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editorial-office@sciformat.ca

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IODINE SUPPLEMENTATION IN CHILDHOOD: PREVENTING THYROID DISORDERS IN THE ERA OF PRECISION MEDICINE

Agata Porwolik (Corresponding Author, Email: agataaporwolik@gmail.com)

Professor Zbigniew Religa Student Scientific Association at the Department of Biophysics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Jordana 19, 41-808 Zabrze, Poland

ORCID ID: 0009-0003-5533-5377

Hanna Porwolik

Medical University of Silesia, Katowice, Poland

ORCID ID: 0009-0001-5004-3725

Radosław Szydłowski

Medical University of Silesia, Katowice, Poland

ORCID ID: 0009-0000-5771-3990

Patryk Cyran

Professor Zbigniew Religa Student Scientific Association at the Department of Biophysics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Jordana 19, 41-808 Zabrze, Poland

ORCID ID: 0009-0001-8350-7151

Magdalena Bodera

Provincial Specialist Hospital of St. Barbara No. 5, Sosnowiec, Poland

ORCID ID: 0009-0002-8890-214X

ABSTRACT

Iodine deficiency disorders (IDDs) are a group of conditions that have been identified as one of the most preventable but persisting important causes of irreversible neuro-cognitive impairment among paediatric populations across the world (Bertinato, 2021; Feei & Brough, 2025; Zimmermann & Andersson, 2021). Existing universal supplementation programmes are showing to be inadequate as they do not accommodate the new regional deficiencies and the concomitant risk of iodine excess (Kalarani & Veerabathiran, 2022; Seetharaman et al., 2024). This paper proposes a paradigm shift in paediatric endocrinology to precision medicine, in which the iodine interventions are tailored to each child. Wearable biosensors, which continuously monitor physiological and biochemical parameters, complex mobile-health applications which can track dietary intake in real-time, support adherence, and education, as well as comprehensive telehealth platforms which allow remote care (Fernández-Luque et al., 2021; Foster et al., 2022; Kim et al., 2023; Magsayo & Khatami, 2025; Majeed-Ariss et al., 2015; Mercuri et al., 2021; Rashid, 2024; Zhou et al., 2024). Integration of advanced biomarkers and multi-omics data (genomics, proteomics, metabolomics and microbiomics) - integrated with AI/ML algorithms - will help to dynamically predict risk, implement early intervention strategies and design protocols for the supplementation of these individuals (Bidlemaier et al., 2022; Dhanka et al., 2025; Giorgini et al., 2023; Lu et al., 2025; Mehta et al., 2025). By combining technology with personalised care, this strategy promises to optimise iodine nutrition, protect neurodevelopment and enhance the long term health outcomes of all children (Delange, 2007; Milanesi & Brent, 2016; Untoro et al., 2007).

KEYWORDS

Iodine Deficiency, Pediatric Endocrinology, Thyroid Disorders, Personalized Supplementation, Precision Medicine

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Introduction

IDDs remain a major public health problem that has a disproportionate negative impact on paediatric populations worldwide (Feei & Brough, 2025). Despite universal salt iodisation (USI) programmes being put in place for more than three decades, currently two billion people are at risk of insufficient iodine intake and an estimated 12 million children were at risk of iodine deficiency in 2019 (Bertinato, 2021; Liu et al., 2025; Zimmermann, 2011; Zimmermann & Andersson, 2021). Iodine is indispensable for the biosynthesis of thyroid hormones, on which essential processes of growth, metabolism and neuro- development depend (Bertinato, 2021; Liu et al., 2025; Milanesi & Brent, 2016; Zimmermann, 2011). Exposure to iodine insufficiency in fetal or in infant development may lead to hormonal insufficiencies that lead to irreversible intellectual and cognitive sequelae (Bertinato, 2021; Feei & Brough, 2025; Fuzi & Loh, 2022; Liu et al., 2025; Milanesi & Brent, 2016; Zimmermann, 2011).

Contemporary supplementation strategies which are often described as "one size fits all" have inherent limitations. At the same time, USI initiatives have led to a higher intake of iodine in diets but also raised questions about iodine excess, which can upset the regulation of thyroid function (Kalarani & Veerabathiran, 2022; Lee et al., 2023; Rohner et al., 2020). Iodine deficiency is re-emerging even in areas previously characterised by robust iodisation programmes, due to an increase in the use of non-iodised salts, a reduction in iodine content in dairy products and dietary choices such as veganism (Seetharaman et al., 2024). These developments highlight the need for more sophisticated strategies, which are more geared toward precision medicine and move past generic recommendations.

Precision medicine involves tailoring healthcare to the individual's genetic profile, environmental exposures, and lifestyle using digital tools that enable the perfecting of the accuracy of the diagnosis and the treatment regimen (Bidlemaier et al., 2022; Fernández-Luque et al., 2021). This individualised approach has great potential to improve personalised pharmacotherapy and, thus, to reduce the risks of over- or under-dosing children with thyroid diseases (Steffens et al., 2023).

Treatment and prevention of IDD in childhood: The clinical implications of the potential for irreversible neurocognitive disorder in the setting of IDD warrants the urgency for refined interventions. A research gap thus remains in what efforts can be made to establish how to maintain optimal levels of iodine concentration, particularly in situations where iodized salt is the main source of dietary iodine, all the while addressing reduction in salt intake. Continuous efforts are needed to improve the dietary guidelines for iodine that are appropriate for various physiological stages and population groups, including adolescents and pregnant women, who are especially at risk (Guo et al., 2025; Iannuzzo et al., 2022). The research reported further aims to devise better and individualised approaches to iodine supplementation to ultimately ensure optimal health and developmental outcome in children in the age of precision medicine.

Methodology

PubMed and google scholar databases were searched using the keywords: "Pediatric Endocrinology," "Digital Monitoring Tools," "Thyroid Disorders," "Iodine Deficiency," and "Precision medicine." A selection of the relevant materials was then analyzed.

Physiology and Molecular Mechanisms

Understanding the complex physiological and molecular mechanisms that regulate the integral role of iodine in thyroid function is of prime importance for the development of effective iodine supplementation strategies during childhood. The process begins with active uptake of iodide from the blood into thyroid follicular cells, which is a critical process in which the sodium-iodide symporter (NIS) plays the major role. This transmembrane glycoprotein is strategically found on the basolateral membrane of thyroid cells, actively transports iodide against an electrochemical gradient, and maintains high concentrations of iodide within the thyroid gland, much more than in the plasmas (Carro & Nicola, 2022; Li & Zhang, 2022). The regulatory control of NIS activity by thyroid-stimulating hormone (TSH) is important for ensuring an optimal efficiency of the thyroid gland in uptake of available iodide (Wang et al., 2020).

Following uptake, iodide is transported to the apical membrane and organified and synthesized to thyroid hormones. This is a very important stage of the process, as it takes place the oxidation of iodide to elemental iodine catalyzed by an enzyme called thyroid peroxidase (TPO) in the presence of hydrogen peroxide (Gelen et al., 2022; Rajalakshmi & Begam, 2021). The activated iodine is then bound to certain tyrosine molecules on a large glycoprotein called thyroglobulin that is produced inside the thyroid cells and stored in the lumen of the thyroid follicles. This process of iodination results in the formation of monoiodotyrosine

(MIT) and diiodotyrosine (DIT) (El-Akad et al., 2025; Gelen et al., 2022; Rajalakshmi & Begam, 2021). Subsequently, these iodotyrosines are converted in a coupling reaction, also catalyzed by TPO, to the main thyroid hormones: two molecules of DIT are converted to the compound thyroxine (T4) and one molecule of MIT and one molecule of DIT to the compound triiodothyronine (T3) (Benvenga et al., 2021; El-Akad et al., 2025). These immature hormones are bound to thyroglobulin in the colloid until necessary. Upon appropriate stimulation, thyroglobulin is internalized and subjected to lysosomal enzymatic digestion and both T3 and T4 are released into the systemic circulation (Gelen et al., 2022). Although the main hormone secreted is T4, by the thyroid gland, T3 has been recognized to be the more biologically active form, often produced from T4 by the deiodinase enzymes in peripheral tissues (Lipp, 2021; Russo et al., 2021; Salas-Lucia & Bianco, 2022).

The whole cascade of the thyroid hormone synthesis and release is strictly controlled by the hypothalamic-pituitary-thyroid cascade, sometimes called the TSH/TRH axis. The hypothalamus produces TRH that in turn stimulates the anterior pituitary to produce TSH. TSH then acts upon the receptors on the thyroid gland and stimulates every aspect of thyroid hormone production including iodine uptake, organification, coupling, and hormone secretion (Gelen et al., 2022; Stojković, 2022). Conversely, high levels of T3 and T4 in the circulation exert a negative feedback mechanism of both the hypothalamus and the pituitary, and suppresses TRH and TSH secretion respectively, carefully maintaining the homeostasis of the thyroid hormone (Davidsen, 2022; Li & Zhang, 2022).

Thyroid hormones are essential to normal brain development and somatic growth with specific periods of critical brain development from gestation to early childhood. They participate in very fundamental processes during neurodevelopment such as neuronal proliferation, migration, differentiation, myelination and synaptogenesis, all of which are crucial for optimal cognitive and neurological function. Deficiency in these important periods can lead to severe (and often irreversible) brain development problems. Beyond neurodevelopment, the thyroid hormones also modulate the metabolic rate, control the somatic growth, and ensure the proper functioning of virtually all organ systems (Amirikandbon et al., 2023; Chagas et al., 2021; LI et al., 2026; Meng et al., 2024).

Furthermore, it is imperative to recognize the profound age-dependent variations in thyroid physiology found at all the different life stages of neonates, children, and adults (Soliman et al., 2025). The fetal and neonatal thyroid systems are in a dynamic state of maturation and make these populations more susceptible to the fluctuation of iodine status. Neonates, with their rapid growth and organ system development, have relatively increased iodine demands and less developed thyroid regulatory system, so they are susceptible to iodine deficiency and excess (Kalarani & Veerabathiran, 2022; LaFranchi, 2021). These age-specific physiological considerations call for the adoption of specific approaches to the supplementation of iodine in order to assure optimal thyroid function and positive health outcomes throughout childhood.

The efficiency of thyroid hormone synthesis is also deeply affected by interactions with other important micronutrients as well as a range of environmental factors. Selenium and iron, for example, are important cofactors in many enzymes of thyroid metabolism. Selenium is part of the function of the deiodinases which is responsible for conversion of T4 to active T3 and selenoproteins also provide protective effects against oxidative stress within the thyroid (Köhrle, 2023). Iron deficiency can affect thyroid hormone synthesis especially in populations that are already iodine deficient (Strombom, 2020). Conversely, environmental goitrogens, substances found in some food items (e.g. cruciferous vegetables) or chemicals (e.g. perchlorates) can interfere with iodide uptake or organification and thereby with thyroid hormone production, especially in the background of insufficient iodine intake (Ahmad et al., 2021; Đuričić et al., 2022). These complex interactions emphasise both connections and a necessity of a holistic perspective when conceptualizing and applying supplementation strategies.

Etiology of Iodine Deficiency

The cause of the re-emergence of iodine deficiency is multifactorial and includes changing dietary habits, environmental factors and socioeconomic inequalities. A major contributing cause is the shift towards increased consumption of non-iodized salts, as much of the salt in the diet, especially with processed food, is not iodized (Daniel et al., 2017; Moore et al., 2022; Seetharaman et al., 2024). Changes in the practices of food production, such as reduced concentrations of iodine in dairy, make this problem even worse (Seetharaman et al., 2024). Moreover, the increase in particular nutritional tendencies, such as vegan diets or other restrictive dietary habits can cause insufficient iodine supply by the traditional sources (Seetharaman et al., 2024). Environmental determinants are also involved; for example, depletion of soil iodine content due to geological conditions and agricultural factors like flooding, deforestation and erosion can also result in an increase of risk

of ID in affected areas (Ayalew et al., 2021). Socioeconomic factors such as large family sizes, poor economic statuses and insufficient maternal education on iodized salt have also been linked to an increase in iodine deficiency (Ayalew et al., 2021).

Certain demographic groups are particularly susceptible to iodine deficiency due to increased physiological demands or specific lifestyle factors. Pregnant and lactating women have higher needs for iodine, for their fetal development and for breastfeeding, thus they can be predisposed to iodine deficiency if their needs are not met. Infants and young children are also extremely vulnerable because of the importance of thyroid hormones for neurodevelopment at an early age (Delange, 2007; Iannuzzo et al., 2022; Untoro et al., 2007). Adolescents are another high-risk population, as they tend to not show adequate iodine levels as a result of dietary changes, such as drinking less milk (Nyström et al., 2016).

This complicated interaction between epidemiological patterns and causing factors emphasizes the importance to continue vigilance on iodine deficiency in childhood and continued development of targeted and individualized interventions to eradicate iodine deficiency in childhood effectively..

Clinical Implications in Endocrinology of Children

Iodine deficiency, as a persistent and profound global health challenge, is the foundation of a spectrum of severe clinical consequences in pediatric endocrinology, in essence, the compromise of healthy growth, intricate development, and overall well-being of children (Bertinato, 2021; Feei & Brough, 2025; Zimmermann & Andersson, 2021). It is the number one preventable cause of brain damage worldwide, thus stressing the importance of the proper and necessary intake of iodine to promote healthy synthesis of thyroid hormones (Feei & Brough, 2025). Insufficient iodine affects this synthesis, triggering a chain of developmental disturbances that are collectively called IDD's (Bertinato, 2021; Zimmermann & Andersson, 2021). Of these, congenital hypothyroidism is the most devastating outcome in childhood as a consequence of insufficient production of thyroid hormones during the extremely sensitive fetal and neonatal periods of development. Thyroid hormones are not supportive, but indispensable for normal organogenesis and further maturation of virtually all organ systems of the body, with special emphasis on the central nervous system that is developing at this time, as well as skeletal, cardiovascular and metabolic pathways. A lack of this nutrient in the womb or at the critical period of early postnatal development can lead to serious and often irreversible neuro-developmental damage, indicating the vulnerability from conception to early childhood (Bertinato, 2021; Feei & Brough, 2025; Fuzi & Loh, 2022; Liu et al., 2025; Milanesi & Brent, 2016; Zimmermann, 2011). Manifestations range from subtle developmental delay, which may at first be unrecognized, to the characteristic and unmistakable appearance of cretinism - massive mental retardation, deaf-mutism and severely stunted stature. Early detection strategies (especially screening programs for neonatal thyroid-stimulating hormone) are therefore of paramount importance. Such screenings are important to monitor IDD's and allow timely initiation of thyroid hormone replacement therapy to reduce the most severe long-term effects and significantly improve development in affected babies (Delange, 2007).

Beyond the immediate profound influence of congenital hypothyroidism, iodine deficiency is generally known to be one of the main etiological factors contributing to widespread neuro-cognitive impairment (Liu et al., 2025; Zimmermann, 2011). This global challenge impacts on an alarming cohort of children with estimates that indicate that the global number of children affected by iodine deficiency in 2019 alone equaled to approximately 12.1 million (Liu et al., 2025). The complexity of the role of thyroid hormones in orchestrating a myriad of complex neuro-developmental processes, means that the insufficient production, as a result of insufficient iodine, inevitably results in a variety of deficits in essential neurological functions. These processes include the processes of neuronal proliferation, precise neuronal migration to anatomically appropriate locations, subsequent neuronal differentiation into specialized cell types, myelination of nerve fibers and synaptogenesis - all key processes for optimal cognition, learning and overall neurological integrity (Amirikandbon et al., 2023; Chagas et al., 2021; LI et al., 2026; Meng et al., 2024). The clinical spectrum of the resulting impairments varies from subtle yet significant reductions in overall intellectual ability, marked learning impairments, long-lasting attentional deficits and demonstrably poorer academic performance to more severe and often irreversible mental developmental disabilities (Fuzi & Loh, 2022; Liu et al., 2025; Rohner et al., 2020). This array of impairments together creates awareness of the long-term and pervasive weight that is borne not only by the people affected, and their families, but also by society, in terms of reduced educational achievement and loss of workplace productivity. Even mild-to-moderate iodine deficiency, which is much more common than severe deficiency in many areas, has been consistently and robustly associated with significant decrease of cognitive function in children (Feei & Brough, 2025).

Thyroid hormones can be considered as critical regulators of somatic growth, the complex maturing process of bone, and whole metabolism (Bertinato, 2021; Liu et al., 2025; Milanese & Brent, 2016; Zimmermann, 2011). Consequently, iodine deficiency is directly implicated in a spectrum of growth disorders in children, usually in the form of stunted growth, delay in bone age and a general retardation of physical maturation (Zimmermann & Andersson, 2021). These hormones have strong growth-promoting influences through a two-fold process: affecting the secretion and action of growth hormone, and also directly stimulating the development of cartilage and bone. When thyroid hormone levels become insufficient, these highly fine-tuned functions will be greatly disrupted, resulting in impaired linear growth and impaired physical development. Beyond growth, the thyroid hormones regulate the metabolic rate of the body, energy expenditure and nutrient utilisation optimisation, impacting almost all the body's tissues and physiological functions (Meng et al., 2024; Zimmermann, 2011). Insufficient amounts of iodine, leading to low levels of thyroid hormones, can have a serious impact on normal metabolism processes, precipitating lipid metabolism changes and impaired glucose metabolism, as well as reducing thermogenesis. Clinically these disturbances may manifest as chronic fatigue, increased cold intolerance and noticeable changes in weight which have a profound impact on the child's energy levels and physical activity and quality of life. Moreover, these metabolic dysregulations can be a basis for predisposing children to other endocrine or metabolic disorders later in life when left undiagnosed and untreated.

Iodine deficiency can also play a major role in pubertal delay. The underlying mechanisms are complex and they involve intricate interplay within the rather broader endocrine system. Thyroid hormones are closely interwoven in the entire endocrine system of the body and deficiency can lead to the dysfunction of the very fine equilibrium of the hypothalamic-pituitary-gonadal axis, responsible for the initiation and regulation of puberty (Iannuzzo et al., 2022; Nyström et al., 2016). Such disruption can cause delay in the appearance of secondarily sex characteristics and menarche in girls with considerable psychosocial impacts on affected adolescent girls in addition to inherent physiological implications (Iannuzzo et al., 2022; Nyström et al., 2016). Adolescents are a particularly vulnerable demographic; they tend to have inadequate levels of iodine, owing to an increased metabolic demand during the growth spurt coupled with changing eating behaviours, e.g., decreased consumption of milk, and increased consumption of processed foods that are commonly fortified with non-iodized salt (Daniel et al., 2017; Nyström et al., 2016; Seetharaman et al., 2024). These converging factors make the risk of pubertal delay and other thyroid related problems even higher, making the need for specific interventions for this age group very pertinent. The clinical picture might also be complicated by the presence of co-existence of micronutrient deficiencies. For example, the lack of iron and selenium is of particular interest because they are essential cofactors for many enzymes in both thyroid hormone synthesis and metabolism and their absence can further decrease the thyroid function and worsen the clinical effects of iodine deficiency (Köhrle, 2023; Strombom, 2020). Additionally, the environmental goitrogens, which are substances present in some food sources (e.g., cruciferous vegetables, such as broccoli and cabbage) or chemical compounds (e.g., perchlorates), could interfere with the uptake or organification of iodine within the thyroid gland, making the effects of insufficient iodine intake even more pronounced and could further worsen the adverse clinical outcomes (Ahmad et al., 2021; Đuričić et al., 2022).

Finally, the effects of iodine deficiency reach on oral and craniofacial development. Although the specific details about these consequences are less well elaborated in general literature as compared with the neuro-cognitive consequences, the rather extensive roles of thyroid hormones in growth (in general), cellular differentiation, and tissue maturation in multiple organ systems strongly suggest their critical role in the complex nature of the processes underlying oral and craniofacial morphogenesis. The influence of thyroid hormones on bone development and remodeling is well known - processes necessary for proper development of the facial structures and timely occurrence of tooth eruption. Disruptions to these basic processes during the early stages of development could in theory cause anomalies in jaw development, inappropriate tooth formation, and generally faulty facial asymmetry. Further specific research in this area would greatly improve our understanding of the specific mechanisms and degree of these impacts. It is also important to realize that the delicate balance that is required for optimal thyroid function is inherently fragile, and both a lack of iodine and chronic iodine excess may disrupt the homeostasis of thyroid function, leading to a variety of thyroid dysfunctions. This is commonly referred to as "U" shaped association between iodine exposure and risk of thyroid disease (Kalarani & Veerabathiran, 2022; Lee et al., 2023). The dual risk highlights the complexity of determining and implementing the strategy of iodine supplementation, especially in the context of personalized medicine (in which the overall aim is to find the best balance between the intake of iodine and the targeted avoidance of under- and overdosing)(Steffens et al., 2023). The future of medicine, which looks to digital tools

and a better understanding of an individual's unique genetic predisposition, environmental exposure and lifestyle factors, in an effort to refine diagnostic accuracy and target prevention and treatment strategies, is known as precision medicine, and holds immense promise for the refinement of diagnostic accuracy and individualization of prevention and treatment strategies for these diverse pediatric endocrine disorders (Bidlingmaier et al., 2022; Fernández-Luque et al., 2021). This individual approach is particularly pertinent for highly vulnerable groups such as pregnant and lactating women and young children, owing to their distinctly higher iodine needs, which requires careful and context-specific consideration in order not to create a situation of iodine deficiency or even potential iodine excess (Delange, 2007; Guo et al., 2025; Iannuzzo et al., 2022; Untoro et al., 2007). Therefore, a careful and continuous assessment using a comprehensive battery of diagnostic tools that include urinary iodine concentration, level of serum thyroglobulin and TSH, all with age-specific reference ranges, are important to a successful intervention and ultimately optimal health and developmental outcome throughout childhood (Brough, 2022; Prpić, 2021; Soliman et al., 2025; Verhagen et al., 2020; Wallborn et al., 2020).

Current iodine supplementation strategies

Current iodine supplementation strategies are mainly guided by wide-scale public health interventions aimed at lowering the persistent prevalence rate of iodine clinical consequences of deficiency, which are a major risk factor among paediatric populations (Bertinato, 2021; Feei & Brough, 2025; Zimmermann & Andersson, 2021). Central to these efforts has been the implementation of USI, which has been shown to be successful in decreasing the prevalence of disorders associated with iodine deficiency in diverse regions of the world during the past 3 decades, by substantially increasing the dietary intake of iodine of a significant proportion of the population (Bertinato, 2021; Rohner et al., 2020; Zimmermann & Andersson, 2021). The approach involves iodination of widely used common table salt and therefore covers a large segment of the population through a simple dietary item.

Specific recommended daily allowances for iodine are strictly determined by such authoritative bodies as the WHO, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, and the American Thyroid Association. These guidelines provide recommendations for the public health programs as well as for the individual clinical management with regards to optimal iodine intake at different stages of development: for children aged 0-5 years 90 micrograms, for 6-12 years 120 micrograms, and for adults and pregnant or lactating women 150 and 250 micrograms, respectively (Guo et al., 2025; Zimmermann & Andersson, 2021). Complementary biomarkers that include TSH and serum thyroglobulin are nowadays recognized increasingly for their usefulness to examine iodine status and thyroid function, especially in vulnerable groups of the population. TSH, for example, plays a critical role in neonatal screening for congenital hypothyroidism (Berlińska & Świątkowska-Stodulska, 2024; Brough, 2022; Delange, 2007; Feei & Skeaff, 2014; Ristić-Medić et al., 2009; Sivalogan et al., 2025; Soliman et al., 2025). Clinical controversies and emerging concerns about the health implications of iodine excess highlight the limitations inherent in a "one size fits all" paradigm and an imperative to refine interventions (Lee et al., 2023; Seetharaman et al., 2024). Factors such as concomitant micronutrient deficiency (e.g selenium, iron) and exposure to environmental goitrogens make the efficacy of supplementation programmes more complex and influence thyroid function (Ahmad et al., 2021; Ayalew et al., 2021; Đuričić et al., 2022; Köhrle, 2023; Strombom, 2020).

Consequently, while the provision of universal salt iodization remains a highly effective public-health intervention, iododormion supplementation in modern times has a tendency to move towards the more individual and targeted approach, often with the application of principles of precision medicine to optimise iodine intake whilst taking great care to avoid under- or overdosing, especially in vulnerable paediatric populations (Bidlingmaier et al., 2022; Fernández-Luque et al., 2021; Iannuzzo et al., 2022; Steffens et al., 2023). Such ongoing refinement is needed to ensure that the amount of iodine provided to children is commensurate with their particular physiologic needs to protect their cognitive and physical development from the adverse effects of iodine deficiency and excess.

Precision Medicine and Innovations in the Future

The field of precision medicine is a promising one, and could change the course of pediatric endocrinology, especially as it relates to iodine supplementation. Rather than relying on generalized one size fits all public health strategies, it calls for highly individualized interventions that aim to prevent thyroid disorders occurring in children. This new sophisticated paradigm brings the integration of the individual unique genetic profile, environmental exposures and lifestyle factors for the patient to the forefront, greatly improving

the accuracy of diagnosis and facilitating the carefully designed prevention and treatment protocol (Bidlingmaier et al., 2022; Fernández-Luque et al., 2021). A fundamental aspect of this paradigm is an exquisite knowledge of the genetic variability in thyroid hormone metabolism; individual differences in genes containing the code for key proteins can have a dramatic effect on the homeostasis of iodine (Steffens et al., 2023). For example, polymorphisms of the sodium-iodide symporter modulate the uptake of iodide into follicular cells, whereas alterations of the thyroid peroxidase gene modulate the generation of hormones and genetic variations in deiodinase enzymes (D1, D2, D3) modulate the peripheral conversion of T4 into the more active T3 or its inactivation (Carro & Nicola, 2022; Li & Zhang, 2022; Lipp, 2021; Russo et al., 2021; Salas-Lucia & Bianco, 2022; Wang et al., 2020). As a result, certain inherent genetic differences influence the way individuals absorb, metabolise and respond to iodine, and this can shape a person's susceptibility to IDD, or, conversely, dysfunction that may develop due to an iodine excess (Kalarani & Veerabathiran, 2022). This refined understanding is important for the development of truly personal supplementation strategies that go far away from current recommended daily allowances to consider the physiology of personal demands (Guo et al., 2025; Iannuzzo et al., 2022). The dream is to have an optimal iodine intake for each child, with a precise adjustment of dosage to avoid under- or overdosing, a very important objective given the established U-shaped relationship between iodine exposure and risk of thyroid disease (Kalarani & Veerabathiran, 2022; Lee et al., 2023).

For such precision to be realised, the use of advanced biomarkers and metabolomics is becoming indispensable. While urinary iodine concentration is still useful in population-level surveillance, some limitations in individual evaluation, particularly in paediatric cohorts because of variable urine volumes and age-dependent creatinine excretion, are well known (Beckford et al., 2019; Iannuzzo et al., 2022; Wallborn et al., 2020). In the light of precision medicine, a laboriously assembled collection of biomarkers is an indispensable aid. This array should include age- and sex-specific reference intervals for thyroid-stimulating hormone (TSH), free thyroxine (fT4), and serum thyroglobulin. The latter biomarker, being highly sensitive to both iodine deficiency and excess, however requires further validation of assay specific reference ranges in infants (Berlińska & Świątkowska-Stodulska, 2024; Brough, 2022; Feei & Skeaff, 2014; Pearce & Caldwell, 2016; Ristić-Medić et al., 2009; Sivalogan et al., 2025; Soliman et al., 2025). Beyond classical assays, metabolomic profiling provides an extensive overview of the biochemical environment of a person and can reveal subtle metabolic perturbations that can refer to iodine insufficiency or subclinical thyroid dysfunction before obvious clinical signs appear and therefore allow for earlier and more specific interventions (Bidlingmaier et al., 2022; Fernández-Luque et al., 2021). Concurrently, the emerging studies on the microbiome-thyroid axis interactions shed light on another and complex layer that affects iodine status and thyroid health. The gut microbiome modulates the absorption of nutrients, such as iodine, induces alterations in the enterohepatic circulation of thyroid hormones and modulates systemic immune responses leading to predisposition to autoimmune thyroid disease (Ahmad et al., 2021; Đuričić et al., 2022). Future innovations in precision medicine may be targeted dietary interventions, specific prebiotics, or probiotic formulations aimed at optimizing the composition of the gut microbiota to improve iodine utilization and provides support of the general thyroid function of susceptible children.

Concurrently, the technology developments are leading the way to novel ways of approaching delivery and constant monitoring. Nano-formulations and better bioavailability is a great leap in iodine supplementation. Nanoparticle encapsulated iodine may have the advantages of improved absorption, protection against degradation, and targeted delivery to specific tissues, thus leading to more consistent and stable levels of iodine in the pediatric patients who may have difficulty with conventional supplementation due to their absorption issues or rapid excretion (Steffens et al., 2023). This innovative approach could overcome barriers to efficacy and safety and this can result in more predictable physiological responses and minimal fluctuations that can be experienced with traditional iodine sources. Finally, integration of digital monitoring tools is an important aspect of the adaptive management of precision medicine. These tools include a broad range of technologies, such as wearable sensors, mobile health applications, and advanced telehealth technologies, which can deliver continuous and real-time data (Fernández-Luque et al., 2021). Such data streams can include the exact monitoring of dietary iodine intake, real-time monitoring of urinary iodine excretion patterns, symptoms and adherence to personalised supplementation regimens. Using artificial intelligence and machine learning algorithms, these are digital tools that can analyze huge amounts of individual data to identify trends, make predictions to prevent potential imbalances and dynamically adjust supplementation protocols.

The emerging field of precision medicine promises to change the face of pediatric endocrinology, specifically with regard to iodination, from generalized, "one-size-fits-all" public health strategies to highly

individualized interventions to prevent thyroid disorders in children (Bidlemaier et al., 2022; Fernández-Luque et al., 2021). This cutting-edge paradigm promotes the integration of a patient's individual genetic makeup, environmental exposures and lifestyle factors to greatly improve the accuracy of diagnosis and carefully customize prevention and treatment protocols (Bidlemaier et al., 2022; Fernández-Luque et al., 2021). A cornerstone of this shift includes a greater knowledge of genetic variability in the metabolism of thyroid hormones, recognizing that individual variability in the genes for important proteins can have a strong influence on iodine homeostasis due to, for example, genetic polymorphisms affecting the sodium iodide symporter, which can directly affect the uptake of iodide into thyroid follicular cells; or genetic variability in thyroid peroxidase, which can affect your ability to synthesize hormones; or genetic variability in deiodinase enzymes (D1, D2, D3) leading to variations in the peripheral conversion of T4 to the more active form T3 or its inactivation (Carro & Nicola, 2022; Li & Zhang, 2022; Lipp, 2021; Russo et al., 2021; Salas-Lucia & Bianco, 2022; Steffens et al., 2023; Wang et al., 2020). Such intrinsic genetic variations mean that individuals will absorb, metabolize and react to iodine differently and thus determines their unique predisposition to IDD's or even predisposing them to thyroid dysfunction from iodine excess (Kalarani & Veerabathiran, 2022). This nuanced understanding is absolutely important in order to develop truly personalized supplementation strategies that are able to move beyond current recommended daily allowances and take into account an individual's specific physiological requirements (Guo et al., 2025; Iannuzzo et al., 2022). The goal is to find the optimal intake of iodine for each child, carefully walking through the fine line that must be found in order to avoid under or overdosing, in a crucial imperative situation, since the existence of a "U-shaped" relationship between the amount of iodine exposure received in the population and the risk of developing thyroid pathologies has been established (Kalarani & Veerabathiran, 2022; Lee et al., 2023). In order to make it possible to achieve such precision, advanced biomarkers and metabolomics are becoming indispensable. While the urinary iodine concentration is a useful tool for monitoring at a population level, it has established limitations for use in evaluating individuals, especially among the pediatric population owing to variable urine volumes and age-dependent creatinine excretion (Beckford et al., 2019; Iannuzzo et al., 2022; Wallborn et al., 2020). Precision medicine approaches will incorporate an extensive collection of biomarkers such as age and sex-specific reference ranges of thyroid-stimulating hormone fT4, and serum thyroglobulin which is a sensitive marker of both iodine deficiency as well as excess, but with a recognized need for further validated assay-specific reference ranges for infants (Berlińska & Świątkowska-Stodulska, 2024; Brough, 2022; Feei & Skeaff, 2014; Pearce & Caldwell, 2016; Ristić-Medić et al., 2009; Sivalogan et al., 2025; Soliman et al., 2025). Beyond these, metabolomic profiling, which presents a detailed picture of the biochemical state of an individual, offers the possibility of determining subtle metabolic changes pointing to an iodine insufficiency or to a subclinical thyroid dysfunction, long before the first signs of overt clinical symptoms appear, thus allowing earlier and more targeted interventions (Bidlemaier et al., 2022; Fernández-Luque et al., 2021). Furthermore, the emerging studies of microbiome grub etc thyroid are making us aware of another complicated level of influence on iodine status and thyroid health. The gut microbiome is multifaceted in its role, influencing the absorption of nutrients, such as iodine and influencing the enterohepatic circulation of the thyroid hormones, as well as modulating immune responses throughout the body which can have an effect on autoimmune thyroid diseases (Ahmad et al., 2021; Đuričić et al., 2022). Future innovations in precision medicine may be targeted dietary interventions, specific prebiotics, or probiotic formulations aimed at optimizing the composition of the gut flora to improve iodine utilization and provides support of the general thyroid function of susceptible children. Concurrently, the technology developments are leading the way to novel ways of approaching delivery and constant monitoring. Nano-formulations and better bioavailability is a great leap in iodine supplementation. Nanoparticle encapsulated iodine may have the advantages of improved absorption, protection against degradation, and targeted delivery to specific tissues, thus leading to more consistent and stable levels of iodine in the pediatric patients who may have difficulty with conventional supplementation due to their absorption issues or rapid excretion (Steffens et al., 2023). Finally, integration of digital monitoring tools is an important aspect of the adaptive management of precision medicine. These tools include a broad range of technologies, such as wearable sensors, mobile health applications, and advanced telehealth technologies, which can deliver continuous and real-time data (Fernández-Luque et al., 2021). Wearable sensors, continuously miniaturised and robust to be used in children, can be used to non-invasively monitor physiological parameters such as heart rate, respiratory rate and levels of activity and there are developments towards devices able to monitor various other biomarkers from biofluids such as sweat or interstitial fluid, although the direct measurement of iodine levels is currently a research frontier (Kim et al., 2023; Magsayo & Khatami, 2025; Wong et al., 2023; Zhou et al., 2024). Mobile health applications can be important interfaces

to monitor dietary intake in detail, thus enabling parents or older children to record food intake containing iodine, to monitor adherence to nutritional guidelines, as well as helping to monitor symptoms or adherence to medication for chronic diseases (Majeed-Ariss et al., 2015; Rashid, 2024). These apps can also support personalised education and inform the collection of data for measurement of iodine status including the prompt and recording of information relating to the collection of urinary samples, although app-guided UIC measurement is not currently widely established in clinical practice (Seetharaman et al., 2024). Telehealth platforms are another way of expanding the precision medicine approach by facilitating remote consultations and virtual follow-ups, and interdisciplinary collaboration between healthcare providers, which is particularly important for areas with pediatric patients in remote and not so accessible areas or those with limited access to specialized endocrine care (Mercuri et al., 2021). These platforms can secure transmission of the wealth of patient-generated health data from wearables and mobile apps to clinicians for proactive clinical management and greater engagement of both patients and families in a child's health care (Chow et al., 2024; Foster et al., 2022; Whitehead et al., 2023).

Such data streams enable collection of large and longitudinal data important for pediatric health research, sustainable and scalable infrastructures for routine data management, and enable better understanding of the complex interplay of factors affecting pediatric health (Foster et al., 2022; Mozún et al., 2024; Vesoulis et al., 2022). With the help of artificial intelligence and machine learning algorithms these digital tools are able to analyze large amounts of data, both individual and population level, to detect trends, predict possible imbalances in iodine status and adapt supplementation protocols dynamically. This gives both clinicians and families actionable insights which helps promote an active treatment towards the iodine nutrition and thyroid health management (Dhanka et al., 2025; Giorgini et al., 2023; Lu et al., 2025; Mehta et al., 2025). Moreover, such digital platforms are capable of integrating various data streams such as environmental data such as local iodine content in drinking water or soil in combination from satellite-based sensors to provide a broad understanding of an individual's iodine exposure and risk factors (Bondi et al., 2022; Clark et al., 2024; Pinchoff et al., 2019; Yang et al., 2021). This ability to combine information about the environment with genetic and lifestyle information is an unprecedented chance to develop highly individualized and adaptive approaches for iodine supplementation; to move beyond the generalized recommendations to meet the unique needs of each child. Ultimately, by combining synergistic effects of understanding genetic predispositions, evidence-based advanced biomarkers, environmental factors, and state-of-the-art digital technologies, precision medicine is attempting not only to prevent the global load of iodine deficiency and its associated neurocognitive impairments but also to guarantee optimum health and developmental pathways for every child in a truly (Bertinato, 2021; Delange, 2007; Feei & Brough, 2025; Liu et al., 2025; Milanesi & Brent, 2016; Rohner et al., 2020; Untoro et al., 2007; Zimmermann, 2011; Zimmermann & Andersson, 2021).

Digital Health Instrument and Artificial Intelligence in Individualized Iodine Supplementation

As a flexible and complex arena for pediatric endocrinologic care and thyroid hormone supplementation, the integration of digital monitoring tools is fast becoming an indispensable part of the adaptive management that is inherent in precision medicine. These innovative tools include a wide range of technologies, from sophisticated wearable sensors, sophisticated mobile health apps to complex telehealth platforms, all of which aim to deliver continuous real-time data which is critical in individualizing care (Fernández-Luque et al., 2021). The possibilities for innovation in this area are huge and go way beyond the ability to collect data to include predictive analytics, personalized intervention, and proactive health management.

Advanced wearable biosensors are one of the frontiers of non-invasively monitoring patients, especially in pediatrics. While current wearables are good at tracking general physiological numbers such as heart rate, respiratory rate, and activity levels, the next generation of wearables seeks to offer direct biochemical tracking (Kim et al., 2023; Magsayo & Khatami, 2025; Wong et al., 2023; Zhou et al., 2024). Imagine being able to have miniaturized, skin-interfaced biosensors that can continuously and non-invasively measure iodine metabolites, thyroid hormone levels or specific micro-RNAs indicative for thyroid function from biofluids like sweat or interstitial fluid. This capability would overcome the limitations of intermittent blood tests or single spot urine samples that only give a snapshot on the iodine status, which can be especially difficult for pediatric collection (Beckford et al., 2019; Iannuzzo et al., 2022; Wallborn et al., 2020). The development of such advanced sensors poses great engineering challenges in the categories of accuracy, selectivity, miniaturization, biocompatibility, long-term stability, and power management. Moreover, the data produced by these continuous monitors would be voluminous and complex and require powerful algorithms to filter out the noise, guarantee data integrity and detect clinically relevant patterns. For example, very small variations over time in

the amount of iodide present in sweat over the course of a day may yield a more dynamic picture of iodine intake and metabolism than the traditional methods, to be able to adjust dietary recommendations or the dosing of supplementation in real time. The capability to monitor several biomarkers simultaneously and continuously, including biomarkers related to co-factors micronutrients such as selenium and iron, could offer an overview of the thyroid health situation in order to detect a potential deficiency or excess of the micronutrients before they lead to overt clinical symptoms (Köhrle, 2023). The development of 'smart patches' or 'e-skin' technologies, integrating cross-modal perception and wireless communication, promises to make such detailed, non-invasive monitoring a reality, reducing the responsibility on children and their caregivers while vastly improving the level of detail (Kim et al., 2023; Zhou et al., 2024).

The sophistication of artificial intelligence and machine learning models are of paramount importance in turning this wealth of continuous data into something that can be used to take action. Going beyond mere trend analysis, AI algorithms with capabilities that go far beyond can create individual predictive models for each child. These models would incorporate genetic vulnerabilities (i.e., polymorphisms in iodine transporters/deiodinases), environmental factors (i.e., iodine content in drinking water, presence/absence of goitrogens using sensors from space-borne satellites), diet (e.g., daily habits using mobile devices), and real-time physiological data (e.g., daily physiological data from wearable devices) (Bondi et al., 2022; Carro & Nicola, 2022; Clark et al., 2024; Li & Zhang, 2022; Pinchoff et al., 2019; Russo et al., 2021; Wang et al., 2020; Yang et al., 2021). For instance, a reinforcement learning algorithm might be capable of adjusting recommended iodine doses or the supplement dosage dynamically based on a particular child's unique response to the food, activity, and observed changes in biomarkers to optimize the balance to ensure thyroid euthyroidism in the absence of iodine deficiency nor excess (Steffens et al., 2023). This approach to adaptive learning would be a major advance over current static guidelines allowing truly dynamic and individualized care. AI could also enable the development of "digital twins" for pediatric patients - virtual versions that will simulate an individual's physiological responses to various interventions of iodine, enabling clinicians to test out different scenarios virtually before testing them in real life. Furthermore, AI-driven anomaly detection systems may be able to identify some obvious deviations in biomarker patterns which may be associated with the early stages of another thyroid dysfunction or non-compliance with a regimen, allowing for timely clinical intervention. The integration of AI for processing of multimodal data such as electronic health records, imaging, and wearable sensor data would greatly improve diagnostic accuracy, treatment personalization and even help to have pre-emptive medicine for thyroid disorders (Dhanka et al., 2025; Giorgini et al., 2023; Lu et al., 2025). However, the development and implementation of such AI/ML systems into pediatric care requires rigorous validation of the method, addressing possible biases in the algorithms, ensuring privacy of the data, and developing trust between caregivers and patients (Chow et al., 2024).

Enhanced mobile health applications will be the main interface of patients and caregivers in this precision medicine framework and will become intelligent and interactive health coaches. Beyond the simple logging of dietary intake and medication adherence, these apps will feature gamification techniques to boost engagement and compliance, especially among adolescents who typically have a deficiency in their iodine levels due to changing dietary habits (Daniel et al., 2017; Majeed-Ariss et al., 2015; Nyström et al., 2016; Rashid, 2024). Imagine apps which offer educational modules to reach consumers with interactive recipes on iodine rich foods and personalised recipes as well as virtual rewards for achieving nutritional goals. They could also incorporate the techniques of cognitive behavioral therapy to assist manage anxiety that is related to chronic conditions or encourage healthy behaviors. Personalized feedback from the AI system through the app could explain in an age appropriate and culturally sensitive manner why certain adjustments are being made to their iodine plan. Moreover, mobile health applications could be used to develop peer support networks, where children and families with similar experiences can connect with each other and share what they are experiencing, so that they can feel less isolated and become more motivated. Augmented reality features could for instance enable children to scan food items in order to see at a glance how much iodine they contain or allow interaction with educational content in an interesting way. These apps would be crucial in monitoring symptoms so that caregivers can report new or worsening symptoms that could indicate thyroid imbalance which would then interact with sensor data and AI analytics to see if there are alerts for clinical review. The design of these apps needs to focus on ensure that the apps are user-friendly, offer data security, and promote accessibility across a variety of socioeconomic and technological landscapes to promote equitable access and engagement (Whitehead et al., 2023).

The development of telehealth platforms will also be revolutionary. Moving beyond the simple video consultation, the future of telehealth solutions could see virtual reality environments being added for more

immersive and engaging educational sessions with patients or even remote physical examinations using special purpose peripherals. Imagine being able to perform virtual thyroid palpation or assessment of growth parameters in a child with haptic feedback and high resolution imaging sent via a secure telehealth platform from a fairly remote location. AI driven chatbots could be used to provide first line support for routine queries, triaging urgent concerns, and guiding the data collection process for caregivers, freeing up the time of human clinicians for more complex cases. These platforms will work as a central place to gather securely all the patient generated health data, together with clinical data, and transmit it to the healthcare team (Foster et al., 2022; Mercuri et al., 2021). This smooth data flow allows proactive clinical management, in which virtual multidisciplinary team meetings and ensuring that specialists can communicate effectively, no matter the geographical distance. For pediatric patients living in remote or underserved regions, such increased telehealth capabilities may be a dramatic way to enhance access to specialty endocrine care and overcome geographical barriers and inequalities in health.

Finally, the complex integration of multi-omic data into a single platform, including genomics, proteomics, metabolomics, and microbiomics, will be the scientific platform for these innovations. Genetic sequencing can be used to recognize the variants of iodine metabolism and thyroid hormone that impact thyroid hormones and we can do personalized risk stratification and prophylactic interventions (Steffens et al., 2023). Proteomics can inform about expression patterns of protein related to thyroid function, while metabolomics can identify specific metabolic pathways affected by the state of iodine and this offers very sensitive indicators for subtle imbalances before overt clinical changes occur (Bidlemaier et al., 2022). Research into microbiome-thyroid interactions will help to inform specific dietary interventions or certain prebiotics, or probiotic formulations aimed to optimize the composition of gut microbiota and consequently improve iodine utilization and support overall thyroid function (Ahmad et al., 2021; Đuričić et al., 2022). The difficulty is combining and interpreting these massive and diverse datasets in a clinically relevant way, where advanced AI/ML algorithms come in handy (Mehta et al., 2025). This convergence of biological, clinical, environmental, and digital data enables the development of truly comprehensive, dynamic, and individual iodine management plans to be developed.

However, the successful implementation of these innovations also requires careful consideration of ethical considerations and regulatory frameworks. Issues such as data privacy, cybersecurity, informed consent for data sharing, algorithmic bias and equitable access of these leading-edge technologies are paramount especially in the context of vulnerable pediatric populations. Regulatory bodies will have to keep up quickly with the rate of technological development, to ensure the safety, efficacy, and ethical implementation of these digital health solutions. Building trust between caregivers and patients, as well as between healthcare providers and patients, will be key to widespread adoption and success of these new technologies (Chow et al., 2024). Moreover, these digital tools are part of the generation of huge volumes of real-world evidence, which can feed back into a "learning health system" in a continuous loop. This continuous process of data collection, analysis, intervention and outcome evaluation enables the ongoing refinement of best practices and guidelines of pediatric iodine supplementation with the goal of the future being a place where care is not only personalized but continually improving based upon collective insights (Mozún et al., 2024; Vesoulis et al., 2022).

This enables clinicians and families to have concrete information to proactive control the iodine nutrition and the thyroid health. Ultimately, the synergistic combination of an understanding of genetic predispositions, cutting-edge biomarkers and environmental influences, and innovative digital technologies, is the goal of precision medicine, to not only prevent the global burden of iodine deficiency and associated neurocognitive impairments but to ensure optimal health and developmental trajectories of every child in a truly individualised (Bertinato, 2021; Delange, 2007; Feei & Brough, 2025; Liu et al., 2025; Milanesi & Brent, 2016; Rohner et al., 2020; Untoro et al., 2007; Zimmermann, 2011; Zimmermann & Andersson, 2021).

Discussion

Future medicine shift away from conventional, generalized iodine supplementation towards highly individualized interventions is appropriate. This paradigm shift is driven by the need to take into account the unique genetic profile of the child, the environmental determinants and lifestyle factors in an individual's life in precision iodine strategies and in this way move away from a "one size fits all" paradigm. A deeper understanding of genetic variability in thyroid hormone metabolism is underlined as critical to tailor-made time- and individual-specific supplementation; to allow an optimal intake of iodine to be established, preventing either deficiency or excess. Including more high-tech biomarkers including serum thyroglobulin and metabolomics profiling, allows more accurate assessment of the individual tuberculosis status and enables

the early identification of early dysregulations. Moreover, the authors reinforce the central role of the digital monitoring tools, such as wearable sensors, mobile health apps, and complex telehealth systems, which provide continuous and real-time data. When coupled with technological advances of artificial intelligence and machine learning algorithms, these technologies allow for dynamic prediction, early intervention and adaptive calibration of supplementation protocols. This holistic approach to iodine nutrition, involving significant integration, ultimately aims to guarantee ideal iodine nutrition and positive neuro-developmental outcomes for every child under a continually evolving and improving healthcare framework.

Conclusions

The transformation to precision medicine in ending pediatric endocrinology is a shift from iodine supplementation. By synergistically combining knowledge about the genetic predispositions, advanced biomarkers and environmental influences with state-of-the-art digital technologies, the goal is to move beyond the general recommendations and to meet the individual needs of each child. It is hoped that this individualized framework will help to alleviate the burden of iodine deficiency worldwide and associated neuro-cognitive impairments to ensure optimal health and developmental trajectories. The ongoing fusion of data, from wearable sensors, mobile applications and telehealth platforms, reviewed by artificial intelligence and machine learning will support the proactiveness of Iodine nutrition and thyroid management, making the care both personalized and also adaptively improved over time. This entire approach is a crucial step towards protecting the wellbeing of the children in this modern era of medicine.

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