this subject must not atrophy.

To begin with, early in the results (2000 -2005 section) Glinoer[66] is reluctant on providing estimates on the recommended level of iodine intake. The reason provided for this is that it is a matter of personal appreciation in conjunction with how long the individual has been deprived of adequate iodine intake. From the at-risk group perspective (pregnant and lactating women) this is an important drawback because definitive estimates in numerical values would help clarify if they are at risk of ID. Importantly, the use of qualitative terms (mild, moderate, or severe) to describe a problem with a specific cut off range (150 µg/d) for either iodine sufficient or deficient invites room for confusion. In connection with the aims of this review, the previous remarks prove why at this place in time the re-evaluation of population iodine intake is immediately required. Adding to the subject of unmet needs, Vandana *et al.*[64] provides a quote from Leslie De Groot of the Endocrine Society: "*No agreement regarding necessary screening of all new pregnant women for thyroid status could be reached by the society*". This shortfall which carries unquantifiable risks in pregnant women comes 7 years later (2010) after Glinoer[66] fails to offer estimates about iodine sufficiency during pregnancy. This account further fortifies the need for addressing not only the at-risk group recommended level of iodine take but also population iodine status. As the dialogue matures on the recommended level of iodine intake, findings between 2000 – 2010 reveal some interesting insights. 1) Fluctuating levels of iodine supply for pregnant and lactating women as recommendations shift between 150-300 µg/d; reference range covers WHO's recommendations, but the level of iodine supply remains undetermined. And 2) a comparison in the degree of consequences between severe ID and mild-moderate ID, when quantitatively 150 µg/L UIC is the only standard value for determining adequate or inadequate iodine sufficiency. So not only is there no consensus on the recommended level of iodine supply during pregnancy, but the possible repercussions of ID hang in the balance of whether they belong to severe, mild or moderate ID. They find themselves being shifted from one place to another. The catalogue of reasons for why iodine intake require re-evaluation receives another candidate.

Interweaved into the accounts discussed above, the results shed some light on the change in dietary trends and iodine deficiency mentioned in the introduction. This short account from Williamson *et al*.[81] supports one of the rationales for undertaking this review, as the

participants (10%; 83 out of 831) identify milk as major sources of iodine rich food. The former is not surprising, as observed early in the introduction, there is a decrease in milk consumption in the present age. This finding has implications on both aims put forward in the introduction and sustains them by 1) calling for public health authorities to provide effective iodine intake recommendation in women of childbearing age, especially in a country (UK) that has no I prophylaxis. And 2) a decline in milk consumption, makes a fertile ground for proposing the use of seaweed as complimentary iodine-rich food in the absence of milk. As demonstrated by the results, seaweed intermittent seaweed supplementation confirms the bioavailability of iodine in seaweed and therefore it should be recognised as competent alternative. More enquiry on the efficacy of seaweed supplementation was able to answer the difficult questions on how, when and which when it comes to seaweed supplementation without fostering nutritional supplement dependency as iodine-rich sources in the diet are varied.[5,15,16,66-70,75,107-109,111] For instance, the use of single minerals for supplementation or biofortification as a response to population deficiencies have their benefits but are limited. A long-term approach orientated towards achieving and maintaining high-quality diets through food diversification is required to enhance both public and maternal micronutrient status.[7,118,107-111]

In the absence of the seaweed proposition consider the following. A decline in milk consumption and a shift towards a long-term consumption of iodine deficient diets (fast foods and plant-based milk), the perfect conditions for increasing the risk of individual ID are created and maintained. Confidently, these conditions have propagated the resurgence of population-based ID and the lack of policy reforms coupled with ambiguous recommendations for adequate iodine intake will only allow this issue to develop further.

Returning to the evaluation iodine status the years of 2010-2015 provide a startling conundrum because despite substantial evidence spanning nearly two decades on the negative effects of severe ID on brain development. The debate amongst investigators shifts away from reaching a consensus of the recommended level of iodine to discussing the possible effects for mild-moderate ID. This can be observed as the dialogue matures, were the possible repercussions of mild-moderate ID are proposed, but their severity is questionable in contrast to those observed for severe ID. This is perplexing as the comparisons are superfluous because brain damage remains brain damage no matter how subtle. And if in future research the qualitative terms, mild to moderate ID attain a quantitative value, would this standard value be used to discriminate between minor and severe brain damage? The previous comment is accompanied by the fact that iodine intake recommendations remain undetermined for the at-risk groups, as they fluctuate across the literature. If the previous accounts are not enough to draw the publics and health authority's attention to this issue on the repercussions of mild-moderate ID, take the following into account. For both gestational and post parturition development, an increased risk in expressive language delay and reduced educational outcomes is recognised for infants born to mothers with mild-moderate ID.[68-70,75] Yet, the benefits of iodine supplementation on infant and childhood development due to a lack of RCT's is questioned as more evidence is required on their post parturition benefits.[60,63,68-70,75] Interestingly, it seems that the lack of RCT's in a field with exemplary literature on the negative effects of minimal ID, the possible patho-physiological repercussions associated with mild-moderate ID remain a matter of speculation. What is troubling about the presentations made above, is how the patho-physiological repercussions associated with mild-moderate ID seem to be caught in what the author can only best describe as a "tug of war" between investigators until further evidence is made available. Consequently, the field is torn between taking advice on the benefits of entering pregnancy in a euthyroid manner or to treat complications once they have manifested.

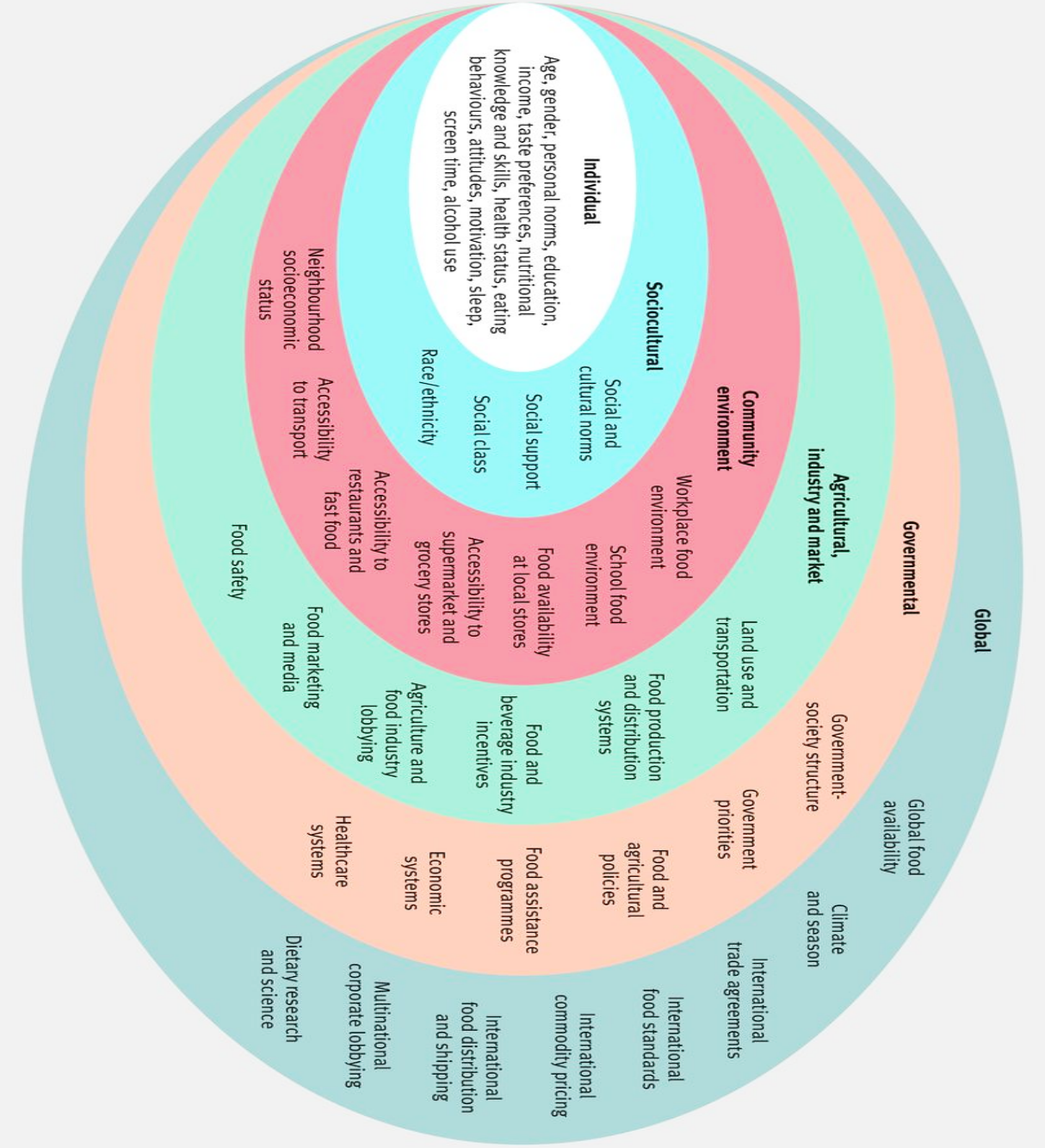
Finally, the analysis on the evolution of iodine status across the last two decades has surprisingly demonstrated that the RDI of iodine for the at-risk groups in not based on experimental evidence. Such a finding not only sustains the author's argument for a much-needed re-evaluation on the recommended level of iodine supply for pregnant and lactating women but complements the rationales (change in dietary trends and concentration of iodine by extrathyroidal tissues) behind the undertaking of this review. As the dialogue develops between the years of 2000 and 2019, the utilisation of USI as preventative measure for ID drifts with the wind as an unceasing debate on the long-term effects of mild-moderate GID take centre stage. Little attention is afforded to determining the level of iodine supplementation. What is clear, is that iodine supplementation should commence prior to conception. Failing to recognise or wantonly disregarding the warnings presented on this subject will see the matter remain a matter of speculation.

4.1 - Complexities governing Iodine Deficiency

In order to provide a full view about ID in this discussion it is important complement the accounts given above by addressing a consortium of influences that contribute to the difficulty of addressing ID. Gathered from the literature, the influences include diet, limited knowledge on the mechanisms governing iodine bioavailability and possible patho-physiological repercussions, a lack of educative interventions and policy reform.[5,70,75,80,81,101,107,108,115] From the results analysed the commencement of anti-thyroid therapy to combat maternal hyperthyroidism that induce foetal hypothyroidism also makes a perfect candidate to the complexities of dealing with ID. The former, also provides another rationale for revisiting dietary iodine intake values. In addition, personal knowledge (Figure 8) can also be added to the list.[122] Similar to the IDD framework (Figure 4), figure 8 fortifies the rationale for the re-evaluation dietary iodine intake levels.

However, these reciprocal gestures (influences) are the foundation on which ambiguous recommendations associated with population iodine status have been formulated on. Evidently, ID rests upon an ever-shifting fabric of factors and its elimination is not an easy task that can be solved by a quick scheme as there are many contending factors to deal with. For instance, recommendations and plausible solutions have been offered by investigators throughout the review, as for whether they have been put into practice, that remains to be seen. Simultaneously, there is little to no time to wait for the enactment of a "new" solutions. The fusion of diverse high-quality diets with the national IDD control framework (Figure 4) is a good place to start working towards achieving and maintaining adequate iodine intake and status for the population.

Figure 8. Multi-layered influences on dietary choice. Credit, Mozaffarian *et al.*[122]



Schematic depicts a plethora of factors beyond personal knowledge and preference that strongly influence dietary choices and patterns.[122] At the core lies the individual with their knowledge on nutrition and other multiple factors that contribute to their dietary habits.[107,109,110] Beyond that sociocultural norms such as parental or early childhood diets influence the individuals choice of food.[122] The individual remains as the locus from which the ripple like effect begins but at the periphery other agencies are constantly influencing their food choices from afar; they are interwoven to the tapestry of the current food system. In short, these multi-layered influences can be used as barriers, targets, facilitators, and effect modifiers of food policies by governments.[121,122]

Furthermore, one may assume that the success of such a scheme (utilisation of IDD framework alongside diverse high-quality diets) is definite if the HCPs, public health authorities and the public are working in unison and the framework protocols are followed. Sadly, this is half of the truth because the bridge between science and politics is the other half that determines the policies implementation and foreseeable success.[120] To get from one end to the other is no easy task, the viaduct is liable to obstacles such as ineffective communication between scientists and policy makers, differences in opinion prior to decision making and economic interests (industry and scientists).[120-122] All together they stall enactment of policy revision due to mistrust.[120-122] In accordance, it is easy to believe that the decisions made regarding policy reforms are done through a rational process when scientific evidence is presented; this is not the case.[120-122] For example, the industry can temporarily denounce the evidence presented by claiming that the data on the effectiveness of interventions is insufficient, and call for further trials or they can fund scientific research that supports their ideologies, sequentially allowing them to control the narrative and heighten the level of distrust between the public and policy makers.[120-122] Furthermore, public political will is essential when it comes to advocating for national nutrition policy because it is the backbone on which matters either flourish or wither upon.[120-122] This holds true for this review as it begs the public to get involved on the rhetoric regarding the re-evaluation of the recommended iodine intake values.

As a result, the vignette above demonstrates the complexities governing the current food system. However, it is evident that government agencies, HCPs, and the public must coordinate at a local, national, and international level to address this more-than diet-related issue. Complementary approaches as suggested, may prove to be more beneficial and synergistic than single approach interventions when it comes to ID. [107,121]

Summarising this discussion, the accounts on the complexities of ID sets up a good opportunity to reacquaint with USI. An intervention that has its rank as a prophylaxis for ID traced alongside the utilisation of other prophylaxis. The results show USI lose its importance amongst pregnant women as it is considered "*it not ideal*" during pregnancy, in order to avoid salt abuse (>5 g/d) due to its association with CVD.[6,22,53, 66,67,107] Consequently, this appears to mark the decline of USI as a primary preventive measure for IDD, and this is seen in the results analysis, where the dialogue shifts towards the implications of mild-moderate ID and how effective various supplements are at any given stage of pregnancy.[65,67,68] This is not to say that USI becomes redundant. Far from it, it is considered as the safest and most cost-effective prophylactic for ID and remains in sight but at the periphery as it recommend for iodine sufficiency now and then.[1,22,60,68-70,75] In developing the previous remark, the complexity of ID grows more intricate because the decline of USI may serve as another precursor to the re-emergence of IDD thus adding weight to the postulations made in both in the introduction and result. This is in addition to other factors mentioned glut of influences (e.g., change in dietary trends). How so? Well, the implementation of pharmacological and non-pharmacological therapeutic vectors plus the campaigns for health risks associated with excessive salt intake may have eclipsed the efficacy of the once prominent therapeutic vector by drawing it to the background. It is fair-minded to consider that what followed after, primarily, was the treatment of IDDs or their symptoms with "advanced" prophylactics whilst little attention was paid to monitoring population iodine status of supposed iodine sufficient region.[5,52,64,65,75] Secondly, an instability between public health campaigners and the public because it seems counterproductive to endorse iodised salt fortification and increase its consumption whilst simultaneously advocating reduction in salt consumption due to other health related issues. From this material it is not overreaching to synthesise the following. The relucatance in monitoring population iodine status as the years go by due to the success of USI and the

confusion brought about by conflicting health campaigns, pose as strong influences that led to the decline of population iodine status and the resurgence of ID. Such a strong remark stands if applied to developed countries or regions that were deemed iodine sufficient prior to the re-emergence of ID.

The objective, to show why ID has earned its place as a key tenet of any government's public health agenda has been achieved. The matter must be recognised as more than a nutritional crisis it is both a political and scientific problem. A rather fascinating one to debate with considerable fervour. However, to remain on the subject of the implications of mild-moderate ID and the efficacy of supplements; in their right are noble aims, yet they are secondary to the primary issue. That is, raising population iodine status. And if the debate continues, the trade of symptoms for others and a shift in the locus of disease from place to place will continue.

4.1.2 - Emerging themes (dietary trends & metabolic syndrome, psycho-nutrition)

Prior to the undertaking of this review, the development of distal MetS was taken into consideration (Table 5) due to the sympathetic connections between glands and how a dysregulation in one system can offset a chain reaction of events if not addressed. Being mindful of the previous comment, it was sensible to proceed with the notion that thyroid dysfunction as a result of chronic ID could potentially serve as a precursor to the development of MetS. Simultaneously, thyroid dysfunction could later appear as a component[124] of an already clinically diagnosed MetS. Fortuitously, these notions were not exclusive to the author and the material presented here not only supports those suppositions, but better elucidates an emerging theme between changes in dietary iodine intake and metabolic dysfunction. The author hopes that the material succeeds in capturing the public's attention.

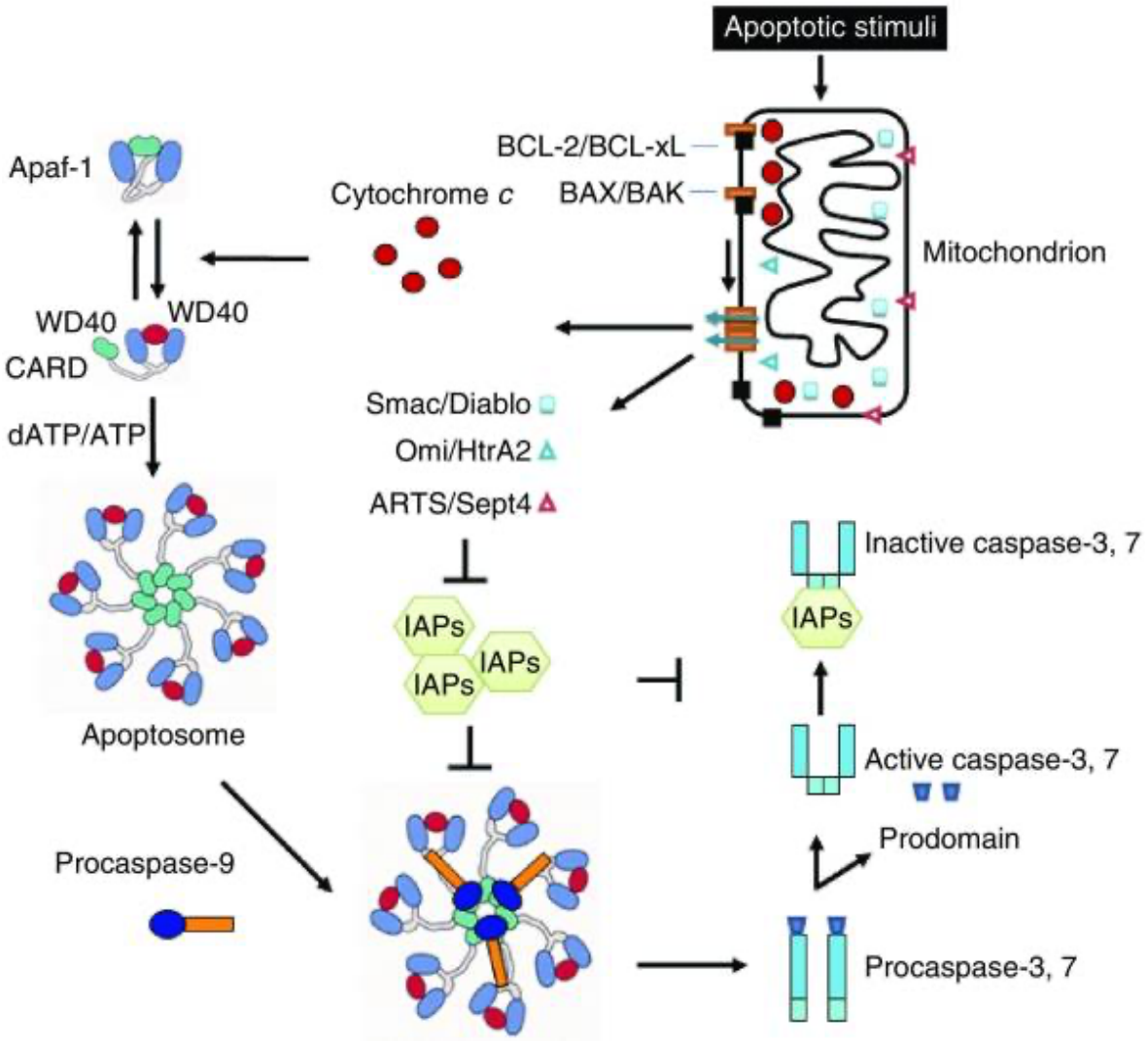
4.1.3 - Dietary trends & Metabolic Syndrome (MetS)

To better appreciate these associations, the decrease in iodine consumption in the last two decades can be mapped across the critical analysis, where a change in dietary choices is mentioned alongside the adoption of diets deemed iodine deficient.[9-12,40,75] The trend resurfaces again in the seaweed proposal were investigators tried to address changes in dietary choices by seeking other avenues of increasing dietary iodine intake alongside the current diet. Of note, soil impact on food health is not discussed in these accounts and this is not surprising, yet considerable attention should be afforded to this area. Nevertheless, during the two decades, ID was drawing some attention and getting drawn into associations with an increased risk of developing MetS; specifically, breast cancer. In support, incidence of breast cancer with distant metastasis in childbearing age women (25-39) has been observed at an accelerated rate, the insidious trend is usually seen in women between the age of 40-50, but not at this rate.[125]

What follows, is a probing into why an advanced-age disease would preferentially affect younger women. The proposition put forward for this, is that dietary iodine play's a protective role against breast cancer.[111,125] This view, that iodine is capable of granting cell membrane and mammary tissue protection and thus maintain the integrity of the mammary gland is implicit with the earlier findings of Teas *et al.*[111] that mention its antioxidant, anti-proliferative and apoptotic inducing properties.[15,112,118,125] Further support is offered by the findings of

Mišurcová *et al.*[110], which emphasises the importance of minerals when it comes to deferring premature aging and the prevention of degenerative diseases including cancer. In this scenario these properties reshuffle the deck of associations (folate supplementation, vaccination and advanced-age at first pregnancy) between them and breast cancer and bring ID to the forefront as the strongest link to breast cancer in this age group in relation to diet.[125] The previous remark is sustained by noting that the incidence of breast cancer in Japanese women is exceptionally low due to their more than adequate consumption of dietary iodine.[111,112,125] However, once they emigrate and adopt a western diet their incidence rate of breast cancer increases.[111,112,125] Eager to elucidate the link between iodine and breast cancer. The dialogue provides some observations on the beneficial properties attributed to iodine in animal models of breast cancer; iodine supplementation in seaweed form or not demonstrated tumour growth and breast cancer suppression.[111,125] In contrast, Teas *et al.*[111] notes that such effects are not demonstrated by non-food-based supplements (KI). Either way, it seems that the mechanisms governing the anticancer effects of iodine are complex. Yet, some solid molecular evidence on the apoptotic and suppressive effects of iodine have been demonstrated in thyroid cancer cells.[126] Observations revealed that iodine-induced apoptosis is mitochondrial-mediated, and in this molecular switch (Figure 9), the initial regulatory step for mitochondrial apoptosis is mediated by a family of B-cell lymphoma 2 (Bcl-2) proteins (Bcl2, Bcl-xL, Mcl-1; pro-survival group).[126,127] Furthermore, in cancer cells, the anti-apoptotic properties exhibited by Bcl-2 and Bcl-xL were tested for their role in iodine-induced apoptosis and the results showed significantly up-regulated Bcl-xL expression in contrast to Bcl-2 at a high dose of iodine (100 μM).[126] In addition, a knockdown of Bcl-xL expression by specific Bcl-xL siRNA (silencing RNA) was performed to confirm the function of Bcl-xL, as a result there was a significant increase in the number of apoptotic cells.[126,127] As briefly demonstrated, the up-regulation of Bcl-xL expression is capable of protecting thyroid cancer cells from iodine-induced apoptosis and simultaneously, the anti-tumour effects attributed to iodine seem to be influenced by Bcl-xL in a reciprocal manner. [11,110,115,126] In order to stay on course, it is important to succinctly acknowledge that iodine more than influences Bcl-xL, but also modulates the expression of p53 and p21 (tumour suppressors) through the Mitogen-Activated Protein Kinase (MAPK) pathways.[126,127] Such findings severe the data analysed in the results and discussion in a positive manner because they reinforce the importance of maintaining iodine replete stores and in turn cast a gaze on why the recommended level of iodine intake should reconsidered.

Figure 9. Iodine-induced apoptosis is mitochondrial-mediated. Credit, Xiong *et al.*[127]



From the top right-hand corner, the schematic depicts an overview of the mitochondria-mediated caspase activation pathway. Upon apoptotic stimulation Bax/Bak form oligomeric complexes that mediate the release of cytochrome c into the mitochondrial cytosol. An apoptosome consisting of Apaf-1 and cytochrome c is formed and this complex stimulates activation of the initiator caspase, caspase 9, which cleaves and triggers effector caspases (caspase 3/7) that induce apoptotic cell death. The molecular cascade also consists of other pro-apoptotic proteins (Smac, Omi, ARTS) that repress the endogenous regulators (IAPs) in order to enhance apoptosis.[127]

(WD40) WD40 repeat domain, (BCL) B-cell lymphoma (CARD) Caspase recruitment domain, (Apaf-1) Apoptotic protease activating factor-1, (IAPs) Inhibitors of apoptosis proteins, (Smac/Diablo) Second mitochondrial activator of caspases, (Omi/ HtrA2) Mitochondrial serine protease, (ARTS/ Sept4) Septin gene protein, (dATP/ATP) Deoxyadenosine triphosphate.

It is fair minded to proceed with the notion that tissues that exhibit the sodium-iodide symporter such as breast tissue, are physiologically capable of displaying the protective effects described above. That is, if there is an adequate and intermittent supply of iodine and are not metabolically dysfunctional. The brief examination on thyroid cancer cells, ties in well with breast cancer because both malignant diseases are known to occur metachronously or synchronously.[128] The nexus between the two is not surprising as both glands are regulated by the HPT axis and express the highest levels of NIS due to their uptake and utilisation of dietary iodine.[13,110,128] Supplementing the previous article[125], it is believed that the presence of chronic hypothyroidism, dietary and intracellular iodine deficiency may serve as initiators for thyroid and breast cancer.[128] By contrast, excess iodine is also detrimental and in this case a link between an increased rate of papillary thyroid cancer (PTC) has been reported.[22,65,128] Admittedly, the co-occurrence of breast and thyroid cancer requires more excavation as other MetS components (obesity, CVD), in addition to the above mentioned initiators are interwoven into the tapestry of carcinogenesis initiation.[124,128] There is also the matter of fibrocystic breast disease, a condition associated with ID that affects ~50% of women of childbearing age and if left untreated can progress into breast cancer.[107,125]

Relatedly, a change in iodine nutritional status is thought to have an input into the advancement and maintenance of the clinical syndrome, fibromyalgia.[129-131] A condition which exhibits MetS components and symptoms of ID (anxiety, cognitive difficulties, chronic fatigue, and depression).[124,129-131] Several hypotheses on the aetiology have been proposed, but chronic oxidative stress has the strongest association.[129-131] To a sensitive observer this association is not an overreach, as Teas *et al.*[111] and subsequent investigators have noted that iodine is a potent antioxidant.[15,112,118] Therefore, inadequate consumption of dietary iodine is capable of contributing to this disorder as the protective properties granted by iodine are diminished in its absence. The former is sustained by taking into consideration that a deficiency in other trace elements (Se, Zn, Fe and Mg) adversely affects cellular redox balance.[130,131] This brief encounter serves as another example of how thyroid dysfunction (hypothyroidism), can appear as a component of an already clinically diagnosed MetS because the appearance of hypothyroidism and its symptoms is synchronous with the development of fibromyalgia.[129] However, to say that iodine insufficiency is the basis of this pathoetiology would be an overreach, but as already discussed, the gland plays a pivotal role in metabolism, growth and development thus this issue deserves analytical attention.

Altogether, a plethora of risk factors with bi-directional crosstalk are offered and the presence of one malignancy may serve as a risk factor for distant malignancies as proposed by Rappaport[125]. Undeniably, the importance of dietary iodine amongst younger women should not be taken lightly as the presence of iodine deficient diets and their subsistence not only impair breast and thyroid health, but foetal cognitive development.

4.1.4 - Dietary trends & Psycho-nutrition (MetS)

This section is summarised by bringing into attention the last emerging theme. The link between nutrition and mood disorders (anxiety and depression), a nexus which is based on how inadequate nutritional status contributes to the development or sustenance of such disorders.[118,129,131] The association between the two belongs to the emerging discipline of psycho-nutrition or nutritional neuroscience. A field that is believed to be in its infancy, but the nexus between depression and thyroid dysfunction was described as early as the 1960s.[132,133] Due to the lack of population-based studies the field of nutritional neuroscience remained cautious until it was ready to reveal that nutritional factors are interwoven with human behaviour, cognition, and emotions.[132-134] The previous remark, is sustained by the results and discussion which focuses on foetal cognition and human behaviour to a certain

extent. Therefore, additional insights regarding mood disorders are welcomed as they help to shed some light on the complexities that with the change in dietary trends and in sufficient iodine supply. In contrast, this segment shifts the focus on to pregnant women and those of childbearing age. They are not only at risk of developing postnatal depression due to physiological adaptations of pregnancy, but depression or anxiety due to thyroid dysfunction as a result of insufficient repletion of dietary iodine.[132-135] In support, observations show that depressive symptoms are ubiquitous with those displayed in fibromyalgia or ID patients, especially in hypothyroid individuals.[129-131,133-135] As for how iodine contributes to depressive mood disorders, Rao *et al.*[132] notes that the diet of individuals suffering from mood disorders is far from adequate as it is based on poor food choices. A notable feature of these diets is a severe deficiency in essential amino acids, minerals and vitamins plus omega-3 fatty acids; components which are required in hormone and neurotransmitter synthesis.[129,132] In relation, deficiencies in neurotransmitters such as dopamine, noradrenaline, serotonin, and γ-aminobutyric acid (GABA) have been associated with depression as their absence is considered to diminish the antidepressant effects of the neurochemicals.[132,134] Furthermore, animal studies have shown that TH can influence serotonergic and noradrenergic neurotransmission as administration of T3 displayed increased serotonin levels in the cerebral cortex of rats and in contrast, models with hypothyroidism showed decreased serotonin synthesis.[134,135]

The role of dietary iodine in the synthesis of TH and their contribution to normal physiological function is reiterated and in certain cases, individuals suffering from depression often receive TH as a therapeutic agent.[133-135] Yet, it is worthwhile to note that due to the complexity of this nexus, their efficacy is uncertain as some can find benefits in treatment with T4 alone whilst others opt for compound treatment (T3/T4) or alterative treatment.[134,135] Simultaneously, a mistreatment can delay the correct diagnosis (depression or hypothyroidism) and misattribution of symptoms can occur as both disorders share similar symptoms, especially in the older female population.[133-135] Lastly, other non-nutritional components such as genetic factors or autoimmune thyroid disorders that influence the individuals well-being and affect their quality of life should also be considered when it comes to making associations between nutrition and mood disorders.[133-135]

The cadre of literature presented above support the suppositions put forward on dietary change associations and begs for further analytical attention. Yet, and in a constructive manner, augments the author's preconceived notion from, *"ID serves as a precursor to the development of the aetiologies enumerated above"* into *"ID is a component of the aetiologies presented above"*. Gleaning over the reports made above as anecdotal evidence will only ensure that, these concerns are not seen as a confluence of issues that are not immediately apparent but come together to cause absolute devastation.

4.2 - Brief encounters (seaweed toxicity, processing and cooking methods)

Much of the discussion on excessive iodine consumption and the possible repercussions (thyrotoxicosis) associated with it has been excavated in great deal in the results analysed. To avoid any further regurgitation, this section concentrates on seaweed iodine concentration, toxic elements (heavy metals) and the effects of processing and cooking methods. The relevance of this is owed to safety of seaweed consumption and supports the results of the seaweed supplementation proposal.

The first two factors often lead to the dismissal of seaweed, especially kelp, as a possible supplement for ID.[5,8,59] Understandably, this is done with the individual's safety in mind. Nonetheless, this defenestration of seaweed under the auspices of excessive iodine concentration by investigators is incomplete at best, as it concentrates solely on kelp and does little to explain or educate on the ideas behind the remark. This is because kelp is not the only form of edible seaweeds (appendices) an individual can consume to maintain euthyroid status. By default, the properties of kelp are attributed to other species of seaweed; in a negative manner, which not only prohibits the use of kelp but other edible seaweeds with lower iodine concentrations. In support, instances are record on how the concentration of iodine varies amongst edible seaweed species due to exogenous and endogenous factors.[15,109,111,112] In support, Combet *et al.*[109] demonstrates the presence and use of low-iodine-containing (356 µg/g) seaweed species (*Ascophyllum nodosum)* for supplementation and Teas *et al.*[111] attests to this by using *Alaria esculenta* (93 µg/g). In contrast to Combet *et al.*[109], the study by Teas *et al.*[111] seems to justify the use of *A. esculenta* by acknowledging the excessive iodine content of kelp, 2500 µg/g in comparison to the 93 µg/g used in their study. With good reason as the iodine content serves as dose limiting factor in seaweed consumption. The former holds true for individuals not accustomed to habitual consumption of high iodine-containing seaweeds in comparison to those in Asian countries (Japan, Korea, and coastal China), where the average daily iodine intake is approximately 4-7 g/d per dw or 500-1000 µg/d.[65,111,113] Undoubtedly, this level of iodine consumption raises some safety concerns as the values are beyond European tolerable upper limit (>500 µg).[22,107] Yet, it is difficult to quantify the exact amount of iodine consumed in these regions as it is served as a flavouring, garnish, soup or snack.[111,113] Interestingly, these levels are only tolerated by healthy individuals free from underlying thyroid disorders or comorbidities.[136,137] This is demonstrated by the Wolff-Chaikoff effect, a transient safety mechanism that inhibits TH synthesis and secretion for a few days or a week in response to excessive iodine exposure.[22,65,136,137]

Broadening the dialogue, it is evident that the issue regarding excessive iodine and its metabolism factors in the individual's health; specifically, renal function.[8,22,24] For instance, an association between chronic kidney disease (CKD) and an increased risk in development of hypo and hyperthyroidism via the Wolff-Chaikoff effect and Jod-Basedow phenomenon, has been proposed for CKD patients because of iodine retention due to impaired renal function.[136,137] Simultaneously, iodine-associated hypothyroidism in adult and paediatric dialysis patients has been noted for those on iodine-rich diets (seaweed).[136] Additionally, CKD patients are susceptible to metabolic acidosis, a disorder which interferes with normal thyroid function tests (increased TSH and low T4/T3), and it has also been proposed that total body TH depletion can occur in CKD patients due to heavy protein loss as TH are protein bound.[136,137] Lastly, a retrospective study *(n*=309) on the preservation of renal function by TH replacement therapy (L-thyroxine) in CKD patients observed at 12 months that estimated glomerular filtration rate (eGFR) was significantly lower (p=0.04) in the non-treatment group (129) in contrast to the treatment group (180) for renal function.[137] A follow up (34.8 ± 24.3 months) on renal outcome revealed a 50% decrease in eGFR in the non-

treatment group (27 patients; 20.9%), compared to the treatment group (15 patients; 8.3%).[137]

The statements made above demonstrate the potential of TH therapy, and simultaneously offers a brief insight into the crosstalk between the two glands. In essence, compromised renal function can deter the inclusion of iodine-rich seaweeds into the individual's diet and before the across-the-board dismissal of seaweed use, this factor should be taken into consideration.

With that in mind and shifting the focus to process ad cooking methods. To maintain the idea that the quantity of iodine present in iodine-rich seaweeds is preserved between harvest and consumption is irrational. Food preparation and cooking methods influence final iodine content, and these factors are not reported in accounts that dismiss seaweeds as supplements.[15,114] In support, an account on the influence of processing (washing and dehydration) for *A. esculenta*, *Palmaria palmata*, *and U. intestinalis* showed a slight decrease in iodine content; albeit, a technique that is useful as a preservation method.[114] However, rehydration of the seaweed species (1 to 24hr in deionised water) significantly reduced the iodine content of *A. esculenta* (62%), *P. palmata* (15%), and U. intestinalis (10%).[114] Further reduction in iodine content would have been possible if the previous processes were followed by boiling. For instance, extensive boiling or cooking of dulse is discouraged as this leads to nutrient reduction as the seaweed breaks up.[113] Here, an astute observer would do well to recognise that the damage done by the boiling method can diminish the nutraceutical properties granted by seaweeds and may even affect their bioavailability.

Returning to boiling, Banach *et al.*[114] notes its effects on *S. latissimi* which resulted in approximately a one third reduction of iodine content (126.6 mg I/kg), in contrast to the initial value of 380 mg I/kg per dw after 2 minutes of boiling in freshwater. Moreover, prolonged soaking (1hr in freshwater at 32°C) of *S. latissimi* showed a significant reduction in iodine content; from 4,898 - 6,568 (initial values in May and June) to below 2,000 mg I/kg per dw.[114] Interestingly, and in contrast to other cooking methods, steaming (5 minutes at 105°C) of *Laminaria digitata* or Atlantic kelp led to an increase in iodine concentration ($p<0.05$).[114] Sadly, the initial and end values of the iodine content are not mentioned, but the iodine content is estimated to be above 1,500 mg/kg.[114] Despite the changes that can occur in iodine content as result of further processing of seaweed, it is important to note that for iodine-rich seaweeds, processing alone cannot ensure acceptable concentrations. Yet, the interjection is not intended to deter the use of seaweeds as supplements as there are some with low-iodine-content (Nori; 16 µg/g, sheet average weight 3g).[107] But for safety reasons the remark is made to impart some knowledge to the at-risk groups.

In favour of balancing the arguments made above on the behalf of seaweeds, additions can be made. The plethora of nutraceutical properties associated with seaweed does not grant the supplement immunity from criticism when it comes to human consumption. Such a view is necessary because seaweeds, depending on the level of anthropogenic activities in addition to season, location, and water quality, are liable to toxic metal bioaccumulation; a factor that limits their utilisation as feed or food.[15,110,113,114,138,139] Instantaneously, the high sorption capacity of seaweeds is not seen as a definitive drawback as the mechanism can be utilised to remove environmental heavy metals.[110] Nonetheless, the presence of metals such as arsenic (As; inorganic and total), cadmium (Cd), lead (Pb), and mercury (Hg; total and methyl mercury) in seaweed species has resulted in the employment of threshold values and maximum levels (ML) by the European commission.[113,114,138] This has been done to monitor the potential hazards and toxic effects of the metals.[113,114,138] Despite the measures

put in place. As a food, seaweeds at EU level have no MLs (Table 9), but have MLs for feed and supplement.[114,138] This is perplexing at first, but further enquiry revealed that it is difficult to set standards in seaweed than it is for feed or supplements (finished products) because the concentration is based on the metals present in the surrounding water and uptake capacity.[110,114] In aid, Mouritsen *et al.*[113] notes that age is contributing factor to the concentration of inorganic As in dulse, where levels are below detection limit (0.02 μg g^{-1} dw) in immature dulse in contrast to mature specimens (0.3 μg g^{-1} dw).[114]

Table 9. Overview of maximum levels for heavy metals. Adapted from Banach *et al.*[114]

Hazard	Feed	Food	Food Supplements
Arsenic (total)	40 mg/kg	No standard for seaweed	No standard for seaweed
Arsenic (inorganic)	2 mg/kg	No standard for seaweed	No standard for seaweed
Cadmium	1 mg/kg	No standard for seaweed	3.0 mg/kg wet weight (ww)
Lead	10 mg/kg	No standard for seaweed	3.0 mg/kg ww
Mercury	0.1 mg/kg	No standard for seaweed	0.10 mg/kg ww

Further support shows that kelp species have low inorganic As concentrations that are within the tolerable daily intake level of 2 μg/kg body weight; set by the WHO.[139] Regardless of the low or undetectable levels exhibited in different seaweed species due to the contributing factors, heavy metals are known to be inimical to the individual. The metabolic function of As is unknown.[114,138] The inorganic form in comparison to the organic form; a distinction which should be made when issuing recommendations, is highly associated with health risks.[15,113,114,138] For example, upon excessive consumption or exposure, As can induce adverse health effects such as encephalopathy and gastrointestinal conditions which can result in death.[113,114] Such effects are not limited to As because Cd, Pb, and Hg (methyl mercury) have no known metabolic function and can impair endocrine and renal system function in addition to the nervous system.[113] Further complications which may arise include dermatological issues, peripheral neuropathy and an increased risk in development of various cancers.[113] The potential hazards associated with seaweeds are not limited to heavy metals.[114] The presence of marine biotoxins and pathogens plus anthropogenic factors such as micro and nano-plastics, pesticide residues, polycyclic aromatic hydrocarbons and pharmaceuticals contribute to the level of contaminants in the aquatic environment.[113,114,139] Consequently, the adoption of seaweeds as nutraceuticals warrants further attention in order to discern which food safety hazards may arise instead of keeping them at bay.

The discourse above provides a distillate on the dichotomous functions of seaweeds by enumerating several underreported factors that should be considered before seaweeds are dismissed. It is evident that umbilical ties exist between the individual, seaweeds and the environment. Moreover, the presentation made above provides at least two lessons: (1) recommendations made for the whole population should not be based on individuals that require medical attention and (2) recommendations should not be made without sufficient data to support them. Nonetheless, the author is aware that it is difficult to set recommendations for seaweeds because they are a part of a kingdom, but as already discussed, seaweed consumption has been revitalised.[113,114] Therefore, the immediate task for investigators and health authorities is to open a dialogue and agree upon the species with acceptable iodine content and formulate recommendations. This would aid in rectifying the poor labelling associated with the seaweed-containing products that are plagued by lack of information on seaweed species and iodine content.[107,123,139] The possible benefits are

trifold: (1) acceptable iodine concentrations for the public and at-risk groups are determined for safe consumption, (2) iodine sufficiency at a national level is maintained, and (3) the individual can make an informed choice about the product before adoption into their diet.

4.3 - Limitations

Although the author has tried to maintain a high standard of theoretical and scholarly precision in order to present critically correct evidence that is in favour with their contentions, a reflection into the limitations of this review is warranted. First off, a lack of primary or "real time" data in this review is a weakness that can be employed to question its contribution to the specified field. In translation, what is the purpose of the review and is it useful to scholars and practitioners. The answer is yes, and to better clarify, the issue concerning the lack of primary data is built mainly on the study design which consisted of a 'pre-defined research question' that was synthesised from background research in order to map and assess the research area. The initial step provided guidance towards literature that best answers the research question and hypothesis.[140] Subsequently, the methodology of study selection was reviewed because study design and execution determine the data extracted and its relevance confirms whether study objectives are met or not. For this review the option to include primary data was considered, but in order to address the combined research query it was not plausible for a review that spans several disciplines (nutrition, neurology, and biochemistry etc). Also, factors such financial constraints, limited resources (place or number of participants), and time available to carry out such a task, served as draw backs. However, the use of primary data has several benefits such as up-to-date information, increased accuracy and validity when gathered from a designated population. Other benefits include control over information gathered and ownership of data. But most importantly, the data collected is specific to the enquiry and not across the range, unlike secondary data.

Consequently, secondary data was used, and it provided the foundation to explore the field and find specific areas with knowledge gaps and exploit them.[140] Moreover, the use of numerous empirical findings to address a research question grants the review validity, and power. This is owed to the integration of various worldwide perspectives. Simultaneously, valuable inferences can be made from this pool of data, and this goes beyond recitation of previous research.[140] The previous comment stands true if the appropriate strategy for selecting articles is employed, and for this review, it is well demonstrated in the methodology section. However, secondary data falls short to primary data because the findings of the investigators maybe incomplete or may only fulfil a certain area of the study objectives because it is not 100% specific to the enquiry at hand. In addition, the quality of data is out of the authors control and can be biased. Plus, secondary data may be out-of-date or irrelevant, especially when an article has been retracted. Yet, it is worthwhile to note that "chronological arrogance", coined by C.S. Lewis and O. Barfield is often used to discard useful information from outdated articles or books even though they hold knowledge that is still (to some degree) applicable to this day. The advantage of the former can be seen in the generation of new insights from previous analysis (secondary data). Fortunately, secondary data collection is cost and time effective, provides larger sample size, and allows the synthesis of longitudinal analysis. In short, secondary data was perfect for this study as one aspect of it focused on identifying trends over a time period and compare these to the current age.

Taking all of the above into consideration, possibilities of errors arising (systemic, random and blunders) is something to consider in a study design as these factors directly affect the methods, data, and conclusions.[141] For this review, the focus is not on how to stop errors from arising because they are a critical component to the advancement of science, but to identify retrospect and prospective errors in order to correct them for better study designs in forthcoming studies.[141] Because this review did not use primary data, which can be riddled with instrument/equipment errors due to poor calibration, random errors (temperature fluctuations; some can be controlled) or human errors (data input). Factors capable of affecting the accuracy and precision of data. The former does not apply to secondary data because the author did not determine the content of the information collected, but rather, the errors attributed to the author lay in the collection, analysis, and presentation of the extracted data. For instance, the study collection involved the use of filters to augment a broad query into a specific query. As a result, specific or relevant literature was gathered from a broad database. The obvious advantage of this was a decrease in publication bias. The method granted a fair representation of results (published or unpublished) because selection of evidence that fits the view of the researcher creates a bias representation of positive articles through over presentation of significant articles over non-significant articles. Such actions are detrimental to the respective field because they not only affect the validity and credibility of the work, but transparency, authorship, and public perception.[141] As for disadvantages, the use of a full phrase in literature search can result in missing out of important candidates due to the specificity of the phrase. In addition, the application of filters resulted in omission of articles that are not specific to the query and inadvertently further lowered the sample size at the same time. This has a dichotomous action; the relevance of the literature is increased at the expense of losing intellectual insights that the author could never have anticipated. Consequently, smaller sample size infringes on the data's reliability due to high variability within studies which undermines both the depth and rigour of the review.[140] Such weaknesses can be rectified by using a search strategy that utilises combinations of syntaxes to form various search strings and addressing the study design as these factors determines the literature extracted. Additionally, the synthesised search query either needs to be broader to raise the data sample pool or more-than specific by including key terms that meet the study objectives and this may reduce the number of filters applied and raise the sample pool of eligible data.

Other notable mentions to consider can be found in the content of the studies, where reports are made on weaknesses or limitations. Factors which are out of the authors control but nonetheless require attention. Of significance, is the problem regarding an agreement on methods used for systemic screening of IDD, standardisation of testing instruments and procedures for IQ and psychomotor tests in order to make valid comparisons. This issue must be addressed if comparisons are to be made in this field because different investigators use different methods. Even though they may arrive at similar findings there is still the question, to what degree do they complement each other? The importance of the previous comment has its grip on the rigour, interpretation and presentation of scientific data, especially narrative reviews as they can be linguistically subjective if there is limited access to quantitative data. Another matter to consider, is the use of nutritional epidemiology surveys (i.e., how much iodine do you consume per day/week/month), in studies for data collection. The former is not intended to challenge their efficacy, but the possible weakness here lies in participants generating "on the spot" untrue quantifications or answers on how much of something (food) they consume depending on the scale. Such data or "wild guesses" becomes the data that is used to synthesise hypothetical associations on the subject. Lastly, the literature calls for additional human-based evidence for supplement studies as most of the data is extrapolated from animal studies. Although good models, the weakness detected here is the difficulty in translating findings and assuming that what works in models works the same in humans.

Overall, the main strength of this review can be seen initially in its originality. That is, to the best of the author's knowledge this is the first review to trace the progression of ID in the last two decades in order to gain further insights into ID resurgence, possible pathophysiological effects beyond neurodevelopment, and its relationship to dietary changes. With the goal of bringing awareness to what has been termed a "persistent low-hanging fruit" (ID) of public health to the attention of the public, health authorities and policy makers.[142] The other strength lies in the presentation of the first results (Table 6). Which behaves as a directory that can be used as a quick reference guide to see changes and advancements (recommended iodine intake levels and prophylaxis) between the years of 2000 – 2020. In addition, the narrative review is immixed with quantitative (statistics) data which aids in maximising the authors interpretation of the information. To the author, this has been a demonstration of taking on a promethean task and decimating it into units that are small enough to manage practically and try to figure out how to transfer those insights or solutions to the lived reality. Altogether, this comprehensive review displays hallmarks of adequate contribution because the propositions put forward have the capacity to advance this field and engender new concepts in other fields.[140]

4.1 - Future directions

An aspect of the review was to evaluate the status of USI as a therapeutic vector, and the information gathered revealed its benefits and limitations in the face of other therapeutic vectors. Nonetheless, the future of USI looks promising, partly because it remains the primary preventive measure for ID, but even more, its biofortification properties are being revamped. It seems that "help" is being offered to USI by using food (including condiments) as potential vehicles for biofortification in order to tackle micronutrient deficiencies.[7,107,143] For instance, the use of dual fortified salt (Fe/I) is being considered in iron-fortified flour, and staple crops such as maize and rice in order to assess their potential in improving micronutrient status.[7,143] In aid, biofortification of vegetables has been proposed in Italy, and trials revealed that consumption of fortified vegetables raised the UIC of the candidates (n=50) by 19.6 % ($p<0.05$).[107] Lastly, the use of fortified bread in Australia has been recommend in pregnant women in order to increase their dietary iodine intake.[65,70,107] Due to their success in raising micronutrient status in developing countries, biofortified crops have drawn the attention of developed countries; regions that once exported these methods are now considering their impact in Europe.[143,144] It is evident that micronutrient deficiencies have now captured the attention they have been looking for and require addressing for future generations. This is already in motion as investigators are looking beyond single mineral supplementation by considering delivery of other essential minerals (Se, Zn, Fe) in complex with iodine in order to main normal thyroid function and raise mineral status.[107,143,144] In addition, delivery of folate via fortification is also being considered for pregnant and nursing mothers.[143] The benefits of biofortification go beyond eradicating micronutrient malnutrition and prevention of Keshan or Kashin Beck Disease (KBD) development.[143,144] But also adds back the collective's potential brain power that would have been lost to irreversible cognitive impairment.

As with any promising strategy, drawbacks are present. For biofortification, further data is required on their impact on long-term use, bioavailability and foliar biofortification application.[7,107,144] Moreover, Bouga *et al.*[107] also adds that the ICCIDD does not support individual food iodisation. However, in Pakistan and Bangladesh the use of turmeric in studies has been shown to increase iodine intake and eliminate goitre.[107] Such properties have led turmeric to be considered as an alternative to USI, albeit an unpopular view.[107] It is

puzzling that an effective alternative to USI is met with resistance. Lastly, before implementation it is worthwhile to bear in mind that acceptance of biofortified foods by differing populations and communities will be met with different reactions as they adjust to them; that is if adopted at all.[107]

In passing, several investigators call for the development of novel biomarkers because a long-term indicator of iodine status remains to be identified.[65,68,70] Yet, hair analysis, a method already used in assessing toxics elements and prediction of health outcomes may be a future solution in assessing individual iodine status. Unlike blood, hair is long-term biological indicator.[145,146] Compared to other biological matrices, hair is stable, therefore it is easy to store, transport and collect in a non-invasive manner plus the mineral content is 50 to 100x higher in comparison to blood or urine.[145,146] Overall, a promising diagnostic tool that warrants further investigation because the mineral content remains irreversibly deposited for a longer period (months) unlike blood concentrations that are under homeostatic control.[145,146]

4.2 – Summary

After grappling with a raft of contradictions and ambiguous recommendations, this review can be summarised by stating that both aims have been fulfilled. This is demonstrated not only by the material offered in the data analysed, but in the discussion and subsequent sections. Sections which not only support and strengthen the much-needed re-evaluation of the recommended iodine intake for the at-risk group but provide additional rationales for undertaking this task whilst demonstrating the efficacy of seaweed supplementation. Leaving no stone unturned, the complexities of addressing population-based ID sheds some light on the role of the individual, health institutions and political powers in this public health matter. On top, the addition of emerging themes (change in dietary trends) and brief encounters (seaweed toxicity) to the discussion has proved to be a success. Such ideas are used to talk about what is co-occurring with the resurgence of ID and what could come next alongside what has been reported on ID. As a result, from sample data analysed the hypothesis outlined in the introduction is both true and accepted.

Lastly, to this open-ended story that is straining every sinew for recognition. It begs to ask how long the at-risk groups must wait for RCT on gestational ID, efficacy of iodine supplementation and data on the mechanisms governing the patho-physiological repercussions associated with mild-moderate ID. The former is complexed with the fact that the level of iodine supply remains undetermined by public health authorities. On the other hand, investigators have yet to reach a consensus on systematic screening of IDD and this is coupled with the overconfident use of single spot UIC to characterise the iodine status of pregnant women and using this result to predetermine the adverse outcomes of the offspring. The dialogue for setting in motion policy plans aimed at monitoring iodine status for the whole population is long overdue. This is extremely vital at home (UK), where the guidelines on iodine status were last updated in 1991. It is evident that a promethean task awaits investigators and health authorities in addressing the re-emergence of ID at home and worldwide before the matter becomes another matter of speculation like the repercussions associated with mild-moderate ID.

5 - References

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6. - Appendices

Records exported from Embase: New articles found (*n*=20) from the use of search strings and combinations of search syntaxes instead of 'iodine deficiency and fetus development during pregnancy'.

Thyroid Function in Preterm/Low Birth Weight Infants: Impact on Diagnosis and Management of Thyroid Dysfunction
LaFranchi S.H. (2021). Frontiers in Endocrinology (2021)

Relationship between thyroid status during the first trimester of pregnancy and neonatal well-being
Murillo-Llorente M.T.; Llorca-Colomer F.; Pérez-Bermejo M. (2021). Nutrients (2021)

Consequences of Iodine Deficiency and Excess in Pregnancy and Neonatal Outcomes: A Prospective Cohort Study in Rio de Janeiro, Brazil
Silva De Morais N.; Ayres Saraiva D.; Corcino C.; Berbara T.; Schtscherbyna A.; Moreira K.; Vaisman M.; Alexander E.K.; Teixeira P. (2020). Thyroid (2020)

Iodine status and supplementation before, during, and after pregnancy
Rodriguez-Diaz E.; Pearce E.N. (2020) Best Practice and Research: Clinical Endocrinology and Metabolism (2020)

Maternal iodine status and associations with birth outcomes in three major cities in the United Kingdom
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.; Simpson N.A.B.; Greenwood D.C.; Hardie L.J. (2019). Nutrients (2019)

Iodine content of the best-selling United States adult and prenatal multivitamin preparations
Patel A.; Lee S.Y.; Stagnaro-Green A.; Mackay D.; Wong A.W.; Pearce E.N. (2019). Thyroid (2019).

Thyroid homeostasis in mother-child pairs in relation to maternal iodine status: The MISA study
Berg V.; Nøst T.H.; Skeie G.; Thomassen Y.; Berlinger B.; Veyhe A.S.; Jorde R.; Odland J.; Hansen S. (2017). European Journal of Clinical Nutrition (2017)

The role of nutrition in pregnancy
Clark A. (2015). Medicine Today (2015)

Fetal-maternal outcomes of isolated hypothyroxinemia in pregnancy
Akbaba G.; Akbaba E.; Berker D.; Işık S.; Doğan B.A.; Özuğuz U.; Tütüncü Y.; Danışman N.; Güler S. (2014)

The state of U.S. iodine nutrition: How can we ensure adequate iodine for all?
Pearce E.N.; Leung A.M. (2013). Thyroid (2013)

Thyroid (dys-)function in normal and disturbed pregnancy
Budenhofer B.K.; Ditsch N.; Jeschke U.; Gärtner R.; Toth B. (2013). Archives of Gynecology and Obstetrics (2013).

Iodine deficiency in pregnancy and in women of reproductive age in Erzurum, Turkey
Çetinkaya K.; Ingeç M.; Çetinkaya S.; Kaplan I. (2012). Turkish Journal of Medical Sciences (2012)

Assessment of thyroid function and iodine supply of the group of healthy pregnant women from central Poland
Krasnodebska M.; Niedźwiedźka B.; Kondracka A.; Bartoszewicz Z.; Bar -Andziak E.; Bednarczuk T. (2011).
European Thyroid Journal (2011)

Iodine deficiency in northern paris area: Impact on fetal thyroid mensuration
Luton D.; Alberti C.; Vuillard E.; Ducarme G.; Oury J.F.; Guibourdenche J. (2011). PLoS ONE (2011)

Hypothyroxinemia: A subclinical condition affecting neurodevelopment
Berbel P.; Bernal J. (2010). Expert Review of Endocrinology and Metabolism (2010)

Folic acid, zinc, iodine, selenium and maternal health
Tuerxunjiang M.; Wang Y.-P. (2007). Journal of Clinical Rehabilitative Tissue Engineering Research (2007)

Iodine saturation of Roma neonates in Prague is not at an optimum level
Dlouhý P.; Rambousková J.; Wiererová O.; Pokorný R.; Bílek R.; Kubisová D.; Procházka B.; Anděl M. (2006). Annals of Nutrition and Metabolism (2006)

Dietary iodine intake in pregnancy
Smyth P.P.A.; O'Herlihy C. (2006) Irish Medical Journal (2006)

Treatment of the iodine deficiency in pregnant women in the district of Teplice
Vitnerova N.; Miskova I.; Kotesovec F. (2000). Journal of Czech Medicine (2000)

Mild iodine deficiency during fetal/neonatal life and neuropsychological impairment in Tuscany
Aghini Lombardi F.; Pinchera A.; Antonangeli L.; Rago T.; Chiovato L.; Bargagna S.; Bertucelli B.; Ferretti G.; Sbrana B.; Marcheschi M.; Vitti P. (1995). Journal of Endocrinological Investigation (1995)

Records exported from Embase: New articles found (*n*=22) from the use of search strings and combinations of search syntaxes instead of 'seaweed for iodine supplementation'.

Iodine, Seaweed, and the Thyroid
Smyth P.P.A. (2021). European Thyroid Journal (2021)

Vegans, vegetarians and pescatarians are at risk of iodine deficiency in Norway
Groufh-Jacobsen S.; Hess S.Y.; Aakre I.; Gjengedal E.L.F.; Pettersen K.B.; Henjum S. (2020). Nutrients (2020)

Iodine content of the best-selling United States adult and prenatal multivitamin preparations
Patel A.; Lee S.Y.; Stagnaro-Green A.; Mackay D.; Wong A.W.; Pearce E.N. (2019). Thyroid (2019)

Iodine and thyroid function: A historical review of goiter and the current iodine status in Japan
Fuse Y. (2017). Pediatric Endocrinology Reviews (2017)

Food group intakes as determinants of iodine status among US adult population
Lee K.W.; Shin D.; Cho M.S.; Song W.O. (2016). Nutrients (2016)

Can iodine status be predicted by food group intake?
Lee K.W.; Song W.O.; Cho M.S. (2015) FASEB Journal (2015)

Stability of urinary iodine concentration of school-age children and its representativeness for iodine nutritional status of their parents
Sun Z.; Su X.; Gao Y.; Liu S.; Ye Y.; Li M.; Sun H.; Hu X.; Zhu X.; Sun D. (2014)
Chinese Journal of Endemiology (2014)

Low-level seaweed supplementation improves iodine status in iodine-insufficient women
Combet E.; Ma Z.F.; Cousins F.; Thompson B.; Lean M.E.J. (2014). British Journal of Nutrition (2014)

Acquired hypothyroidism due to iodine deficiency in an American child
Brooks M.J.; Post E.M. (2014). Journal of Pediatric Endocrinology and Metabolism (2014)

Investigation of iodine deficient state and iodine supplementation in patients with severe motor and intellectual disabilities on long-term total enteral nutrition
Takeuchi T.; Kamasaki H.; Yoto Y.; Honjo T.; Tsugawa S.; Hotsubo T.; Tsutsumi H. (2012).
Endocrine Journal (2012)

Teratology public affairs committee position paper: Iodine deficiency in pregnancy
Obican S.G.; Jahnke G.D.; Soldin O.P.; Scialli A.R. (2012).
Birth Defects Research Part A - Clinical and Molecular Teratology (2012)

Treatment of hypothyroidism due to iodine deficiency using daily powdered kelp in patients receiving long-term total enteral nutrition
Takeuchi T.; Kamasaki H.; Hotsubo T.; Tsutsumi H. (2011). Clinical Pediatric Endocrinology (2011)

Antiproliferative effects of molecular iodine in cancers
Torremante P.E.; Rösner H. (2011). Current Chemical Biology (2011)

Iodine status and thyroid function of boston-area vegetarians and vegans
Leung A.M.; La Mar A.; He X.; Braverman L.E.; Pearce E.N. (2011)
Journal of Clinical Endocrinology and Metabolism 2011

Research on iodine deficiency and goiter in the 19th and early 20th centuries
Zimmermann M.B. (2008). Journal of Nutrition (2008)

Iodine supplementation of pregnant women in Europe: A review and recommendations
Zimmermann M.; Delange F. (2004). European Journal of Clinical Nutrition (2004)

Role of iodine in antioxidant defence in thyroid and breast disease
Smyth P.P.A. (2003). BioFactors (2003)

Dietary iodine sources other than fish
Tokudome S.; Tokudome Y.; Moore M.A. (2002). European Journal of Clinical Nutrition (2002)

Dietary iodine intake and urinary iodine excretion in normal Korean adults
Kim J.Y.; Moon S.J.; Kim K.R.; Sohn C.Y.; Oh J.J. (1998). Yonsei Medical Journal (1998)
Existence of iodine deficiency in Hong Kong - A coastal city in southern China
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Thyroid signalling cross-talk with other pathways from in vitro and in vivo models and TR isoform preference. Credit, Brent.[33]

Pathway/nuclear factor or target	Process or tissue	TR isoform	Nature of interaction	Reference
RAR	Neural development	TRα1	Inhibits T3 action generally by direct inhibition of TR	96–98
Retinoic acid	Brain development	TRα1	Stimulates MCT8 expression and thyroid transport	103
COUP-TF1	Expressed early in brain development	TRα1	Blocks TR binding to a TRE and inhibits T3 induction of gene expression	99, 100
PPARα	Liver	TRα1	Fatty acid oxidation	26
PPARγ	Liver	TRβ	Lipid homeostasis	110
LXRα	Liver	TRβ	Cholesterol metabolism	111
LXR	Brain	TRα1	Cortical layering	113
p85α subunit of PI3K	Thyroid and liver	TRβ[A]	Cell proliferation; tumorigenesis	24, 130
β-Catenin	T3 stimulates expression in intestinal epithelium	TRα1	Proliferation; tumorigenesis	133
Adrenergic signaling	White fat	TRα1	Promotes lipolysis	30
Adrenergic signaling	Brown fat	TRα1[B]	Adaptive thermogenesis	27–29
Adrenergic signaling	Heart	TRα1	Tachycardia	30
Adrenergic signaling	Bone	TRα1[C]	Increased bone turnover and bone loss	89, 135

[A]Wild type and mutant. [B]TRβ regulates UCP1. [C]Role also for TRβ.

Criteria for monitoring progress towards sustainable elimination of iodine deficiency disorders. Adapted from Andersson *et al.*[54]	
Indicators **Goals**	
Salt Iodization	
• Proportion of households using adequately iodized salt*	>90%
Urinary iodine	
• Proportion of population with UI levels below 100µg/l	<20%
• Proportion of population with UI levels below 50µg/l	<20%
Programmatic indicators	**At least 8 of the 10**
• An effective, functional national body (council or committee) responsible to the government for the national programme for the elimination of IDD (this control should be multidisciplinary, involving the relevant fi elds of nutrition, medicine, education, the salt industry, the media, and consumers, with a chairman appointed by the Minister of Health) • Evidence of political commitment to USI and elimination of IDD • Appointment of a responsible executive officer for the IDD elimination programme • Legislation or regulations on USI (while ideally regulations should cover both human and agricultural salt, if the latter is not covered this does not necessarily preclude a country from being certified as IDD-free) • Commitment to assessment and reassessment of progress in the elimination of IDD, with access to laboratories able to provide accurate data on salt and UI • A programme of public education and social mobilization on the importance of IDD and the consumption of iodized salt • Regular data on salt iodine at the factory, retail and household levels • Regular laboratory data on UI in school-age children, with appropriate sampling for higher risk areas • Cooperation from the salt industry in maintenance of quality control • A database for recording of results or regular monitoring procedures particularly for salt iodine, UI and, if available, neonatal TSH, with mandatory public reporting	
*Adequately iodized salt refers to at least 15 ppm at household level	

Group, scientific name, and common names of several edible seaweeds. Adapted from Banach *et al.*[114]		
Group	**Scientific name**	**Common names**
Phaeophyta (brown)	*Alaria esculenta*	Atlantic wakame, bladderlocks, winged kelp
	Ascophyllum nodosum	Rockweed, knotted wrack, egg wrack
	Cystoseira barbata	
	Ecklonia bicyclis (syn. Eisenia bicyclis)	Arame
	Fucus serratus	Serrated wrack, toothed wrack
	Fucus spiralis	Spiral wrack, flat wrack
	Fucus vesiculosusa	Bladderwrack
	Halopteris filicina	Sea fern weed
	Halopteris scoparia	Sea flax weed
	Himanthalia elongata	Seaweed spaghetti, thong weed
	Laminaria digitata	Oarweed, Atlantic kelp
	Laminaria hyperborea	Tangle
	Saccharina japonica (syn. Laminaria japonica)	Royal kombu
	Saccharina latissima (syn. Laminaria latissima)	Sugar kelp, sea belt, sweet oar-weed, sweet kelp
	Sargassum fusiforme	Hijiki
	Sargassum muticum	Japanese wireweed
	Padina pavonica	Peacock's tail
	Pelvetia canaliculata	Channeled wrack, múirín na muc
	Undaria pinnatifidaa	Wakame, Japanese kelp
Rhodophyta (red)	*Chondria armata*	
	Chondrus crispus	Irish moss, carrageen
	Erythroglossum laciniatum (syn. Porphyra laciniata)	Red or purple laver
	Gracilariopsis longissima (syn. Gracilaria verrucosa)	Thin dragon beard plant, Ceylon moss, ogo, ogonori
	Gelidium spp.	
	Palmaria palmata (syn. Rhodymenia palmata)	Dulse, red dulse, sea lettuce flakes
	Peyssonnelia squamaria	
	Porphyra dioica	Black laver
	Porphyra purpurea	Purple laver
	Porphyra umbilicalis	Nori, (tough) laver
	Pyropia columbina (syn. Porphyra columbina)	Southern laver
	Pyropia leucosticta (syn. Porphyra leucosticta)	Pale patch laver
	Pyropia tenera (syn. Porphyra tenera)	Gim, nori
	Pyropia yezoensis (syn. Porphyra yezoensis)	Open sea nori
	Sarcodiotheca gaudichaudii	
	Vertebrata lanosa	Wrack siphon weed
Chlorophyta (green)	*Caulerpa spp.*	Sea grapes, green caviar
	Chaetomorpha linum	Flax brick weed
	Rhizoclonium riparium	Rooting green thread weed
	Ulva intestinalis (syn. Enteromorpha intestinalis)	Gut weed
	Ulva lactuca	Sea lettuce, green laver
	Ulva linza (syn. Ulva fasciata)	Slender sea lettuce, doubled ribbon weed
	Ulva prolifera	
	Ulva rigida	(Stiff) sea lettuce