PRIMER

Hypothyroidism

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Abstract | Hypothyroidism is the common clinical condition of thyroid hormone deficiency and, if left untreated, can lead to serious adverse health effects on multiple organ systems, with the

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(primary hypothyroidism) or in the pituitary or hypothalamus (central hypothyroidism). Hypothyroidism can also result from severe iodine deficiency because the synthesis of thyroid hormone requires the trace levels is the hallmark of diagnosis[3] (FIG. 1).

Levothyroxine (LT4), a synthetic form of T_4 that is the mainstay of treatment for hypothyroidism, is the third most commonly prescribed drug in the United States,

Hypothyroidism

Epidemiology

pathophysiology

diagnosis

optimal treatment

quality of life of patients

current knowledge gaps and research priorities

- **Overt hypothyroidism** :TSH levels above the upper limit of the **reference range** while levels fT4 are below the lower limit of the **reference range**
- **subclinical hypothyroidism:**TSH levels are elevated but fT4 levels are still within reference range
- **reference range** : statistically defined by the **2.5th and 97.5th percentiles** of the measured circulating thyroid hormone values in populations defined as healthy

Epidemiology

Primary hypothyroidism

- Primary hypothyroidism prevalence is highest in populations with **high iodine intake or severe iodine deficiency** as compared with populations with a sufficient iodine status
- Prevalence **decreases** with the **declining severity of iodine deficiency** and
- Prevalence **increases** as iodine intake shifts from mild deficiency to **optimal or excessive intake**
- **Improvement iodine status** :increases thyroid **antibody positivity** and therefore the risk of **Hashimoto thyroiditis**

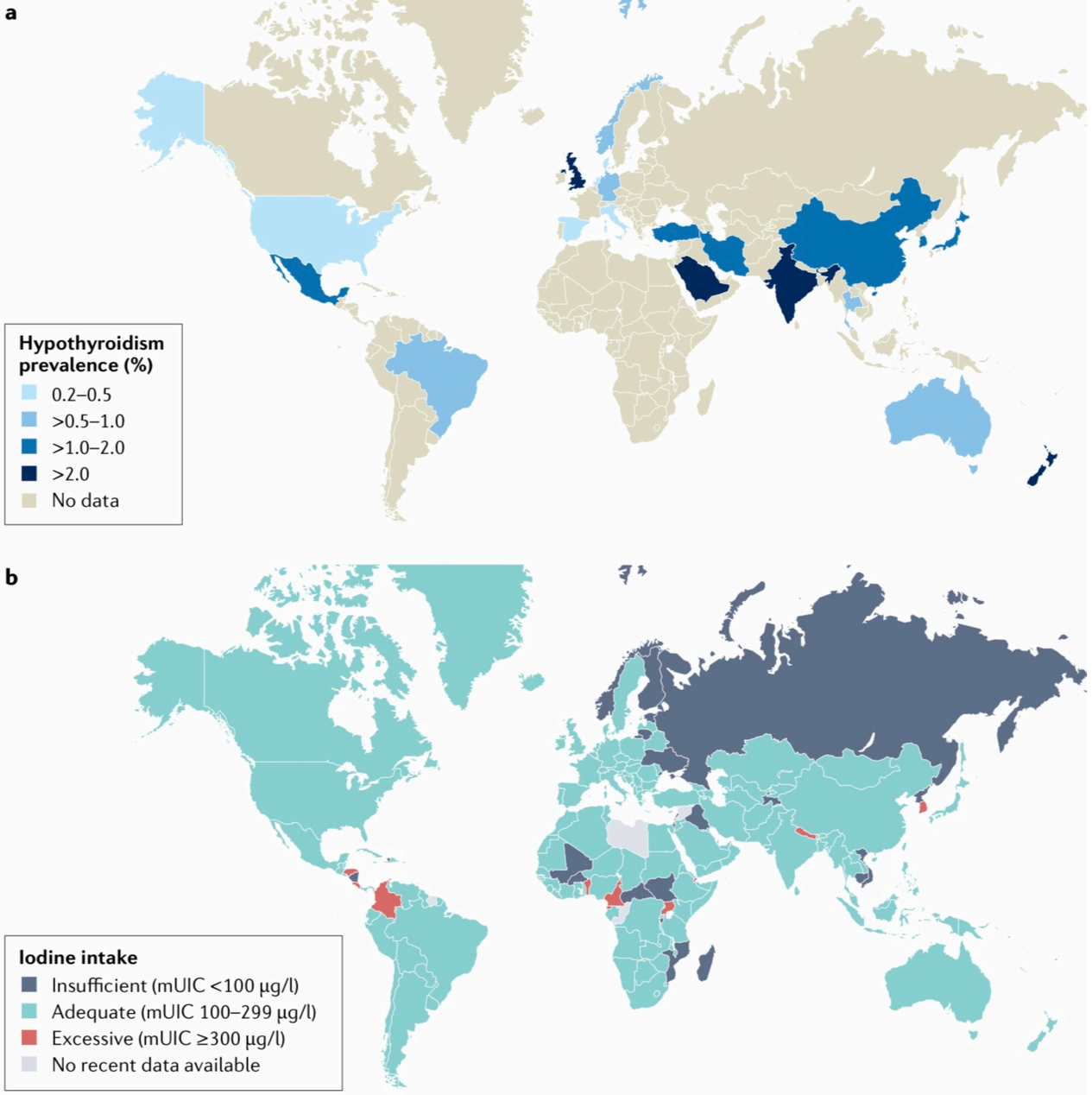


Fig. 2 | **Global prevalence of overt hypothyroidism and iodine status. a** | Worldwide prevalence of overt hypothyroidism based on epidemiological studies (Supplementary Table 1). The median value was calculated for countries for which data are available from multiple studies. **b** | Global iodine nutrition status in 2021 (REF.[186]) based on iodine intake in the general population as assessed by median urinary iodine concentration (mUIC) in school-aged children from studies conducted between 2005 and 2020.

Epidemiology

Primary hypothyroidism

- Hypothyroidism occurrence is dependent on **genetic**, **inherent (for example, sex**) and **environmental factors**
- Individuals with a **TSH-based genetic risk score** in the **highest** quartile had a **2.5-fold** increased odds of hypothyroidism compared with individuals with a genetic risk score in the lowest quartile
- **No** differences were found **between men and women in genetic variants** for TSH and fT4 in sex-stratified GWAS metaanalyses
- Nevertheless, the risk of developing primary hypothyroidism is up to **tenfold** higher in **women than in men**, suggesting **an important contribution of non-genetic factors**

Epidemiology

Primary hypothyroidism

- **TPO antibody** concentrations are **lower** in **smokers** than in non-smokers
- **TSH** levels are **lower** in current **smokers** than in former smokers, and lower in former smokers than in never smokers
- **Smoking initiation results in a significant decrease in serum TSH levels after 1 year in men**
- **Obesity** is associated with **higher serum TSH** in adults and children
- **small for gestational ag**e have **higher serum TSH levels** than children born appropriate for gestational age
- Environmental factors : **vitamin D** and **selenium deficiency,** and **moderate alcohol intake**

Central and peripheral hypothyroidism

- *Central hypothyroidism* : **secondary** hypothyroidism (pathology of **pituitary**) or **tertiary** hypothyroidism (pathology of **hypothalamus**)
- most common causes :**pituitary adenoma ,infiltrative disease , radiotherapy, immune-checkpoint inhibitors** resulted in a surge in hypophysitis
- *Peripheral hypothyroidism :* reduce the effectiveness of thyroid hormone through altered cell membrane transport and metabolism
- rare
- **genetic**(**congenital**) : **decreased sensitivity** to thyroid hormone mutations in MCT8, THRA or THRB, specific set of clinical signs and symptoms.
- **consumptive hypothyroidism : increased** expression **DIO3** (an enzyme that inactivates thyroid hormone) in **tumours** (for example, **gastrointestinal stromal tumours**)

Mechanisms/pathophysiology

Physiological aspects

- Serum TSH levels follow a **circadian** rhythm: levels are **highest** between **9 pm and 5** am and **lowest** between **4pm and 7pm**
- **The thyroid** gland secretes predominantly T4, to a lesser extent, T3, which accounts for up to only ~**20% of circulating T3**
- **remaining T3 is produced by peripheral tissues, such as liver and skeletal muscle**, by the activating enzymes **DIO1** and **DIO2**, respectively
- Most circulating T4 and T3 is bound to transport proteins such as **TBG**, **transthyretin** and **albumin**.
- Only ~**0.02% of T4** and ~**0.2% of T3** are present in an **unbound** form

Physiological aspects

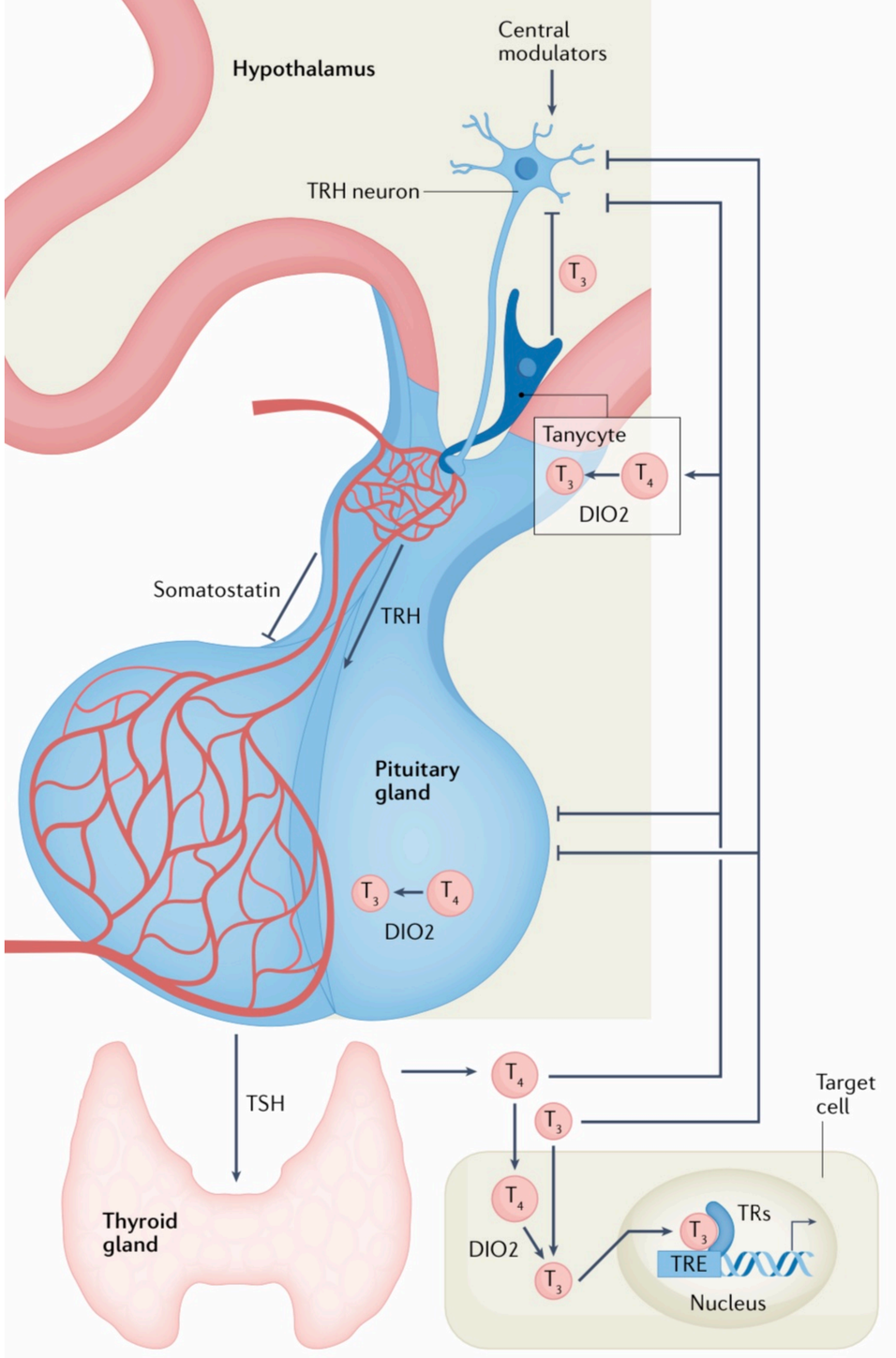
- Binding T3 to the **nuclear T3 receptors** (TRs), modulate hormone-responsive genes and their expression.
- three **THRα** and three **THRβ** isoforms, of which **TRα1**, **TRβ1** and **TRβ2** bind to T3
- TRα1 and TRβ1 are ubiquitously expressed, **TRα1 in brain, heart, and bone** and **TRβ1 in liver, kidney and thyroid.**
- **TRβ2** has **restricted** expression pattern but is the **predominant** isoform expressed in the **pituitary gland** ,is essential for the **negative regulation of TSH**

Mechanisms/pathophysiology

Physiological aspects

- **Intracellular T_3 <u>concentrations</u>** strongly determine the **biological activity** of thyroid hormone
- Regulation of intracellular thyroid hormone concentrations: **fT_4 and fT_3 concentrations in serum**, **activity of the intracellular DIO_1, DIO_2 and DIO_3 enzymes that can activate or inactivate thyroid hormone**

- **TRH** neurons receive various **central modulators and other inputs**
- **TRβ2** expressed in **TRH neurons** mediates **feedback** thyroid hormones
- **DIO2** production of T3 from T4
- Production and release **TSH** from the anterior pituitary is modulated by both **thyroid hormones and TRH**
- In the periphery, only the **free fraction of thyroid hormones can be transported into target cells**
- effects of thyroid hormones are mediated via interaction of the active hormone T3 with the nuclear T3 receptor, which together bind to thyroid response elements (TREs) and modulate the expression of thyroid hormone-responsive genes.



Mechanisms/pathophysiology

Primary hypothyroidism

- **Chronic autoimmune thyroiditis (Hashimoto thyroiditis):**
- most common cause of primary hypothyroidism
- Factors interact in the development of chronic autoimmune thyroiditis:
  genetic ,environmental factors, micronutrients (mainly iodine and selenium), drugs, infiltration, infection, polyglandular syndromes , molecular mimicry between microbial and host antigens
- High concentrations TPOAb and antithyroglobulin antibodies in most autoimmune thyroiditis
- occur in ~**10%** of the **euthyroid** population
- In pregnancy TPOAb positivity in **2–17%**

Mechanisms/pathophysiology

- In **more than 40%** of **pregnant women with thyroid autoimmunity**, serum **fT4 concentration falls in the hypothyroid range during late pregnancy**, which may complicate diagnosing overt hypothyroidism during the third trimester
- This is due to inadequate maternal thyroid capacity in response to increased demands in thyroid hormone production imposed by stimulation of the thyroid by HCG ,increases in TBG, and changes in placental deiodination and renal clearance of iodine during pregnancy
- rates of **miscarriages** and **preterm** delivery are increased with thyroid autoimmunity
- A **negative association** of **TPOAb positivity** during pregnancy with **neurodevelopment** of offspring has been suggested

Mechanisms/pathophysiology

Chronic autoimmune thyroiditis

- **Infiltration** of thyroid tissue by **lymphocytes**, mainly **T helper 1 cells**, alter follicular cell function through **IL-1, TNF ,IFNγ,Chemokines**

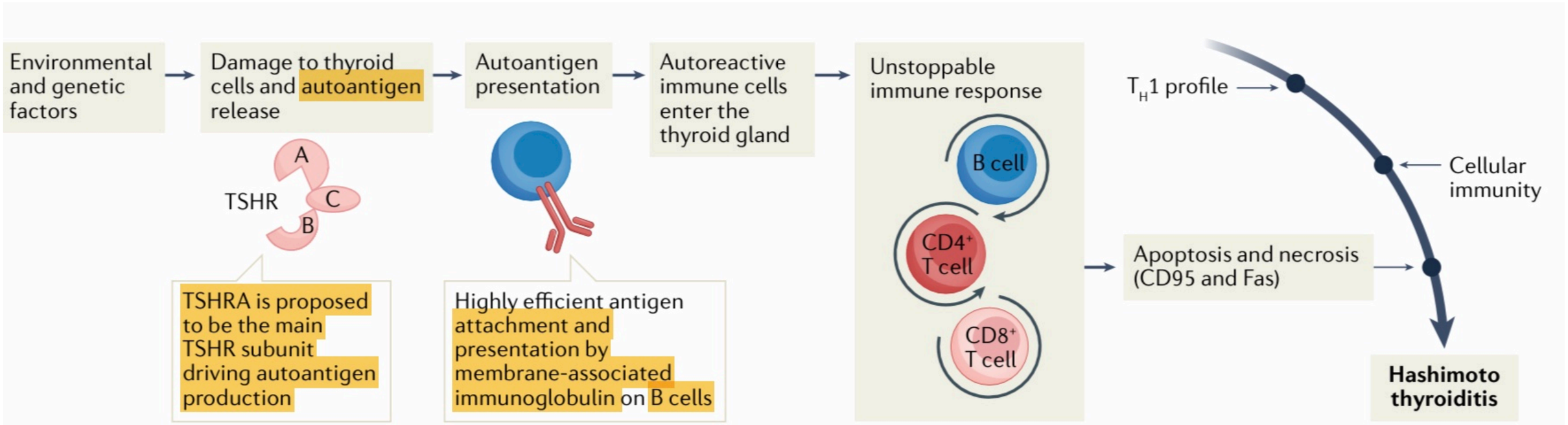


Fig. 4 | **Pathogenetic mechanisms in Hashimoto thyroiditis.** Thyroid autoimmunity is the result of the interplay of genetic and environmental factors that cause damage to thyroid cells, leading to autoantigen release and presentation. Entry of autoreactive immune cells into the thyroid leads to activation of cellular and humoral immune responses, cytokine production, and cytotoxicity and apoptosis. T_H1, T helper 1; TSHR, thyroid-stimulating hormone receptor.

Mechanisms/pathophysiology

Primary hypothyroidism

- Both iodine **deficiency** and iodine **excess** may cause **hypothyroidism** but overt hypothyroidism **mainly** occurs in the context of **severe iodine deficiency** and is commonly accompanied by **goitre**
- following **exposure to high iodine** levels in **high-risk** individuals (such as those who are prone to **Hashimoto** thyroiditis), synthesis of thyroid hormone can be **inhibited** by the socalled **Wolff–Chaikoff** effect without resumption of iodine organification after a few days
- **Hypothyroidism** may be observed **following chronic** administration of large doses of iodine from iodinated *contrast* material, the heavily iodinated antiarrhythmic *amiodarone*, the topical antiseptic *povidone-iodine* or iodine-containing thyroid *supplements* that are available without prescription
- insufficient **selenium** intake is associated with elevated risk of thyroid disease

Mechanisms/pathophysiology

Primary hypothyroidism

- **Ablative** doses of **radioiodine** recommended to treat **Graves** disease
- Radioiodine treatment of **toxic nodular goitre or non-toxic nodular goitre** results in hypothyroidism **in ~25%** of patients
- External radiation doses ≥25 Gy (2,500 rad) head and neck region for malignant tumours : permanent hypothyroidism in >**50%** of patients
- **total thyroidectomy**
- **Near-total thyroidectomy :** removal of most of the thyroid gland except for <**1 g** of thyroid tissue to minimize risk of damaging the **recurrent laryngeal nerve**
- **Subtotal thyroidectomy** removal of most of the thyroid gland except for ~**4–8g** of tissue to maintain **euthyroidism/hypothyroidism in ~50%**

Mechanisms/pathophysiology

Primary hypothyroidism

- **14–27%** of **primary thyroid lymphoma** and **30–40**% of patients with **Reidel thyroiditis**
- infection with **Pneumocystis jirovecii, tuberculosis and brucellosis** have been
- COVID-19 hypothyroidism as a consequence of **subacute** thyroiditis
- **other autoimmune diseases**, particularly **type 1 diabetes mellitus, autoimmune gastric atrophy and coeliac disease (part of autoimmune polyendocrinopathies)**
- **20%** treated with **lithium** will develop hypothyroidism. Lithium **increases intrathyroidal iodine content**, and **inhibits thyroid hormone release**

Mechanisms/pathophysiology

Primary hypothyroidism

- **amiodarone**: 5–15%
- **IFNα** and **IL-2 :** 58% and 32% of patients respectively, activation of autoimmune
- **tyrosine kinase inhibitor** : in 18–52%
- **Immune-checkpoint inhibitors** are associated with immune-related adverse events, including **thyroid dysfunction and hypophysitis**
- **anti-CTLA4 or anti-PD1 monoclonal antibodies:** More than **20%** of patients treated mainly with both in combination, develop either **thyroiditis**, with potentially subsequent hypothyroidism, and up to **15**% develop **hypophysitis**

Mechanisms/pathophysiology

Primary hypothyroidism

- **Cigarette** smoking causes a decrease in serum TSH and TPOAb levels and a decreased risk of hypothyroidism in patients with underlying chronic autoimmune thyroiditis
- **Congenital primary hypothyroidism**
- **dysgenesis: absent**, **underdeveloped** or **ectopic** thyroid gland/Mutations in TSHR, FOXE1, NKX2-1, PAX8 and NKX2-5
- **dyshormonogenesis:** by defective thyroid hormone biosynthesis/ SLC5A5, TPO, DUOX2, DUOXA2, SLC6A4 and DHEAL1

Mechanisms/pathophysiology

Central and peripheral hypothyroidism

- Acquired disease is more common(than congenital)
- Most frequently caused by pituitary **adenoma**
- Most thyrotroph defect is combined with multiple other hormone deficiencies
- **TSH** is often **within reference range** but the secreted TSH isoform, has severely **impaired biological activity**
- **Inappropriately normal serum TSH and low circulating fT4 levels is common in patients with central hypothyroidism**
- **Transient or reversible forms of central hypothyroidism** may occur in patients with **prolonged thyrotoxicosis**, **newborns of hyperthyroid mother**s, treat with **somatostatin**, **glucocorticoids**, **antineoplastic** agents or **dopaminergic** compounds

Aetiology	Mechanism/pathophysiology
Primary hypothyroidism (thyroid)	
Chronic autoimmune thyroiditis (Hashimoto thyroiditis)	Failure of T cell-mediated inflammatory response, cytokine release, infiltration of the thyroid by lymphocytes and development of fibrotic tissue in the thyroid
Disturbed iodine metabolism	Iodine deficiency leads to decreased thyroid hormone production
	Iodine excess leads to thyroid hypofunction in patients with underlying primary thyroid disease
Irradiation and/or thyroidectomy	Ablation of thyroid cells
Genetic disease	Loss of function, pathogenetic variants
Infiltrative diseases and lymphoma	Infiltration of various cells or materials, granuloma and fibrosis formation, and thyroid cell destruction
Infection and/or inflammation	Thyroid cell destruction (most recently COVID-19 infection)
Medications[a]	Lithium: increased intrathyroid iodine content, decreased coupling of iodotyrosine and hormone release
	IFNα and IL-2: possible activation of autoimmune process
	Tyrosine kinase inhibitors: multiple mechanisms described, including effects on thyroid hormone metabolism and transport, and destructive thyroiditis
	Immune-checkpoint inhibitors: immune-related adverse events, including primary hypothyroidism, sometimes preceded by thyroiditis
Industrial and environmental agents	Interference in various steps of intrathyroidal metabolism
Central hypothyroidism (hypothalamic or pituitary)	
Pituitary or hypothalamic lesions and/or damage	Heterogeneous mechanisms leading to altered secretion of TSH by thyrotrophs and/or bioactivity of TSH, involving both hypothalamic and pituitary structures, usually combined with other pituitary hormone deficiencies, including surgery, head trauma, neoplastic lesions, apoplexy, pituitary necrosis, (partial) empty sella, infiltrative lesions or irradiations
Infection and/or inflammation	Infectious (for example, tuberculosis) or inflammatory (for example, sarcoidosis) causes leading to pituitary or hypothalamic infiltration or hypophysitis (for example, due to immune-checkpoint inhibitors)
Congenital	Midline defects, Rathke pouch cyst or genetic mutation; congenital genetic mutations rarely cause isolated central hypothyroidism but are more often part of combined pituitary hormone deficiencies and the most common defective genes are *PROP1* and *POU1F1*
Peripheral hypothyroidism (peripheral tissues)	
Consumptive hypothyroidism	Increased expression of type 3 iodothyronine deiodinase (for example, by tumour cells)
Resistance to thyroid hormone	Tissue-specific hypothyroidism owing to decreased sensitivity to thyroid hormone (resulting from mutations in, for example, *MCT8*, *THRA* or *THRB*)

Diagnosis, screening and prevention

Common symptoms and clinical presentation

- Almost all of the manifestations associated with:

  metabolic processes (such as **fatigue**, **cold intolerance, bradycardia , weight gain**)

  or

  accumulation of matrix glycosaminoglycans in tissue interstitial spaces (leading to **coarse hair and hoarseness of voice**)

- Most common symptom :**fatigue , dry skin, weight gain ,constipation**
- Reduced gastrointestinal tract and gallbladder motility underlying mechanisms for **constipation**, gallbladder hypotonia and **bile duct stone** formation
- **Mild hepatocellular dysfunction** occur
- A risk factor for **NAFLD** and **steatohepatitis**

Common symptoms and clinical presentation

- Impaired **glomerular** and **tubular** function, impaired free water clearance and **hyponatraemia**
- Entrapment **neuropathies** (such as carpal tunnel syndrome) and **metabolic polyneuropathies**
- Impaired memory, poor concentration
- Musculoskeletal symptoms
- Sleep apnea
- Depression, psychiatric disturbances
- Increased vascular resistance, decreased cardiac output, decreased left ventricular function
- Myocardial injury, pericardial effusion
- H**ypertension**, **increased waist circumferenc**e and **dyslipidaemia**

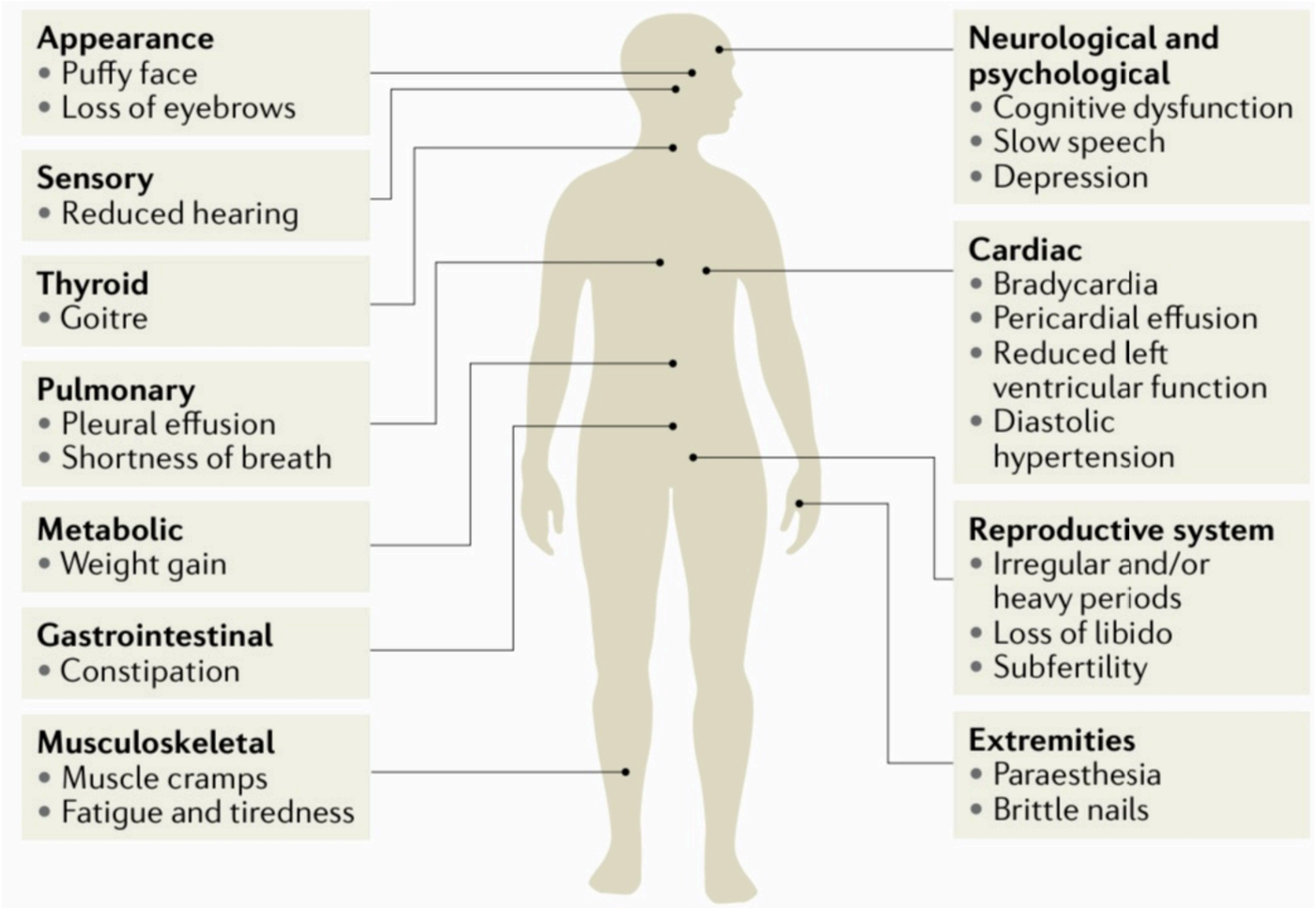


Fig. 1 | **Common symptoms and signs associated with hypothyroidism.** Most symptoms attributed to hypothyroidism are common in the general population and are non-specific. Less common symptoms of hypothyroidism (not shown) include dry skin (when severe, a non-pitting oedema termed myxoedema), hoarseness, anaemia (usually normochromic and normocytic but occasionally macrocytic), increased thrombosis risk (due to impaired coagulation and fibrinolysis) and various neurological (carpal tunnel syndrome and encephalopathy), musculoskeletal (myalgia and increased serum creatine kinase levels) and metabolic (hyponatraemia and increase in serum creatine kinase levels) symptoms.

Common symptoms and clinical presentation

- **12**% of individuals with overt **hypothyroidism**, 7.4% of those with mild (or **subclinical**) hypothyroidism and 7.7% of those who were **euthyroid** reported hypothyroid **symptoms**
- Presence of **symptoms** of hypothyroidism alone has a **low sensitivity and positive predictive value**
- Patients with hypothyroidism Might present with **one or more symptoms** of hypothyroidism or when **abnormal thyroid test** results are noted as part of routine screening tests in the setting of other medical conditions such as dyslipidaemia, atrial fibrillation, cognitive decline, unexplained weight gain or subfertility

Box 1 | **Differential diagnoses of hypothyroidism based on similar presenting symptoms**

Endocrine conditions

- Addison disease: may present with increased thyroid-stimulating hormone levels that normalize after glucocorticoid replacement is commenced
- Obesity (particularly if associated with obstructive sleep apnoea)
- Menopause
- Hypopituitarism
- Type 1 diabetes mellitus
- Hypercalcaemia

Autoimmune conditions

- Coeliac disease
- Pernicious anaemia
- Rheumatoid arthritis

Chronic end organ damage conditions

- Chronic kidney disease
- Chronic liver disease
- Chronic heart failure

Haematological conditions

- Iron deficiency anaemia
- Multiple myeloma

Nutritional deficiencies

- Vitamin B_1, B_{12} or D deficiency
- Folate deficiency

Mental health conditions

- Depression
- Anxiety
- Chronic stress
- Poor sleep pattern

Others

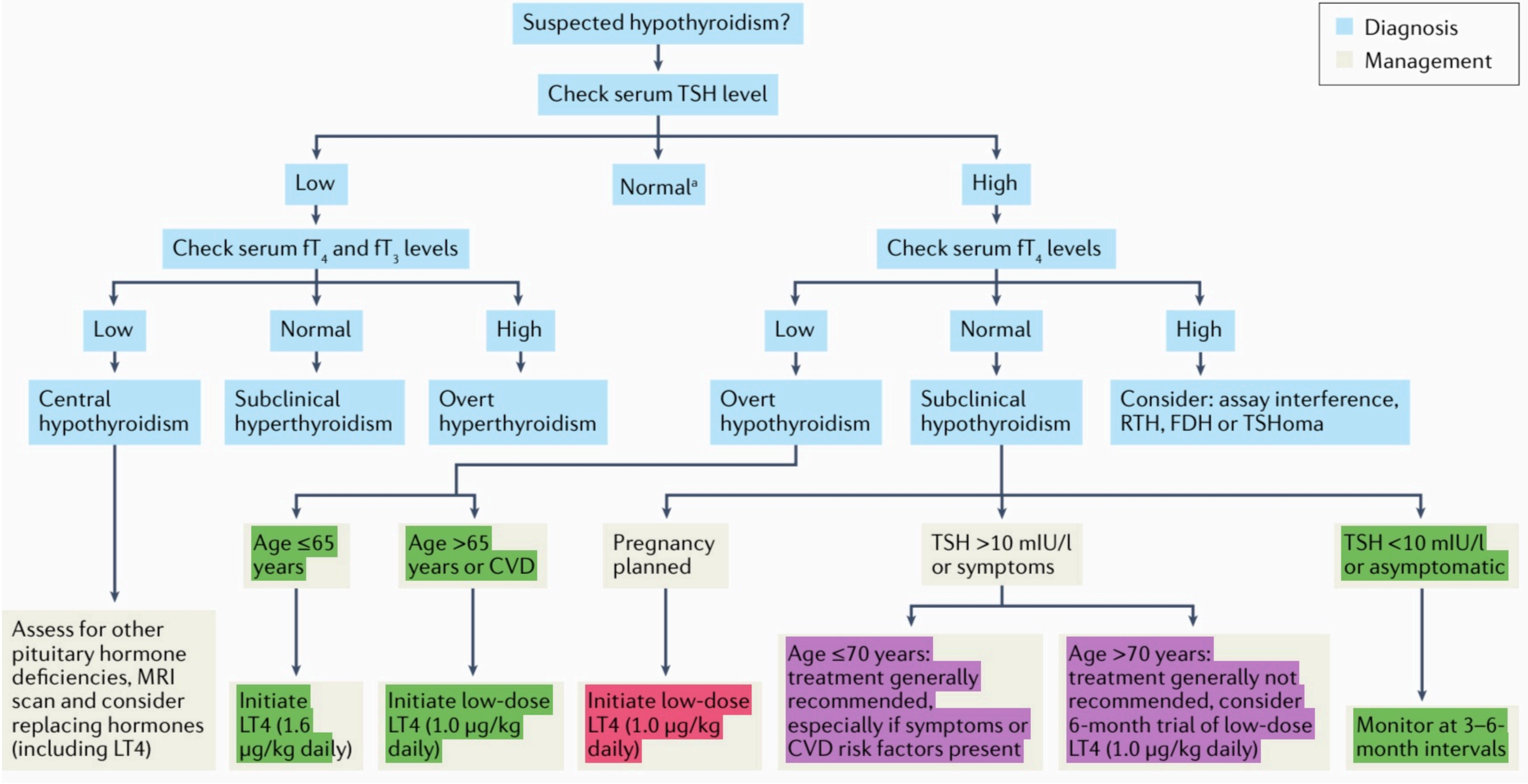
- Chronic fatigue syndrome
- Fibromyalgia
- Post-viral syndromes
- Dementia

Myxoedema coma

- mortality rate of 50–60%
- might present de **novo** or more likely, **precipitated** in a patient with hypothyroidism by a number of drugs, systemic illnesses (such as pneumonia) or other causes
- in **older women** in **winter** and might present with the typical signs of severe hypothyroidism as well as **hypothermia**, **hyponatraemia**, **hypercarbia** and **hypoxaemia**
- treatment with thyroid hormone therapy is initiated in ICU
- **type** of thyroid hormone to administer (**thyroxine**, **triiodothyronine** or **both**) is **unclear**
- **ventilation**, **warming**, **fluids**, **antibiotics**, **vasopressor** agents and **corticosteroids**, are essential for survival

Diagnostic workflow

- **TSH levels** is the most reliable marker for assessing thyroid status ,provided that **pituitary disease** is excluded and patients are **not on medications** that alter TSH secretion
- There is a log-linear relationship between TSH and thyroxine: a **twofold decrease in fT4 levels is associated with a 100-fold increase in circulating TSH**
- TSH–fT4 relationship might be non-linear in some individuals and influenced by **age**, **sex**, **smoking** and **TPOAb** status
- **A**bnormal circulating **TSH** level is the **earliest** indicator of thyroid dysfunction


Diagnosis
Management
Suspected hypothyroidism?
Check serum TSH level
Low
Normal[a]
High
Check serum fT_4 and fT_3 levels
Check serum fT_4 levels
Low
Normal
High
Low
Normal
High
Central hypothyroidism
Subclinical hyperthyroidism
Overt hyperthyroidism
Overt hypothyroidism
Subclinical hypothyroidism
Consider: assay interference, RTH, FDH or TSHoma
Age ≤65 years
Age >65 years or CVD
Pregnancy planned
TSH >10 mIU/l or symptoms
TSH <10 mIU/l or asymptomatic
Assess for other pituitary hormone deficiencies, MRI scan and consider replacing hormones (including LT4)
Initiate LT4 (1.6 µg/kg daily)
Initiate low-dose LT4 (1.0 µg/kg daily)
Initiate low-dose LT4 (1.0 µg/kg daily)
Age ≤70 years: treatment generally recommended, especially if symptoms or CVD risk factors present
Age >70 years: treatment generally not recommended, consider 6-month trial of low-dose LT4 (1.0 µg/kg daily)
Monitor at 3–6-month intervals

Differential diagnosis

- **True subclinical hypothyroidism** must be distinguished from the **recovery phase of non-thyroidal illness** when serum **TSH** levels are often transiently **elevated** (having been low or normal during the acute phase) and **serum fT4 levels** are usually **normal**
- For patients with **apparent subclinical hypothyroidism**, it is recommended that thyroid function should be **retested after 8–12 weeks** to determine whether the TSH elevation is persistent
- **30–50%** of individuals who initially had high serum TSH levels have normal levels on **retesting**

Differential diagnosis

- **Misdiagnosed with hypothyroidism:**
- **Overestimation** of TSH levels due to interference with the TSH assay
- presence of **macro-TSH** can lead to **misdiagnosed** hypothyroidism Rarely
- individuals with **resistance to thyroid hormone due to THRB mutation (high TSH and high fT4 levels), or TSH or TRH resistance (normal fT4 levels)**, can occasionally be misdiagnosed with hypothyroidism

Screening for hypothyroidism

- Despite the high prevalence of hypothyroidism in the general population, there is **no evidence that early detection and treatment improves clinical outcomes**
- ATA, AACE and Latin American Thyroid Society, recommend screening at different intervals among individuals above a particular age, **ranging from every 5 years for individuals >35 years of age** to an **unspecified period for individuals ≥60 years of age, particularly among women**
- Royal College of Physicians in the **UK** concluded that **screening** of the general population is **unjustified** given the low number of overt hypothyroidism cases detected with screening
- **US** Preventive Services Task Force concluded that the available evidence was inadequate to determine the balance of benefits and harms of screening

Screening for hypothyroidism

screening

- **high risk of thyroid dysfunction** with risk factors for hypothyroidism :
- **goitre**
- **previous treatment for hyperthyroidism such as radioactive iodine therapy**
- **partial thyroidectomy**
- **history of neck irradiation**
- **medications** affecting thyroid function
- presence of other **autoimmune** diseases

Screening for hypothyroidism

screening

- Dyslipidaemia
- Hyponatraemia
- Unexplained high levels of muscle enzymes
- Macrocytic anaemia
- Pericardial or pleural effusions without any other cause
- Down syndrome, Turner syndrome
- Pituitary disease,

should also be assessed **regularly** for the development of hypothyroidism

Screening for hypothyroidism

childbearing age

- Women from areas of **moderate to severe iodine deficiency**
- Women with **symptoms** potentially attributable to thyroid dysfunction
- Personal and/or family **history** of thyroid disease
- Recurrent miscarriage
- Unexplained infertility

Screening for hypothyroidism

- In **pregnancy**:
- Screening for **milder** forms of hypothyroidism is **controversial** and remains of **debate** owing to the possibility of **overtreatment** and the lack of evidence that treatment of mild thyroid dysfunction with thyroid hormones improves neurocognitive outcomes in offspring

Dietary modifications to prevent hypothyroidism in individuals at risk

- Adequate intake of iodine is important for underlying **autoimmune** thyroid disease as **iodine deficiency may trigger or worsen hypothyroidism**
- recommended daily dose of iodine is **90 µg for pre-school children**, **120 µg for school children, 150 µg in adults and 250 µg in pregnancy**
- **Chronic excessive iodine intake usually increased serum TSH levels** — in susceptible individuals.
- **Selenium** supplementation may **reduce TPOAb** levels in patients with autoimmune thyroid disease
- There is insufficient evidence that **selenium** therapy normalizes increased serum TSH levels in individuals with chronic autoimmune thyroid disease

Management

Thyroid hormone replacement with LT4

- full replacement doses in adults are **1.6 µg/kg/day**
- **Lower** starting doses in older individuals, mild hypothyroidism or those with untreated cardiovascular disease
- Over- estimate the requirements of individuals with **obesity**, BMI-adjusted dosing algorithms have been developed
- **primary hypothyroidism**, target to the **normalization of serum TSH level**s
- **central hypothyroidism**, target serum **fT4 level in the upper half of the reference range**
- Serum TSH levels should be monitored **6 weeks** after initiation of treatment or any change in dose and then **every 6–12 months thereafter**

- LT4 should be taken ideally **60 min before breakfast** but taking LT4 **30 min before breakfast** or at **bedtime** on an empty stomach is also acceptable
- **Malabsorption** of LT4 might also occur following **bariatric** surgery or owing to **gastrointestinal disorders**
- In patients with **malabsorption**, treatment with **liquid** rather than tablet LT4 formulations might help to stabilize TSH levels
- TSH levels should be monitored after starting or stopping medications that might interfere with LT4 absorption, binding or metabolism(Table 2)

Table 2 | **Medications that alter thyroid hormone absorption, binding or metabolism**

Medications	Mechanism	Effect on LT4 requirements
Calcium carbonate, calcium citrate or calcium acetate; ferrous sulfate; proton-pump inhibitors; aluminium hydroxide; sucralfate; raloxifene; bile acid sequestrants	Decreased LT4 absorption	Increased (if LT4 doses not taken 4 h apart)
Phenytoin; phenobarbital; carbamazepine; rifampin; ryrosine kinase inhibitors	Increased thyroid hormone metabolism	Increased
Bile acid sequestrants	Reduced enterohepatic thyroid hormone circulation	Increased
Oral oestrogens; selective oestrogen receptor modulators; mitotane; opiates; 5-fluorouracil	Increased thyroxine-binding globulin levels	Increased
Androgens; nicotinic acid; chronic glucocorticoid therapy; danazol; L-asparaginase	Decreased thyroxine-binding globulin levels	Decreased
Amiodarone	Inhibition of 5′-deiodination (inhibits production of T_3 from T_4)	Increased

Treatment of subclinical hypothyroidism in adults

- risk for **progression** from subclinical to overt hypothyroidism is **~2–4%** annually and is more likely when patients have positive TPOAb
- **TSH levels >10 mIU/l** are associated with **increased cardiovascular and mortality risk**
- A meta-analysis suggested that **LT4** might **decrease mortality** in patients with **subclinical hypothyroidism aged <65–70 years old but not in older individuals**

Treatment of subclinical hypothyroidism in adults

- **one guideline recommends against** treatment when TSH levels are <**20 mIU/l**
- Most authors suggest individualized consideration of **low-dose LT4** in patients:
- ≤70 years of age
- symptoms potentially referable to hypothyroidism
- cardiovascular risk factors
- goiter
- positive TPOAb
- **planning** pregnancy
- **and/or** have a serum TSH level **persistently** >**10 mIU/l**

Treatment in pregnant women

- Developing fetus relies entirely on maternal thyroid hormones during of **brain development** (usually **before gestation weeks 16–20)**
- Untreated overt hypothyroidism in pregnancy is associated with increased risks for **miscarriage**, **preterm delivery**, **gestational hypertension**, **pre-eclampsia, low birthweight, fetal death and impaired child intellectual development**
- Overt hypothyroidism in pregnancy requires prompt LT4 initiation

Treatment in pregnant women

- **Maternal subclinical hypothyroidism** is associated with increased risks for **pregnancy loss, placental abruption, premature rupture of membranes, preterm delivery, and neonatal death**
- **Maternal hypothyroxinaemia (low fT4 in the setting of normal serum TSH levels)** has also been associated with **adverse obstetric and child neurodevelopmental outcomes**
- clinical trials to date **have not clearly shown** a **benefit of LT4** treatment for **subclinical hypothyroidism or hypothyroxinaemia** in pregnancy
- Current recommendations in clinical practice guidelines are variable (Table 3).

Table 3 | **Clinical guidelines for LT4 treatment of thyroid disease in pregnancy**

Organization (year of recommendations)	Subclinical hypothyroidism	Isolated maternal hypothyroxinaemia
American College of Obstetrics and Gynecology (2020)	Do not treat	Not discussed
American Thyroid Association (2017)	Treat if TSH level >10 mIU/l or if positive for TPOAb Consider treating if TSH level >4 mIU/l without TPOAb positivity	Do not treat
American Society for Reproductive Medicine (2015)	Treat with LT4	Not discussed
European Thyroid Association (2014)	Treat with LT4	Consider LT4 treatment if isolated hypothyroxinaemia is detected in the first trimester

Treatment in pregnant women

- pregnant on LT4 therapy will require an increase in LT4 dosing **(25–30% as soon as pregnancy is diagnosed)** when serum **TBG** levels are markedly increased and thyroid hormone is rapidly metabolized by placental **DIO3**
- Serum TSH levels should be closely monitored, approximately **every 4 weeks during the first half of gestation**
- **In pregnancy and pre-conception period, LT4 dosing should target a serum TSH level of <2.5 mIU/l**

Treatment of women with subfertility

- LT4 treatment started before conception **improves assisted reproductive** technology outcomes when the baseline **TSH >4.0 mIU**/l, particularly in women who are **positive for TPOAb**
- The recommended TSH target level in **treated** women is **<2.5 mIU/l**
- it is **not known** whether pre-conception treatment of **subclinical** hypothyroidism improves fertility or pregnancy outcomes in women who **conceive without assisted reproduction**

Treatment in infants and children

- **congenital** hypothyroidism infants require rapid initiation of LT4 therapy within the first **2 weeks** after delivery
- Starting LT4 doses in infants should be **10–15 µg/kg daily**
- Follow-up every **1–2 weeks** until the serum TSH level normalizes, every **1–3 months** until **12 months** of age, and then **every few months** thereafter until growth is completed
- primary hypothyroidism : **TSH within the age-specific reference range**
- central hypothyroidism: **fT4 in the upper half of the reference range in children**
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Treatment in infants and children

- In children without a clear underlying cause of permanent congenital hypothyroidism, **re-evaluation of the pituitary–thyroid axis** should be performed at **about 3 years of age** to determine whether ongoing LT4 treatment is needed.
- Younger children require higher doses of LT4 per kilogram of body weight than older children:
- 4–6 μg/kg is recommended from 1–3 years of age,
- 3–5 μg/kg from 3–10 years of age,
- 2–4 μg/kg for 10–16 years of age

Treatment in infants and children

- Most children with subclinical hypothyroidism do not progress to overt hypothyroidism ,most are asymptomatic
- Treatment of **subclinical** hypothyroidism in children **over 3 years** of age is considered only:
- **TSH levels are >10 mIU/l**,
- particularly in the setting of **TPOAb positivity**
- **hyperlipidaemia**
- concerns about **growth velocity**
- **Children with milder TSH elevation can be monitored without therapy**

Treatment in older patients

- **≥65–70 years of age** increased risk of adverse effects from excessive LT4 dosing:
- cardiac arrhythmia, progressive heart failure, increased bone turnover leading to osteoporosis, catabolic muscle loss, impaired quality of life and increased mortality
- start with **low** LT4 doses **(25–50 µg daily)**
- **physiological increase in serum TSH** with normal aging which argues against treatment of modest TSH elevations in older patients
- **Subclinical hypothyroidism** : **confirm** the **persistence of TSH elevations** above age-appropriate levels over time prior to treatment initiation as thyroid function might **normalize spontaneously in almost 50% of individuals ≥65 years of** age
- Targeting a serum **TSH of 4–6 mIU/l has been advocated in patients >70 years of age**

Challenges in treatment

- A minority of patients feel unwell on LT4 despite optimal TSH levels
- Normalization of serum TSH level typically **might not fully normalize serum T3 levels**, and it is plausible that persistent symptoms on LT4 monotherapy might **result from low systemic or tissue-specific T3 levels,** particularly in individuals with **polymorphisms in DIO2**, who might not efficiently convert T4 into the active hormone T3
- **Combination T3 and T4** therapy in patients who feel **unwell** on LT4 alone
- **T3-containing therapies should not be used in pregnancy or in young children**

Quality of life

- 84-item instrument Thyroid Patient Related Outcome (**ThyPRO**) is the most commonly used and has been identified as the most appropriate tool
- A **39-item** shortened version, ThyPRO-39, is currently available and includes a composite measure score to evaluate HRQOL
- After 6 months of LT4 treatment, improvement in HRQOL is observed but full recovery is not achieved
- Persistence of **residual symptoms** in patients with hypothyroidism after treatment has been described in up to **15%** of patients

Quality of life

- hypothesized to contribute to reduced HRQOL:
- stigma and the labelling effect of receiving the diagnosis of a chronic disease
- need to take medications every day,
- specific effect of autoimmunity on HRQOL.
- No difference in HRQOL using only LT_4 compared with a combination of LT_4 and LT_3
- There was also no improvement in HRQOL using different doses of LT_4 or desiccated thyroid extract

Quality of life

- **TRUST** trial to **compare LT4 versus placebo** for the treatment of **subclinical** hypothyroidism using ThyPRO as the main outcome in individuals **≥65 years of age**. This trial demonstrated **no benefit** of LT4 treatment on **HRQOL** during 1 year of follow-up
- A more recent analysis that combined data from the TRUST study and the IEMO 80-plus study did **not show any benefits of treatment of subclinical hypothyroidism in individuals ≥80 years of age**

- Further research
- is needed regarding the appropriateness of currently applied reference ranges and treatment thresholds, particularly in pregnancy
- and
- the potential benefit of LT4/liothyronine combination therapy for thyroid-related symptom relief, patient satisfaction and long-term adverse effects.