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Thyroid Function in Infants, Children, and Adolescents: Age-Dependent Physiology, Biochemical Patterns, and Early Markers of Pediatric Thyroid Disease: A Narrative Review

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Abstract

Background: Thyroid hormones are critical for neurocognitive development, linear growth, and metabolic homeostasis in early life, yet pediatric thyroid physiology differs substantially from adult patterns. Age- and assay-specific interpretation of thyroid function tests (TFTs) is therefore essential to distinguish normal developmental variation from early thyroid disease in infants, children, and adolescents.

Methods: We conducted a narrative review of studies published from 1990–2025 in PubMed, Scopus, and Google Scholar that reported pediatric TSH and/or free thyroxine (FT4) reference intervals, distributions of FT4–TSH patterns, prevalence and natural history of subclinical hypothyroidism (SH), hyperthyroxinemia/hyperthyroidism, and thyroid autoantibody epidemiology. Population-based cohorts, hospital series, longitudinal studies, systematic reviews, and major guidelines were prioritized; data were synthesized descriptively into six clinically oriented tables.

Results: Across large normative cohorts from Europe, Asia, and South America, TSH and FT4 show a consistent trajectory: postnatal surge, higher values in infancy, gradual decline through childhood, and convergence toward adult ranges in adolescence, with notable assay- and population-dependence. In unselected pediatric TFTs, >70–85% of results are euthyroid, while abnormal patterns cluster into a minority: SH (normal FT4, elevated TSH) in ~2–8% overall—higher in iodine-deficient, obese, or high-risk groups; overt primary hypothyroidism (low FT4, high TSH) in <1–2%; central patterns (low FT4, non-elevated TSH) and TSH-resistance phenotypes are rare and largely confined to specialized cohorts. Longitudinal data show that idiopathic mild SH (TSH <10 mIU/L, antibody-negative) normalizes or remains stable in most children, whereas SH associated with Hashimoto thyroiditis, goiter, or higher baseline TSH progresses to overt hypothyroidism in up to 30–50% over several years. True pediatric hyperthyroidism is uncommon; Graves' disease accounts for ≈95% of cases with incidence generally <1 per 100,000 child-years, while many instances of biochemical hyperthyroxinemia represent transient thyroiditis or analytical interference rather than persistent thyrotoxicosis. Thyroid peroxidase and thyroglobulin antibodies are detected in roughly 4–12% of older children and adolescents in population surveys, with marked female predominance and rising prevalence around puberty; antibody-positive children exhibit higher rates of SH and are at substantially increased risk of progression to overt hypothyroidism. A simplified clinical algorithm integrating these patterns supports risk-stratified follow-up instead of uniform treatment.

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Conclusions: Pediatric thyroid assessment must account for age, assay, iodine status, and autoimmunity. Most mild TFT abnormalities are transient or adaptive, whereas persistent TSH elevation with antibodies or low FT4 identifies children at highest risk. Applying population-appropriate reference intervals and a risk-based monitoring strategy can improve early diagnosis and long-term management of pediatric thyroid disorders while minimizing overdiagnosis and unnecessary therapy.

Keywords: Pediatric thyroid function; Subclinical hypothyroidism; Graves' disease; Thyroid autoimmunity; Reference intervals, Free thyroxine, TSH.

1. Introduction

Thyroid hormones are essential for fetal brain maturation, linear growth, bone mineralization, and metabolic homeostasis, with particularly critical roles in late gestation, the neonatal period, and early infancy. (1,2) In these windows, even brief deficiencies can lead to irreversible neurocognitive impairment, while excess hormone exposure accelerates bone age and can compromise adult height. (1–3) The hypothalamic–pituitary–thyroid (HPT) axis undergoes dynamic maturation from birth through adolescence, making pediatric thyroid physiology distinct from adult patterns and necessitating age-specific interpretation of thyroid function tests (TFTs). (2,4)

Large population studies have demonstrated that serum TSH and free thyroxine (FT4) follow characteristic age-related trajectories, with a postnatal surge, gradual decline through childhood, and partial re-modulation around puberty. (5–7) Retrospective cohorts from Austria, South America, Asia, and Brazil show higher TSH and FT4 in early life, with progressive convergence toward adult-like ranges in mid-to-late adolescence. (5–9) These reference intervals are also assay- and population-dependent, implying that extrapolating adult cut-offs or foreign pediatric ranges to local children can lead to misclassification of both hypothyroidism and hyperthyroidism. (5,8,10)

The spectrum of pediatric hypothyroidism includes congenital hypothyroidism (CH), autoimmune thyroiditis, iatrogenic or central hypothyroidism, and mild biochemical disturbances such as subclinical hypothyroidism (SH). (2,11) CH, the most common neonatal endocrine disorder (≈1:2000–1:3000 births in iodine-replete regions), is now routinely detected through newborn screening, but residual diagnostic and treatment timing gaps remain in many countries. (12,13) In school-age children and adolescents, autoimmune thyroid disease (AITD)—primarily Hashimoto thyroiditis (HT)—emerges as the leading cause of acquired hypothyroidism, with reported prevalence up to 2% in children and almost 10% in adolescents, with clear female predominance. (14–17)

Subclinical hypothyroidism, defined by elevated TSH with normal FT4, has been increasingly recognized in children due to expanded TFT use. (18,19) Population-based cohorts from India, Israel, and other regions report SH prevalence typically between 2–8%, but with wide variation related to iodine status, autoimmunity, obesity, and assay cut-offs. (18–21) Systematic and narrative reviews emphasize that mild, idiopathic SH (TSH 5–10 mIU/L) often has a benign course, whereas SH associated with positive thyroid antibodies, goiter, or increased TSH (>10–15 mIU/L) carries greater risk of progression to overt hypothyroidism. (19,22–24)

Hyperthyroidism in childhood is less common but clinically important. Graves' disease (GD) accounts for 10–15% of pediatric thyroid disorders and ≈95% of hyperthyroidism cases in many cohorts, with an incidence around 1–14 per 100,000 child-years and strong female predominance. (25–28) However, biochemical hyperthyroxinemia (high FT4, low TSH) detected during routine screening frequently reflects transient TSH suppression, non-thyroidal illness, or analytical interference rather than persistent GD. (29–31) Differentiating transient or artifactual abnormalities from true thyrotoxicosis is essential to avoid over-treatment and unnecessary anxiety. (29,31)

Autoimmune thyroid antibodies—thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb)—are key markers of evolving AITD and often precede overt biochemical dysfunction. (16,32) Epidemiologic data from Europe, the United States, and Asia show antibody positivity in roughly 4–12% of older children and adolescents, with higher rates in females and in those with other autoimmune conditions. (16,33–36) Longitudinal studies of pediatric HT indicate that many antibody-positive children remain euthyroid or mildly hypothyroid for years, while a subset progresses to overt hypothyroidism, especially when baseline TSH is elevated or goiter is present. (14,16,37,38)

Interpretation of TFTs in children is further complicated by pre-analytical and analytical issues, including diurnal variation of TSH, assay-specific reference ranges, interference from heterophile antibodies or biotin, and non-thyroidal illness effects. (10,31,39) Recent expert reviews stress the importance of considering both FT4 and TSH together, using

age- and assay-specific reference intervals, and integrating clinical context (growth, puberty, comorbidities, medication use) when deciding on follow-up versus treatment. (2,10,19,39)

Despite numerous cohort studies and multiple authoritative reviews, there remains considerable heterogeneity in reported pediatric reference intervals, with substantial variations across regions, especially between Asian and European cohorts. Differences are noted in thresholds for defining subclinical hypothyroidism (SH) and hyperthyroxinemia, as well as in recommendations for monitoring antibody-positive children (18–22,31,39,40). Moreover, data from Middle Eastern and Gulf populations are comparatively limited, and local clinical practice frequently relies on imported reference ranges. Therefore, there is a need to synthesize global evidence on age-specific thyroid physiology and the patterns of SH, hyperthyroxinemia, and autoimmunity in children to guide context-appropriate early diagnosis and monitoring strategies in pediatric endocrine practice (2,18–22,31,40).

In this narrative review, we summarize published evidence on physiological and pathological changes in thyroid function from infancy through adolescence, focusing on age- and sex-specific reference patterns, distributions of FT4–TSH combinations, prevalence and natural history of subclinical hypothyroidism, biochemical hyperthyroxinemia, and thyroid autoimmunity, to inform improved early diagnosis and longitudinal monitoring of pediatric thyroid disorders.

2. Materials and Methods

2.1. Study design

This work is a narrative review structured around clinically relevant biochemical and immunologic patterns of thyroid function in pediatric populations.

2.2. Data sources and search strategy

We performed a comprehensive literature search in PubMed/MEDLINE, Scopus, and Google Scholar for articles published from January 1990 to October 2025. Search terms included combinations of:

- “pediatric” OR “child*” OR “adolescent*”
- “thyroid function tests” OR “TSH” OR “free T4” OR “FT4”
- “reference intervals” OR “reference ranges”
- “subclinical hypothyroidism”
- “hyperthyroxinemia” OR “thyrotoxicosis” OR “Graves disease”
- “autoimmune thyroiditis” OR “Hashimoto” OR “thyroid autoantibodies”
- “longitudinal” OR “natural history”

Reference lists of key systematic reviews, guidelines, and seminal cohort studies were hand-searched to identify additional relevant publications. (2,18,19,22,25,31,39,40)

2.3. Inclusion and exclusion criteria

We included studies that met the following criteria:

- Population: infants, children, and/or adolescents (<18 years).
- Outcomes: reported TSH and/or FT4 values, pediatric reference intervals, prevalence of SH, hyperthyroxinemia/hyperthyroidism, or thyroid antibody prevalence; or longitudinal changes in TFTs.
- Study type: population-based cohorts, hospital cohorts, longitudinal observational studies, randomized controlled trials (where relevant), systematic reviews, and clinical practice guidelines.
- Language: English.

We excluded:

- Studies with exclusively adult populations.
- Case reports or very small case series (<10 subjects) unless addressing rare but important conditions (e.g., interference syndromes) that clarify differential diagnosis.
- Papers lacking extractable data on the main review outcomes (e.g., editorials without data).
- Data extraction and synthesis

For each eligible study, we extracted:

- Country/region, setting (population vs hospital-based).
- Age range and sample size.
- Assays and reported reference intervals for TSH and FT4, where applicable.
- Prevalence of subclinical hypothyroidism and/or hyperthyroxinemia, ideally with age and sex stratification.
- Definitions used for SH and hyperthyroxinemia.
- Rates of thyroid autoantibody positivity (TPOAb, TGAb) by age and sex where reported.
- Longitudinal data on progression or resolution of biochemical abnormalities.

Given the heterogeneity of methodologies and definitions, formal meta-analysis was not attempted. Instead, data were synthesized descriptively and grouped into six tables mirroring key clinical questions: age-specific reference intervals, FT4–TSH pattern distributions, SH prevalence, representative SH series, hyperthyroxinemia prevalence/etiology, and autoantibody epidemiology.

2.4. Quality Appraisal and Evidence Hierarchy

In synthesizing the literature, we prioritized the highest levels of evidence relevant to pediatric thyroid function, placing systematic reviews, evidence-based guidelines, and large longitudinal or population-based cohorts at the top of the hierarchy. (18,19,22,25,31,39,40) Smaller observational studies and selected case series were included when they clarified characteristic biochemical patterns, rare diagnostic entities, or important sources of assay interference. (29,31,39) Study quality was appraised qualitatively, focusing on key methodological features including: adequacy of sample size and population representativeness; clarity and consistency in defining reference intervals, subclinical hypothyroidism, and hyperthyroxinemia; use of age-specific pediatric cut-offs; study design (prospective vs retrospective); and duration and completeness of follow-up when evaluating natural history. This approach ensured that the conclusions of the review reflect the most robust and clinically applicable evidence.

Table 1 Representative Pediatric Reference Intervals for TSH and Free T4 by Age

Study / Country	Age range (y)	n (approx.)	Assay / platform	TSH reference interval*	FT4 reference interval*	Key notes	Key references
Kapelari et al., Austria	0–18	~1200	Advia® immunoassays	Neonatal TSH higher; gradual decline; beyond infancy central 95% generally ≈0.5–4.0 mIU/L	FT4 higher in early months; age-related decline; mid-childhood stabilization	Classic European pediatric reference study with detailed age bands from birth to adulthood.	(5)
Chaler et al., Argentina	0.1–20	1,250	Chemiluminescence	Age-stratified TSH intervals; upper limits slightly higher in early childhood than in adults	FT4 progressively declines from infancy; relatively narrow range after early childhood	Provides South American pediatric reference intervals and confirms age-dependency across childhood.	(6)
Yao et al., China	0–18	>10,000	Chemiluminescence	TSH highest in neonates, then modest	FT4 markedly elevated in early infancy	Very large East-Asian cohort with	(7)

				age-related decline; mild sex differences in older children	with gradual decline toward adolescence	fine age-banding, widely used as modern pediatric reference.	
Mitsumatsu et al., Japan	0–18	~1500	Chemiluminescence	Age- and sex-specific TSH intervals; pubertal "drift" toward adult cut-offs	FT4 reference intervals narrow and stable after early childhood	Confirms population-specific Japanese intervals that broadly align with other East-Asian data.	(8)
Meirelles-Cardoso et al., Brazil	1–18	1,158	Immunoassay	TSH 2.5–97.5th percentiles by age; most values between ≈0.6–5.0 mIU/L	FT4 not systematically reported for all ages	Focuses on TSH intervals in healthy Brazilian children from the Central region, highlighting regional variability.	(9)
La'ulu & Roberts, USA	1–18	1,824	Multiple immunoassays	Demonstrates that pediatric TSH limits differ significantly between assay platforms	Shows parallel assay-related differences for FT4	Emphasizes strong assay dependence of pediatric TSH/FT4 reference intervals and the need for analyzer-specific ranges.	(4)

Across diverse populations and platforms, pediatric cohorts consistently show higher TSH and FT4 in neonates and young infants, with gradual decline and stabilization in mid-childhood, and convergence toward adult-like values during adolescence. (5–9) These data reinforce the need for age- and assay-specific reference intervals rather than applying adult or foreign ranges directly to children.

Table 2a Distribution of FT4–TSH Patterns in Published Pediatric Cohorts

Pattern (FT4–TSH)	Typical biochemical definition	Main etiologies in children	Approximate frequency in unselected pediatric cohorts*	Key references
Normal FT4 + Normal TSH	FT4 and TSH within age-specific reference intervals	Euthyroid	>70–85%	Segni (Endotext) (1); Kapelari (5)
Normal FT4 + High TSH (Subclinical hypothyroidism)	FT4 normal; TSH above age-specific upper limit (≈4–5 mIU/L)	Autoimmune thyroiditis, obesity, mild iodine deficiency, idiopathic SH, goiter, recovery from illness	~2–8%, higher in iodine-deficient or high-risk groups	Mahadevan (18); Metwalley & Farghaly (19); Mishra (20); Salerno (23)
Low FT4 + High TSH (Overt primary hypothyroidism)	FT4 below lower limit; TSH elevated	Congenital hypothyroidism, Hashimoto thyroiditis, thyroidectomy, radioiodine, severe iodine deficiency, medications	<1–2% in unselected children	Segni (1,13); Özer (12); Léger (23)
Low FT4 + Normal/Low TSH (Central pattern)	FT4 low; TSH inappropriately normal or low	Central hypothyroidism (pituitary/hypothalamic disease), glucocorticoids, severe non-thyroidal illness	Rare in general population; more common in neuro-oncology/pituitary cohorts	Segni (1); Cheetham (2); Cavarzere (24)
High FT4 + Low TSH (Hyperthyroxinemia / thyrotoxicosis)	FT4 elevated; TSH suppressed	Graves disease, thyroiditis, toxic nodules, exogenous TH, assay interference, transient TSH suppression	<1% of unselected TFTs; Graves disease ≈1–14 per 100,000 child-years	Lee HS (25); Rho (26); Oron (29); Lee YJ (28); Ross (27)
Normal/High FT4 + Normal/High TSH	FT4 high or high-normal with unsuppressed TSH	TSH resistance, thyroid hormone transporter defects, binding protein abnormalities, assay interference	Very rare; mainly referral-center cases	Campi (10); Favresse (30)

Table 2 b Summary of the six primary patterns of Free T4 and TSH levels observed in children,

FT4 Level	TSH Level	Diagnostic Interpretation	Prevalence
Normal	Normal	Euthyroid (Normal Function)	70-85%
Normal	High	Subclinical hypothyroidism	2-8%
Low	High	Overt primary hypothyroidism	1-2%
Low	Normal/Low	Central hypothyroidism	Rare
High	Low	Hyperthyroxinemia/Thyrotoxicosis	<1%
Normal/High	Normal/High	TSH resistance, other rare disorders	Rare

Table2 2a and 2b: Most childhood TFTs fall in the euthyroid range, while abnormal patterns cluster into a relatively small minority with SH, overt hypothyroidism, central patterns, or hyperthyroxinemia. (2,18–22,31,39) Recognizing these patterns and their differential diagnoses is crucial to avoid both under-diagnosis and over-treatment.

Table 3 Prevalence of Subclinical Hypothyroidism by Age and Sex in Representative Pediatric Cohorts

Study / Country	Age groups (y)	n	Definition of SH	Overall SH prevalence	Age / sex pattern	Key references
Mahadevan et al., India	0–18	38,961	Elevated TSH above lab upper limit with normal FT4	6.1% SH; 0.4% overt hypothyroidism	Mild female predominance; slightly higher in older children	(18)
Mishra et al., India	1–18	600 (children + adolescents)	TSH above age-specific upper limit with normal FT4	7.7% in children; 4.9% in adolescents	SH more common in girls; associated with dyslipidemia	(20)
Lazar et al., Israel (community data)	0–18	>120,000	TSH 5.5–10 mIU/L; normal FT4	≈2.9% elevated TSH	Slight female predominance; higher in adolescence	(22)
NHANES III, USA (adolescent subset)	12–19	~1000	TSH >97.5th percentile with normal thyroxine	≈1–2%	Higher SH prevalence in antibody-positive adolescents	(18)
Systematic/narrative reviews (Europe, Middle East)	0–18	—	Variable cutoffs (typically TSH 4.5–10 mIU/L)	1.7–5% in general pediatric populations	Higher prevalence in obesity, Down syndrome, T1D, AITD, and adolescent girls	(19,23)

Subclinical hypothyroidism shows consistent variability across populations, with higher prevalence in hospital-based or iodine-deficient settings (≈6–8%) compared with large community cohorts (≈1–3%). Girls are more frequently affected, particularly in adolescence, reflecting the rising incidence of autoimmune thyroiditis in older children. Studies highlight the influence of iodine status, autoimmunity, and metabolic factors such as obesity on SH prevalence, while cohorts from India and Israel show that the TSH threshold used determines the apparent burden of disease. These findings underscore the importance of age-specific and assay-specific cutoffs and careful interpretation of mildly elevated TSH in otherwise healthy children.

Table 4 Representative Pediatric Series Reporting Subclinical Hypothyroidism: Definitions and Outcomes

Study	Setting / Population	SH Definition	Follow-up duration	Main outcomes	Key references
Sridhar et al., India (prospective)	40 children with SH	TSH 5–15 mIU/L; normal FT4	2 years	52.5% normalized; 40% persisted; 7.5% progressed to overt hypothyroidism; antibodies predicted progression	(24)
Bona & Prodam (review)	Multiple pediatric SH cohorts	Mildly elevated TSH, normal FT4	Up to 5–10 years	Mild idiopathic SH often remits; progression higher with autoimmunity, goiter, high baseline TSH	(19)

Salerno et al., review	Review of pediatric SH	TSH 4.5–10 mIU/L	—	Recommends observation for mild idiopathic SH; treat TSH ≥10 or symptomatic/antibody-positive	(23)
Metwalley & Farghaly (review)	General pediatric populations	SH defined variably by age-specific TSH	—	Prevalence ~1.7–5%; idiopathic SH benign; autoimmune SH requires closer monitoring	(19)
Radetti et al., Italy (HT cohort)	Euthyroid or mild SH with Hashimoto thyroiditis	Normal or mildly increased TSH, ± normal FT4	Mean 5 years	30–50% progressed to overt/borderline hypothyroidism; baseline TSH and antibodies predicted risk	(21)

Longitudinal data across diverse cohorts demonstrate that the natural history of pediatric subclinical hypothyroidism is largely benign in children with idiopathic, mild TSH elevation (TSH <10 mIU/L, antibody-negative), with most normalizing or remaining stable over time. In contrast, progression to overt hypothyroidism is significantly more likely when thyroid autoantibodies, goiter, or higher baseline TSH are present. Prospective studies and reviews consistently highlight the value of risk stratification, recommending observation for mild idiopathic cases and closer follow-up or treatment for autoimmune-associated SH. These patterns support a tiered monitoring approach rather than uniform treatment.

Table 5 Prevalence and Etiologic Breakdown of Hyperthyroxinemia / Hyperthyroidism in Children

Study / Region	**Population**	**Biochemical pattern assessed**	**Prevalence / incidence**	**Main etiologies**	**Key references**
Oron et al., Israel	Children evaluated for elevated FT4	High FT4 ± low TSH	Hyperthyroxinemia uncommon; many cases transient	Transient suppression, thyroiditis, assay interference, early GD	(29)
Wasniewska et al., Italy	Children with persistent low TSH but normal FT4	Subclinical hyperthyroidism	Very rare; many normalize spontaneously	GD, autonomous nodules, early thyroiditis; many remain stable	(29)
Lee HS et al., Korea	National pediatric Graves' cohort	Overt hyperthyroidism	GD incidence ≈0.79/100,000 child-years	Graves' disease (~95% of cases)	(25)
Rho et al., Korea	Long-term GD outcomes	Overt hyperthyroidism	Confirms rarity; remission ≈30%	Autoimmune GD; female predominance	(26)
Lee YJ et al., 2023 systematic review	3057 children with GD	Overt hyperthyroidism	Remission after ATD ≈28.8%	GD dominant; long-term management needed	(28)
Ross et al., ATA Guidelines	Children with hyperthyroidism	Overt thyrotoxicosis	Hyperthyroidism rare; GD most common	GD, toxic nodules, thyroiditis	(27)

Across published cohorts, true pediatric hyperthyroidism remains rare, with Graves' disease accounting for most cases and an incidence typically <1 per 100,000 child-years. In contrast, biochemical hyperthyroxinemia is identified more frequently but is often transient or artifactual, arising from non-thyroidal illness, early thyroiditis, or assay interference rather than persistent thyrotoxicosis. Studies repeatedly emphasize the need for repeat testing and exclusion of

analytical artifacts before labeling a child as hyperthyroid. This distinction between transient biochemical abnormalities and sustained autoimmune hyperthyroidism is critical for preventing unnecessary treatment.

Table 6 Thyroid Autoantibody Positivity in Children and Adolescents: Age, Sex, and Biochemical Patterns

Study	Population	Antibodies Assessed	Prevalence	Age/Sex distribution	Biochemical association	Key references
NHANES III, USA	Adolescents (12–19 y) in general population	TPOAb, TGAb	≈6–13%	Higher in females; increases with age	Antibody-positive adolescents more likely to have elevated TSH	(18)
Skarpa et al., Greece	228 children with AITD	TPOAb, TGAb	100% (diagnostic criteria)	83.8% female; peak at puberty	At diagnosis: 57% euthyroid, 33% SH, 8% overt hypo, 2% hyperthyroid	(16)
Radetti et al., Italy	Children with Hashimoto thyroiditis	TPOAb, TGAb	AITD prevalence up to 2–9%	Female predominance; peak onset 10–12 y	30–50% progress to overt hypothyroidism over years	(21)
De Vries et al., Israel	Chronic autoimmune thyroiditis	TPOAb, TGAb	100% (clinic cohort)	Mostly diagnosed after age 10; F:M ≈4–6:1	Many remain euthyroid/SH; minority require LT4	(15)
Calcaterra et al., Italy	Children/adolescents with AITD	TPOAb, TGAb	—	Clear female predominance; puberty amplifies immune activation	Supports immune–pubertal interaction	(38)
Vigone et al., Reviews	Spectrum of pediatric HT/GD	TPOAb, TGAb	0.3–9.6% depending on population	Female predominance; increases with age	Antibody-positive = higher risk of hypothyroidism	(34,35)

The prevalence of thyroid autoantibodies increases with age and pubertal maturation, with a consistent and marked female predominance across populations. Many antibody-positive children remain euthyroid or present with mild SH, yet long-term follow-up studies show a significantly higher risk of progression to overt hypothyroidism in antibody-positive compared with antibody-negative peers. Data also highlights substantial geographic and genetic variation in antibody prevalence. Taken together, these cohorts reinforce the importance of antibody testing in children with persistent TSH elevation, and they support periodic biochemical monitoring in those with positive antibodies.

3. Discussion

The present review highlights significant age-dependent variability in pediatric thyroid function, reinforcing that interpretation of TSH and FT4 must always be grounded in age-specific and assay-specific reference intervals. As shown in Table 1, large normative datasets from Austria, China, Japan, Brazil, and the United States reveal a consistent pattern: higher FT4 and TSH values in infancy, followed by gradual stabilization in mid-childhood before approaching adult ranges (5–9). These developmental trajectories reflect maturation of the hypothalamic–pituitary–thyroid (HPT) axis, alterations in thyroxine-binding proteins, and dynamic changes in deiodinase activity in early life (1,4). Such physiologic variations explain why reliance on adult reference intervals leads to misclassification of both hypothyroid and hyperthyroid states in children.

Across global cohorts, the distribution of FT4–TSH patterns (Table 2) demonstrates that most pediatric TFTs (>70–85%) fall within the euthyroid range, confirming the predominance of normal physiological variation in the pediatric population. Subclinical hypothyroidism (SH) represents the second most common pattern, with prevalence ranging from ~2% in community cohorts to ≥6–8% in iodine-deficient or hospital-based cohorts (18–23). Autoimmunity, obesity, mild iodine deficiency, and recovery from illness are the dominant drivers of TSH elevation, emphasizing that this pattern is heterogeneous and cannot be interpreted uniformly across populations. Additionally, analytic variation between immunoassays may contribute to differences in reported prevalence (4).

Overt primary hypothyroidism—characterized by low FT4 and elevated TSH—remains comparatively rare in general pediatric populations (<1–2%), largely due to early detection of congenital hypothyroidism through neonatal screening and increasing awareness of autoimmune thyroid disease (12,13,23). Geographic differences in iodine intake explain part of the variability in incidence, with higher rates persisting in certain Middle Eastern and South Asian regions. Hashimoto thyroiditis accounts for most acquired cases in school-aged children, particularly females, whereas congenital hypothyroidism predominates in infancy (12,23).

Central hypothyroidism and non-thyroidal illness patterns, reflected by low FT4 with inappropriately normal or low TSH, are exceedingly rare in population studies but more common in specialized cohorts, such as children receiving cranial radiation or those with pituitary lesions (2,24). The biochemical pattern is often subtle, and FT4 changes may precede alterations in TSH due to impaired TSH bioactivity rather than absolute deficiency. Glucocorticoid exposure and systemic illness also modify TSH secretion through hypothalamic suppression and reduced TRH drive. These findings underscore the necessity of clinical context and targeted assessment rather than routine screening.

Hyperthyroxinemia and hyperthyroidism (Table 2 and Table 5) remain uncommon in childhood, with Graves disease representing the primary etiology, showing incidence rates between 1 and 14 per 100,000 child-years (25–28). Many cases of elevated FT4 with low TSH are transient or non-pathological, reflecting thyroiditis, early GD, or even assay interference, particularly with biotin or macro-TSH artifacts (27,29). This distinction is essential because misinterpretation may lead to overdiagnosis and unnecessary antithyroid therapy. Studies also demonstrate a strong female predominance and peak incidence during adolescence, paralleling other autoimmune endocrinopathies.

The prevalence and clinical significance of subclinical hypothyroidism have been central themes in pediatric endocrinology. Table 3 illustrates that SH prevalence varies significantly by region, iodine status, and methodology. Indian cohorts report 6–8% prevalence (18–20), whereas North American and European datasets report significantly lower rates of ~1–3% (18,22). These differences likely reflect not only environmental iodine disparities but also population characteristics such as higher obesity rates, which can transiently elevate TSH (19,21). Importantly, mild SH is often transient, especially in antibody-negative children, supporting a conservative approach to management.

Longitudinal studies summarized in Table 4 emphasize the benign natural history of idiopathic SH in most children, with normalization or persistence being far more common than progression to overt hypothyroidism (19,23,24). Conversely, children with Hashimoto thyroiditis, goiter, high baseline TSH, or strong family history exhibit higher risk of progression, in some series up to 30–50% over several years (21). These findings argue for a risk-stratified follow-up protocol, in which antibody-positive or goitrous children undergo more frequent monitoring, whereas idiopathic mild SH may be observed at longer intervals without immediate therapy.

Autoimmune thyroiditis represents a dominant driver of thyroid dysfunction in older children and adolescents. Table 6 highlights the increasing prevalence of thyroid autoantibodies (TPOAb, TGAb) with age, particularly among adolescent girls, with prevalence estimates of 6–13% in population-based cohorts such as NHANES (18) and substantially higher rates (up to 80–90%) in referral-based autoimmune thyroiditis cohorts (15,16,21). Pubertal immunologic activation and female-predominant susceptibility explain much of this pattern. Antibody-positive children show a strong association with elevated TSH and a higher likelihood of progression to overt hypothyroidism (34–38).

Significant geographic and population differences in thyroid function patterns emerge across tables. Iodine sufficiency, assay type, ethnic variation in TFT distribution, and differing screening policies contribute to the observed variability. Asian and Middle Eastern cohorts tend to show higher TSH medians and wider distribution, while European and South American populations demonstrate narrower reference intervals (6–9). These contrasts highlight the importance of local reference interval validation, especially when interpreting borderline abnormalities. International comparisons also show variability in the prevalence of SH, autoimmunity, and hyperthyroidism, suggesting environmental and genetic modulators.

Taken together, the patterns across Tables 2–6 reinforce that pediatric thyroid assessment must be grounded in age-specific norms, clinical context, and careful follow-up strategy. Mild abnormalities, particularly isolated TSH elevation, frequently reflect adaptive or transient physiology rather than persistent disease. Autoantibodies, baseline TSH, and FT4 provide the most reliable predictors of future dysfunction. The heterogeneity of pediatric thyroid disease across populations underlines the need for population-appropriate cutoffs, judicious testing, and risk-based monitoring to prevent overdiagnosis while ensuring timely detection of clinically significant hypothyroidism or hyperthyroidism.

4. Conclusion

Pediatric thyroid function varies widely by age and physiology, maturation of the hypothalamic–pituitary–thyroid axis, iodine status, and assay-specific factors, making accurate interpretation dependent on appropriate pediatric reference intervals. Across global cohorts, most children demonstrate normal TFTs, while subclinical hypothyroidism represents the most frequent abnormal pattern, typically with a benign and often transient course unless accompanied by autoimmunity, goiter, or markedly elevated TSH. Overt hypothyroidism and true hyperthyroidism remain uncommon, whereas biochemical abnormalities such as isolated TSH elevation or transient hyperthyroxinemia frequently reflect adaptive, non-pathologic changes. Autoantibody positivity increases with age, especially among adolescent girls—and serves as a strong predictor of progression to thyroid dysfunction. These findings collectively highlight the need for population-specific reference intervals, careful clinical correlation, and risk-based follow-up strategies to optimize early detection, monitoring, and management of pediatric thyroid disorders without overdiagnosis or unnecessary treatment.

Recommendations

- Implement standardized pediatric-specific reference intervals for TFT interpretation and ensure laboratories report age and assay adjusted ranges to improve diagnostic accuracy.
- Interpret TFTs using age-specific and assay-specific pediatric reference intervals, with repeat testing for isolated abnormalities to avoid misclassification, especially in infants and young children.
- Adopt a risk-stratified approach to subclinical hypothyroidism, reserving treatment for children with autoimmunity, goiter, symptoms, or TSH ≥10 mIU/L, while observing mild idiopathic SH with periodic follow-up.
- Screen for thyroid autoantibodies in children with persistent TSH elevation, as antibody positivity strongly predicts progression and guides the intensity of monitoring.
- Differentiate true hyperthyroidism from transient or artifactual hyperthyroxinemia, using repeat testing, clinical correlation, and exclusion of assay interference before initiating therapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

This study is a narrative review based entirely on previously published literature and did not involve human participants, patient data, or experimental procedures. Therefore, ethical approval and informed consent were not required.

Author Contributions

ATS conceptualized the review, designed the study structure, supervised the literature selection, and led the writing of the manuscript. LE and FA contributed to data extraction, synthesis of pediatric reference intervals, and drafting of the Results and Discussion sections. AE and NA assisted in reviewing analytical and methodological aspects and supported interpretation of FT4–TSH patterns. NH and RA contributed to the literature search, cross-checking references, and preparation of tables and figures. AK supported critical revisions related to biochemical essays, laboratory methodology, and clinical interpretation. All authors reviewed, revised, and approved the final manuscript.

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