

Global epidemiology of hyperthyroidism and hypothyroidism

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Abstract

Thyroid hormones act on almost all nucleated cells and are essential for growth, neuronal development, reproduction, and regulation of energy metabolism. Hypothyroidism and hyperthyroidism are common conditions that affect all populations worldwide, with potentially devastating health consequences. Iodine nutrition is a key determinant of thyroid disease risk, however, other factors such as ageing, smoking status, genetic susceptibility, ethnicity, endocrine disruptors and the advent of novel biologic agents also influence thyroid disease epidemiology. In this report, we review the global incidence and prevalence of hyperthyroidism and hypothyroidism, highlighting geographical differences and the impact of environmental factors such as iodine supplementation. We highlight the pressing need for detailed epidemiological surveys of thyroid dysfunction and iodine status in developing countries. In the developed world, the prevalence of undiagnosed thyroid disease is likely falling, due to widespread thyroid function testing and relatively low thresholds for treatment initiation. However, continued vigilance against iodine deficiency remains essential in developed countries, particularly in Europe.

Introduction

Thyroid hormones act on almost all nucleated cells and are essential for normal growth and energy metabolism¹. Thyroid dysfunction is common, readily identifiable and easily treatable but if undiagnosed or untreated can have profound adverse consequences^{2,3}. Despite an increase in thyroid disease awareness and the availability of sensitive laboratory assays for the measurement of thyroid hormones it is remarkable that instances of extreme thyroid dysfunction continue to occur^{4,5}. Hypothyroidism and hyperthyroidism most commonly arise from pathology within the thyroid gland (primary thyroid disease), although rarely they may arise from disorders of the hypothalamus or pituitary (central) or from peripheral causes⁶. Conditions causing thyroid dysfunction are summarized in **Figure 1**.

Because the clinical presentation of thyroid disease is highly variable and often non-specific the diagnosis of thyroid dysfunction is predominantly based on biochemical confirmation. The complex inverse association between the pituitary derived thyroid stimulating hormone (TSH) and the thyroid hormones, free thyroxine (FT4) and free tri-iodothyronine (FT3), renders TSH the more sensitive marker of thyroid status⁷. Accordingly, overt hypothyroidism is defined as TSH concentrations above the reference range and FT4 levels below the reference range while subclinical hypothyroidism is defined as TSH levels above the reference range, but FT4 levels within the population reference range⁸. Likewise, the reverse hormone pattern is applied in the definition of overt (low TSH, high FT4) and subclinical hyperthyroidism (low TSH, normal FT4).

Iodine is an integral component of thyroid hormones but is unevenly distributed globally⁹. Over a billion people worldwide live in iodine deficient areas with populations at greatest risk residing in remote mountainous regions such as in South-East Asia, South America and Central Africa¹⁰. Population differences in iodine nutrition play a major role in the global prevalence of thyroid dysfunction. Nodular thyroid disorders are more prevalent in iodine deficiency while autoimmune thyroid disorders including Hashimoto's thyroiditis and Graves' disease occur more frequently in iodine-replete populations. However, a multitude of other risk factors including genetic and ethnic susceptibility, gender¹¹, smoking¹², alcohol consumption^{9,13-15}, presence of other auto-immune conditions¹⁶, syndromic conditions¹⁷ and drug exposures^{18,19} also influence thyroid disease epidemiology²⁰ (**Table 1**). Lastly, the detection of thyroid dysfunction is driven by clinical practice trends²¹ and in recent decades, progressive lowering of treatment thresholds together²² with increased thyroid function testing

with sensitive assays has led to a higher prevalence of so called borderline or mild cases²². This review summarises the current epidemiology of hyperthyroidism and hypothyroidism and highlights global differences and environmental factors that influence disease occurrence.

Epidemiology of Hyperthyroidism

Overview

The prevalence of overt hyperthyroidism ranges from 0.2 to 1.3% in iodine sufficient parts of the world^{23,24} (**Table 2**). In the UK Whickham study the incidence of hyperthyroidism was estimated at between 100-200 cases per 100,000 a year with a prevalence of 2.7% in women and 0.23% in men, taking into account both established and possible cases²⁵. These figures were considerably higher than earlier retrospective data from the USA which reported an incidence of 30 cases per 100,000/year for Graves' disease in the period 1935-1967²⁶. A 20-year follow up of the Whickham cohort showed an ongoing incidence of 80 cases/100,000 women/year^{24,27}. In the United States National Health and Nutrition Examination Survey (NHANES III) overt hyperthyroidism was detected in 0.5% of the population while 0.7% of the population had subclinical hyperthyroidism²⁴ with an overall prevalence of 1.3%. Studies from several other countries including Sweden^{28,29} Denmark³⁰, Norway³¹, and Japan³² have all reported comparable incidence and prevalence rates. A meta-analysis of European studies estimated a mean prevalence rate of 0.75% and an incidence rate of 51 per 100,000 per year²³.

Global variation in the epidemiology of hyperthyroidism (Figure 2)

The prevalence and incidence of thyroid dysfunction is difficult to compare across countries due to differences in diagnostic thresholds, assay sensitivities, population selection, and fluxes in iodine nutrition and population dynamics (**Table 2**). Furthermore, the precise causes of hyperthyroidism are not always reliably defined. The prevalence of overt hyperthyroidism is roughly similar in Europe and the United States (0.7 vs. 0.5%)^{23,24}. In Australia a slightly lower prevalence of 0.3% was reported for each of overt and subclinical hyperthyroidism³³ while a five-year incidence of hyperthyroidism was estimated at 0.5%³⁴. In general the incidence of hyperthyroidism corresponds with population iodine nutrition with higher rates in iodine deficient countries, mostly due to an excess of nodular thyroid disease in the elderly^{35,36}. For example in Pescopagano, an iodine deficient village of Southern Italy, the prevalence of hyperthyroidism was much higher at 2.9% than in iodine sufficient countries, mostly due to an excess of cases of toxic nodular goiters³⁷. A cross sectional study in China

reported a higher prevalence of overt and subclinical hyperthyroidism in an iodine sufficient area compared to an iodine deficient area (1.2% vs 1.0%; $P < 0.001$)³⁸. These differences were however not seen either in China or in Japan when iodine sufficient areas were compared to areas with excessive iodine intake^{32,39}.

In Africa the epidemiology of thyroid dysfunction has proved more challenging to monitor due to a lack of comprehensive population based studies⁴⁰. Existing studies are largely sourced from hospital based cohorts that exclude large segments of the rural population⁴¹ and are unlikely to be representative of the general population. A population study from several elderly care homes in Cape Town indicated a prevalence of 0.6% and 1.7% of hyperthyroidism and hypothyroidism respectively, with two-thirds of cases being previously undiagnosed⁴². However, this study only included a population of Caucasian or mixed descent, and not black South Africans. In Johannesburg in 1981, the incidence of Graves' disease was 5.5 per 100,000/year which was substantially lower than rates reported in the rest of the world⁴³. However, a 60% rise in Graves' disease incidence was observed over a 10 year period possibly due to improvements in dietary iodine intake amongst urban migrants⁴³. Recent hospital based studies from Ghana show that contrary to earlier reports, Graves' disease is not uncommon, comprising 54% of all cases of thyroid dysfunction⁴⁴ although there may be ascertainment bias. While this may be due to improvements in iodine nutrition subsequent studies in the aftermath of iodisation in Ghana has shown marked increases in the incidence of both Graves' disease and nodular disease suggesting a role for improved diagnosis⁴⁵.

Aetiology and clinical phenotype

Graves' disease is the most common cause of hyperthyroidism in iodine replete populations. Other common causes include toxic multinodular goiter and autonomously functioning thyroid adenoma¹⁰ while less common causes are thyroiditis, pituitary TSH secreting adenoma, and drug induced hyperthyroidism. In iodine sufficient countries Graves' disease accounts for 70-80% of patients with hyperthyroidism²⁹ whereas in areas with iodine deficiency, Graves' disease constitutes about half of all cases of hyperthyroidism with the other half attributable to nodular thyroid disease³⁵. These differences were elegantly demonstrated in the classic epidemiological studies conducted by Laurberg *et al* in the ethnically identical Northern European populations of Iceland and Denmark. They showed a

high prevalence of Graves' disease in the iodine sufficient Iceland compared to a predominance of toxic multinodular goiter in Denmark with its lower iodine intake³⁵.

The clinical phenotype in hyperthyroidism also shows geographical variation. Compared to patients with nodular disease Graves' disease patients are younger, have higher thyroid hormone levels, and are more likely to present with overt than subclinical hyperthyroidism²⁹. Cardiovascular complications appear to be more prevalent in areas where toxic multinodular goitres are common in part due to the older age of patients with nodular disease. Sub-Saharan African populations suffer a disproportionate cardiovascular disease burden and it is uncertain whether this is due to genetic susceptibility or to socio-economic factors that promote late presentation and poor disease control⁴⁶. Ethnicity does seem to influence the risk of developing certain disease complications. For examples Graves ophthalmopathy is six times more common in Caucasians than in Asians⁴⁷. Furthermore, the rare but serious complication of hyperthyroidism, thyrotoxic periodic paralysis is significantly more common in Asian men. In China and Japan⁴⁸ periodic paralysis has an incidence of 2% compared to 0.2% in North America⁴⁹. The genetic basis of this condition has been extensively studied and variations in certain HLA haplotypes such as DRw8, A2, Bw22, Aw19, and B17 have been identified in patients of Chinese or Japanese origin⁵⁰.

Graves' disease

Graves' disease is characterized by hyperthyroidism and diffuse goiter; ophthalmopathy, pretibial myxedema and thyroid achropachy may also be observed. The pathogenesis of this enigmatic condition remains incompletely understood but the central pathogenetic event is the unregulated stimulation of the TSH receptor by autoreactive TSH receptor antibodies (TRAbs). Graves' disease has been described throughout the globe¹⁰ and predominantly affects women (female: male ratio 8:1), typically in their 3rd to 5th decades of life². Recent observational studies suggest that the clinical phenotype of Graves' disease, at least in Western countries, is becoming milder, presumably due to earlier diagnosis and treatment⁵¹. Graves ophthalmopathy occurs in 20-30% of patients while pretibial myxedema is now rarely observed⁵². A recent European survey showed a declining incidence of severe thyroid eye disease possibly due to reduction in smoking rates together with more effective management of early stage disease in multidisciplinary clinic set-ups⁵³.

Toxic nodular disease

Toxic nodular goitre is the most frequent cause of thyrotoxicosis in the elderly, especially in iodine deficient areas⁵⁴. Solitary toxic nodules are more common in women than in men with a 1:5 M:F ratio reported in some studies^{29,55}. In low iodine intake area the incidence of toxic multinodular goitre was 18.0 cases per 100,000/year compared to 1.5 cases per 100,000/year in a high iodine intake area ($p < 0.001$)³⁵. The incidence of solitary toxic nodules was similarly higher in low iodine intake (3.6 vs. 1.6 per 100,000/year; $p < 0.05$)³⁵. In a stable iodine sufficient area of Sweden, incidence rates for toxic multinodular goitre and solitary adenoma were 4.3 and 1.8 per 100,000/year respectively²⁹.

Thyroiditis

Thyroiditis is characterized by a self-limiting course of thyrotoxicosis, followed by hypothyroidism, and then return to normal thyroid function⁵⁶. It is slightly more common in females than males (ratio of 1.5:1)⁵⁷ and permanent hypothyroidism occurs in 10-20% of cases. Acute painful thyroiditis often presents following a respiratory tract infection⁵⁸ while painless thyroiditis may occur post-partum in up to 9% of otherwise normal women. Details of the epidemiology of painless thyroiditis are however limited. One registry study in Minnesota showed an estimated incidence of 4.9 cases per 100,000/year with permanent hypothyroidism in 15% of people⁵⁹. On the other hand a Danish scintigraphy based study estimated the incidence of painless thyroiditis to be only 0.49 cases per 100,000/year⁶⁰. Data from iodine-rich coastal areas of Japan suggested that as much as 10% of thyrotoxic patients had painless thyroiditis in contrast to 2.4% of thyrotoxic patients in New York⁶¹. Some authors have argued that this variation may be due to increases in iodine intake in previously iodine deficient regions⁶¹ although ascertainment bias remains possible. A poll of endocrinologists indicated that silent thyroiditis was uncommon in Europe, Argentina, and coastal areas of the United States but was more prevalent around the Great lakes of the United States and Canada⁶².

Drug induced hyperthyroidism

The iodine-rich compound Amiodarone has been available since the 1960s and remains widely used as an anti-arrhythmic agent. Amiodarone induced thyrotoxicosis is more common in iodine deficient areas⁶³ and appears to be more common in men⁶³. The reported prevalence is highly variable ranging from 1-38%⁶³⁻⁶⁵ with more detailed reported rates of 3% in North America⁶⁶ and 5.8% in Japan⁶⁷. However, these results need to be interpreted

with caution as the precise definition of AIT and the frequency of patient monitoring are key determinants of the observed prevalence. Other drugs that cause thyrotoxicosis include interferon- α , lithium, tyrosine kinase inhibitors, highly active antiretroviral therapies (HAART), immune checkpoint mediators and the humanised monoclonal antibodies used in the treatment of multiple sclerosis. Although these drugs may cause transient thyrotoxicosis through destructive thyroiditis the immune modifying agents such as interferon- α , HAART, and alemtuzumab may in addition induce Graves' diseases through less well-defined immune reactivation mechanisms.

Subclinical hyperthyroidism

Precise estimates of the prevalence of subclinical hyperthyroidism are difficult because epidemiological studies use different diagnostic thresholds. Studies report figures ranging from 1 to 5%⁶⁸ although some of these include patients on levothyroxine¹⁰. Data from the NHANES III study suggest a bimodal peak at age 20-39 years and at 80 years and above²⁴. The NHANES study also showed that women were more likely to have a TSH level less than 0.4 mU/l and that ethnicity influenced the risk of having subclinical hyperthyroidism with blacks having a prevalence of 0.4%, Mexican Americans 0.3%, and whites 0.1%²⁴. In Asia, prevalence ranges between 0.43% to 3.9% of the general population. Globally, the greatest risk factor for subclinical hyperthyroidism aside from levothyroxine use is iodine deficiency with the prevalence of subclinical hyperthyroidism rising to 6-10% in iodine deficient areas, largely due to toxic nodular goitres¹⁰. In the UK a TSH level <0.1 mU/L was observed in 5.8% of levothyroxine-treated patients while 10.2% had TSH 0.1-0.5 mU/l with women more likely to be over-replaced²². There is limited data on the risk of progression from subclinical to overt hyperthyroidism. In a Scottish database comprising 2,024 cases of subclinical hyperthyroidism the vast majority of untreated patients did not progress to overt hyperthyroidism and a third returned to normal thyroid status seven years later⁶⁹. Other studies showed that patients with more severe grades of subclinical hyperthyroidism progressed more frequently to overt disease^{70,71}.

Iodine induced hyperthyroidism

Iodine-induced hyperthyroidism, the Jod-Basedow phenomenon, is commoner in older persons with long standing nodular goitre and in regions of chronic iodine deficiency⁷² undergoing iodine supplementation. Iodisation programs temporarily increase the risk of

iodine induced hyperthyroidism; the risks are principally to the elderly who may have co-existing cardiac disease and also to those with limited access to healthcare⁷². Radiographic contrast agents, also cause iodine induced hyperthyroidism. Individuals with pre-existing multinodular goitre or those from iodine deficient areas are at greatest risk^{73,74}.

Pregnancy

Thyrotoxicosis in pregnancy has an estimated incidence of 0.2% for overt thyrotoxicosis and 2.5% for subclinical thyrotoxicosis. More recent data from the USA estimates the incidence to be 5.9 per 1000 pregnant women per year⁷⁵. The greatest risk of hyperthyroidism appears to be in the first trimester⁷⁶. Graves' disease is the most common cause of thyrotoxicosis in pregnancy² although other causes may also occur during gestation. The occurrence of hyperthyroidism in pregnancy may however be over-estimated by inclusion of cases of gestational thyrotoxicosis, a benign and transient disorder of pregnancy that typically occurs in the first trimester². The management of thyrotoxicosis in pregnancy is complex and has to address the risk of maternal hyperthyroidism with that of fetal harm from transplacental transfer of maternal antibodies and thionamide drugs^{77,78}.

Treatment of Hyperthyroidism

There is surprisingly substantial global variation in the treatment of hyperthyroidism. The choice of anti-thyroid drugs, radio-iodine or surgery may have a modest impact on the epidemiology of hypothyroidism given that radio-iodine and surgery ultimately result in permanent hypothyroidism. Unlike in Europe, USA endocrinologists have traditionally preferred radio-iodine over anti-thyroid drugs. Two-thirds of American Thyroid Association (ATA) respondents favoured the use of radio-iodine as the primary treatment modality for Graves' disease whereas only 20% of members of European and UK thyroid societies would use radioiodine as primary therapy⁷⁹. In Korea 10% of practitioners recommended thyroidectomy as first line treatment for Graves' disease in contrast to other regions where thyroidectomy is hardly used⁷⁹ For pragmatic reasons thyrotoxicosis in African countries is treated with anti-thyroid drugs or surgery due to limited availability of radioisotopes⁸⁰.

Epidemiology of Hypothyroidism

Overview

Iodine deficiency and auto-immune disease (Hashimoto's) account for the vast majority of cases of primary hypothyroidism³. A third of the world's population live in iodine deficient

areas and the devastating consequences of severe iodine deficiency on fetal and child neurological development are well recognised⁹. Furthermore, there is increasing concern of the possible effects of less severe grades of iodine deficiency during pregnancy on offspring cognitive development⁸¹. Changes in diet and agricultural practices have led to the re-emergence of iodine deficiency in countries previously believed to be iodine sufficient including developed countries⁸². In Europe, 44% of school-age children still have insufficient iodine intake and countries such as the UK, Italy, and Spain now appear to be moderately iodine deficient⁸³⁻⁹⁰.

In iodine sufficient countries, the prevalence of hypothyroidism ranges from 1-2%^{10,91} rising to 7% in individuals aged between 85-89 years⁹². In the absence of age-specific reference ranges for TSH an ageing population is likely to result in a higher prevalence of hypothyroidism. Hypothyroidism is approximately 10 times more common in women than men¹⁰. Data from Norway showed that the prevalence of untreated overt hypothyroidism was low at 0.1%, reflecting a fall of 84% from the 1990s. In the UK the rate of new prescriptions of levothyroxine for primary hypothyroidism increased 1.74 fold between 2001-2009²² indicating widespread testing.

Global variation in the epidemiology of hypothyroidism (Figure 3)

The prevalence of overt hypothyroidism in the general population varies between 0.2% and 5.3% in Europe^{93,94} and 0.3% and 3.7% in the USA⁹⁵. depending on the definition used and population studied (**Table 3**). Longitudinal studies from large UK cohorts report an incidence rate of spontaneous hypothyroidism of 3.5 – 5.0 per 1000 and 0.6 – 1.0 per 1000 in women and men, respectively^{27,96}. A survey conducted in Spain reported a prevalence of treated hypothyroidism, untreated subclinical hypothyroidism, and untreated clinical hypothyroidism of 4.2% 4.6 and 0.3%, respectively⁹⁷. In Australia, the five-year incidence of hypothyroidism in individuals aged above 55 years was 0.5% and 4.2% respectively³⁴ while the prevalence of overt and subclinical hypothyroidism is estimated at 0.5% and 5.0% respectively³³. The longest follow-up study is from the UK Wickham cohort^{25,27} where the mean annual incidence of spontaneous hypothyroidism during a 20 year follow-up period was 35 cases per 10,000 surviving women and 6 per 10,000 surviving men²⁷. Higher TSH levels and antibody positive were associated with increased risk of developing hypothyroidism with a positive interactive effect²⁷.

In the NHANES study, the overall prevalence of hypothyroidism was 4.6%²⁴. The prevalence was similar in Caucasians and Hispanic but was markedly lower in individuals of Afro-Caribbean descent (1.7%). A study from Brazil demonstrated similar differences with the highest prevalence of hypothyroidism seen in white (1.6%) compared to people of black (0.59%) or mixed (1.27%) ancestry⁹⁸. A separate study examined thyroid dysfunction in Brazilians of Japanese descent, with 0.8% found to have hypothyroidism and 8.9% subclinical hypothyroidism⁹⁹. Intriguingly overall thyroid dysfunction rates were lower in a study based in Japan¹⁰⁰ despite the older age range of the study population suggesting regional environmental differences.

Data from the Arab world are limited. One systematic review¹⁰¹ evaluated 21 studies that addressed thyroid disease prevalence across ten Middle Eastern countries. However, there was wide heterogeneity in the populations studied and most of the available studies were convenience samples sourced from cohorts with high risk of thyroid dysfunction such as diabetes, thyroid cancer, or surgical and histopathological series. In Tehran, an iodine sufficient area of Iran, the annual incidence rates of subclinical and overt hypothyroidism were 7.62 and 2.0 per 1000 persons, respectively¹⁰² and in the same population thyroid antibodies were detected in 16% of women and 8% of men¹⁰³ figures that are comparable to data from European populations¹⁰⁴

The overall disease burden of hypothyroidism in Sub-Saharan Africa based on largely hospital clinic data, has been generally felt to be minimal, even rare, and substantially lower than the prevalence found in African-Americans. In a small hospital study in Lagos, Nigeria, the majority of patients seen in a thyroid clinic had hyperthyroidism¹⁰⁵. In this study Hashimoto's thyroiditis was diagnosed in only 6% of patients and positive thyroid peroxidase antibodies were detected in 4% of the healthy population¹⁰⁵. However, the significant referral bias and exclusion of large numbers of the general population should question the generalizability of these figures. More recently, thyroid dysfunction has been highlighted in African as well as Asian patients with HIV on multi-drug resistant treatment regimens for tuberculosis with agents like ethionamide that inhibit thyroid hormone synthesis¹⁰⁶.

In China it is striking that in the last decade, the prevalence of subclinical hypothyroidism has increased (16.7% vs 3.22%), along with the proportion of the thyroid peroxidase antibody positive population¹⁰⁷, reflecting the transition to iodine sufficiency^{107,108}. Similar to China, a recent large cross-sectional multi-city study in India reported remarkably high rates of

hypothyroidism (10%) although this included self-reported cases¹⁰⁹. Furthermore, regional variations were seen with higher rates in inland compared to coastal regions¹⁰⁹. There is now a growing appreciation in India that hypothyroidism represents a substantial health problem, despite extensive universal salt iodisation¹¹⁰. The prevalence appears to be substantially higher than in Europe and the USA and whilst genetic and iodine factors are likely to play a substantial role other factors including high levels of endocrine disruptors have been postulated to have an impact¹¹⁰.

Hypothyroidism in pregnancy

In iodine sufficient areas the prevalence of hypothyroidism in pregnancy is around 2%. Optimal control of thyroid status is essential for both obstetric and offspring outcomes although precise treatment thresholds are at present unclear¹¹¹. Correction of both overt hypothyroidism and hyperthyroidism dramatically reduces the risk of fetal loss and preterm birth^{112,113}. Subclinical hypothyroidism before 20 weeks of pregnancy is associated with an increased risk of miscarriage¹¹⁴ and isolated hypothyroxinemia (low FT4 normal TSH) is associated with adverse pregnancy outcomes including prematurity¹¹⁵. Randomised controlled trials in women with gestational subclinical hypothyroidism and isolated hypothyroxinemia however have failed to show benefits of levothyroxine therapy on offspring IQ^{116,117} or obstetric outcomes¹¹⁷. In these trials however levothyroxine was initiated from the end of the first trimester of pregnancy after the early critical phase of fetal brain development. Universal thyroid screening in pregnancy is therefore contentious although it has been shown to be cost-effective in analytical economic models¹¹⁸.

Congenital Hypothyroidism (CH)

Congenital hypothyroidism is one of the most common treatable cause of mental retardation¹¹⁹. Until recently congenital hypothyroidism was estimated to affect approximately 1 newborn in 3500–4000 births¹²⁰ but over the last decade several screening programs have reported an increase in prevalence. Analysis of data from the USA identified a near doubling of the incidence of CH in a 15 year period from 1987 at 1:3985 to 1:2273 in 2002¹²¹. A similar change has also been observed in New Zealand¹²². Some of this increase is due to changes in the ethnicity of the populations studied although lowering of the TSH cutoff has contributed. Despite the clear advantages of birth screening programs it is estimated that only approximately 29.3% of the world's birth population is screened for CH¹²³.

Drug induced hypothyroidism

Several drugs are known to cause hypothyroidism until recently the most notable of which were lithium and amiodarone, and tyrosine kinase inhibitors. Lithium therapy causes overt hypothyroidism in between 5-15% of lithium-treated patients¹²⁴ and in one study of laboratory data the use of lithium increased the risk of hypothyroidism by more than two-fold (OR = 2.31 95%CI 2.05, 2.60 p<0.0001¹⁹). Amiodarone induced hypothyroidism is more common than amiodarone induced thyrotoxicosis in iodine sufficient areas¹²⁵.

Immune checkpoint inhibitors have emerged as key treatments in managing advanced cancers have the ability to reactivate the immune system against cancer cells, but can also induce autoimmune side effects which have a preponderance for the thyroid axis¹²⁶. These agents can be given singly or in combination. Whilst these may not substantially increase the incidence of thyroid disease, the complexity of these patients may result in a substantial addition to specialist thyroid clinics.

The key agents are anti-cytotoxic T- lymphocyte antigen 4 (CTLA-4 e.g. Ipilimumab) anti-programmed cell death protein -1 (PD-1 e.g. Nivolumab and pembrolizumab) and anti-PD-1 ligand molecules (PD-L1 and PD-L2). They have been approved for a variety of cancers including melanoma, non small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma and head and neck cancers¹²⁶.

These immune checkpoint inhibitors can result in primary or secondary hypothyroidism and primary hyperthyroidism. Secondary hypothyroidism is more common with anti CTLA-4 antibodies, where as primary hypothyroidism is seen more commonly with anti-PD-1 and anti-PD-L1 monoclonal antibodies¹²⁶. A recent meta-analysis¹²⁷ of 38 randomized controlled trials comprising 7,551 patients used Ipilimumab (CTLA-4) as a baseline and identified that those who received combination therapy had the highest odds of hypothyroidism OR=3.81 (95%CI 2.10, 6.91), hyperthyroidism OR=4.27 (95%CI 2.05, 8.90) and hypophysitis OR=2.2 (95%CI 1.39, 3.60). Those on PD-1 inhibitors also had a higher risk of developing hypothyroidism OR=1.89 (95%CI 1.17, 3.05) than those on Ipilimumab.

Alemtuzumab a novel treatment for multiple sclerosis has also been associated with a high prevalence of hypothyroidism¹²⁸. Tyrosine kinase inhibitors can result in an increased risk of

hypothyroidism with 27% of treated patients requiring levothyroxine¹²⁹ during their treatment.

Iodine induced hypothyroidism

The underlying mechanism of iodine-induced hypothyroidism is not well understood, but is attributed to a failure of thyroid adaptive mechanisms to an acute iodide load (Wolff–Chaikoff effect). Common sources of excess iodine include supplementation, diet, iodinated contrast agents, and medication. Discussion of the impacts of iodine fortification on the epidemiology of hypothyroidism and hyperthyroidism is shown below.

Effect of iodine fortification on the prevalence and incidence of hypothyroidism and hyperthyroidism

Over the last 25 years many countries across the globe have introduced universal salt iodisation programs which have seen a dramatic decline in the number of iodine deficient countries. As at 2016, 110 countries have now been classed as having optimal iodine intake while insufficient iodine intake persists in only 19 countries¹³⁰. Iodine fortification of all food-grade salt is now mandated in close to 120 countries¹³¹, although voluntary fortification programs do not allow for enforcement. Moreover, these initiatives require regular monitoring to ensure that fortification programmes meet changing demands, given the adverse outcomes of over or undersupply of iodine. In Europe, few countries have regular monitoring, but those engaged in regular studies are using heterogeneous methods and outcomes, which prohibit an appropriate comparison within meta-analyses.

Table 4 summarizes some of the studies with longitudinal data that have surveyed the occurrence of thyroid dysfunction in relation to national iodisation programmes. These studies show variable trends that depend on pre-existing population iodine status, magnitude of iodisation and survey methodology. There is well documented evidence of an increase in the frequency of thyroid autoimmunity following iodisation programmes^{20,40,108,132}. The mechanism of this phenomenon is complex but may be due to iodisation of thyroglobulin,¹³³ which enhances immunogenicity through altered epitope expression¹³⁴. From fortification programs in Denmark, it is apparent that even a cautious iodisation programme is associated with an increase in TPO antibodies from 14.3% and 23.8%¹³⁵. As a result, the incidence of overt hypothyroidism increased almost 20% from 38.3/100.000 per year at baseline to

47.2/100.000 per year, an increase which was most marked in young and middle-aged individuals in an area of moderate iodine deficiency¹³⁶.

A study in Poland showed that hypothyroidism occurred more frequently after a mandatory iodine prophylaxis (2.1% vs. 1.4% in females and 0.3% vs. 0% in males)¹³⁷. In an elderly Icelandic population with relatively high iodine intake, the prevalence of high serum TSH concentrations (> 4mU/l) was 18% whereas in subjects residing in Jutland, Denmark, with low iodine intake, high serum TSH levels were prevalent in 3.8% of the subjects showing that ingestion of smaller quantities of iodine could impact thyroid function in a population at large¹³⁸. Similar to these findings, the prevalence of non-autoimmune hypothyroidism was 12.1% in coastal areas of the Hokkaido Islands, Japan compared to 2.3% in non-coastal areas due to the high iodine intake from seaweed (kelp) consumption¹³⁹. In a five year follow up study in China, the prevalence of subclinical hypothyroidism and thyroid autoimmunity was highest in areas with excessive iodine nutrition status¹⁰⁸. However data from Tasmania¹⁴⁰, Bangladesh¹⁴¹ Sri-Lanka and Italy¹⁴² did not show an increase in hypothyroidism following iodine fortification although a minimal rise in TSH was observed in Italy¹⁴².

One offshoot of iodisation is the risk of thyrotoxicosis secondary to excessive iodisation. A growing number of countries, 10 as at 2016, are now classed as having excessive iodine intake status. In the past, cases of iodine-induced thyrotoxicosis were observed following salt iodisation programmes or increases in dietary iodine intake¹⁴³⁻¹⁴⁶. Most notable of these occurred in the Tasmanian state of Australia¹⁴⁵, in Harare, Zimbabwe¹⁴⁴, and Kivu in Northern Zaire¹⁴³. In these areas increases in cases of toxic nodular goitres were observed in the aftermath of iodisation with fatalities resulting from cardiovascular complications in some areas¹⁴³. Susceptible population groups are typically elderly with longstanding nodular goitres. However, iodine induced thyrotoxicosis is transient and limited to instances of precipitous increases in iodine intake in areas of longstanding iodine deficiency or in urban migrants from iodine deficient areas⁴⁰. A chronic state of excessive iodine nutrition has raised concerns in some sub-Saharan African countries⁹ and excess iodine nutrition has been reported amongst refugees and displaced populations within the region who rely on iodised salt sourced from food aid from regional governments and international aid agencies^{147,148}. While these important observations call for continued vigilance of iodine supplementation programmes they should not deter from the goals of eradication iodine deficiency.

Conclusion

This review has summarised the current epidemiology of hypothyroidism and hyperthyroidism and examined factors that affect disease prevalence. In iodine-sufficient areas, the majority of thyroid dysfunction is due to thyroid auto-immunity and data from Europe and other parts of the world has revealed the influence of variation in iodine status and the impact of iodine supplementation on the epidemiology of thyroid dysfunction^{9,23,82}. Other factors that may impact on the epidemiology of thyroid disease is the increasingly widespread use of thyroid function testing⁹³ lowering of thresholds for treatment, and introduction of novel therapeutic agents with effects on thyroid function. Also, this work has demonstrated striking geographical and ethnic differences in thyroid disease epidemiology. In African-American populations the frequency of hypothyroidism appears to be lower than in Caucasians²⁴. Careful re-analysis of NHANES indicates that non-Hispanic blacks had 54% lower risk of hypothyroidism than non-Hispanic whites, but had over a threefold higher risk of hyperthyroidism¹⁴⁹. Data from Brazil shows a similar pattern with blacks having the lowest prevalence of hypothyroidism and those of dual heritage and whites having a higher prevalence (**Table 3**)⁹⁸. In India striking regional variations in the prevalence of hypothyroidism has been reported raising the need for standardization of assay methods and regional and population specific reference ranges.

A greater understanding of the genetic variants responsible for variation in TSH and thyroid hormone levels is emerging, but only a small proportion (<10%) of the genetic architecture has been explained to date^{150,151}. Variants have been identified which increase the risk of Graves' disease^{150,152} and also TPO antibody positivity¹⁵⁰. Greater understanding of the genetic architecture is required particularly in non-Caucasian populations. Analysis of differences in risk variants identified in different populations would provide enhanced insight into the variations in thyroid disease globally and may also explain borderline TSH abnormalities. Currently, many individuals with modest TSH abnormalities are started on treatment²² but such individuals would have spontaneously reverted to normal without intervention¹⁵³. A recent trial of thyroid hormone therapy for older adults with subclinical hypothyroidism, the TRUST trial¹⁵⁴, identified that up to 60% of potentially eligible elderly individuals with an elevated TSH had returned to euthyroidism when reassessed for the trial. The clinical significance of subclinical thyroid dysfunction or of variations in thyroid hormones within the laboratory reference range remain contentious¹⁵⁵⁻¹⁵⁸ and beyond the

scope of this review. However, genetic risk factor profiles may in future augment other risk factors in stratifying individuals with borderline TSH abnormalities¹⁵¹.

There is still considerable controversy as to whether healthy adults in iodine sufficient areas will benefit from screening for thyroid disease. Targeted screening for thyroid dysfunction in pregnancy is commonplace and universal thyroid screening in pregnancy continues to generate impassioned debate¹¹¹. The prevalence of unsuspected thyroid disease is low in developed countries but a substantial proportion of individuals will have evidence of minor thyroid dysfunction⁹³. However, at present no appropriately powered prospective, randomized, controlled, double-blinded interventional trial of either levothyroxine therapy for subclinical hypothyroidism or anti-thyroid therapy for subclinical hyperthyroidism exists in the healthy general younger adult population although data are emerging for older individuals¹⁵⁸.

It is striking that up to 50% of cases of subclinical hyperthyroidism have arisen from levothyroxine treatment especially as the threshold for treatment has fallen²². Whilst studies are urgently needed in the developed world on the incidence and prevalence of thyroid disease, studies are also needed on the consequences of current prescribing practice in the developed world with a greater clarification of treatment thresholds in pregnancy as well as the general population. Ongoing data capture of the prevalence and incidence of thyroid disease is still required in the developing world especially in areas where there are fluxes in population iodine nutrition. In the developed world, endeavours such as EUthyroid, a collaborative venture, promoting monitoring of iodine status and its consequences on thyroid disease epidemiology will be crucial. Such initiatives will need to be supported by appropriate randomised controlled trials in subclinical thyroid disease and in optimal management of hypothyroidism.

Tables and Figures Legends

- Table 1** Risk factors for developing Hypothyroidism and Hyperthyroidism
- Table 2** Incidence and Prevalence of Hyperthyroidism in Iodine Sufficient and Iodine Deficient Countries
- Table 3** Incidence and Prevalence of Hyperthyroidism in Iodine Sufficient and Iodine Deficient Countries
- Table 4** Longitudinal studies of iodine supplementation and frequency of hyperthyroidism and hypothyroidism
- Figure 1** Causes of Hypothyroidism and Hyperthyroidism
- Figure 2** Map of overt hypothyroidism prevalence (selective populations used when representative data not available)
- Figure 3** Map of overt hyperthyroidism prevalence (selective populations used when representative data not available)

Table 1 Risk factors for developing Hypothyroidism and Hyperthyroidism

Risk factor	Hypothyroidism	Hyperthyroidism	Comment
Female Sex ²³	+	+	Sex hormones and the skewed inactivation of the X chromosome, are suspected to be triggers
Iodine deficiency	+	+	Severe iodine deficiency may cause hypothyroidism
Iodine excess	+	+	Excess iodine status may trigger hyperthyroidism typically in elderly individuals with longstanding thyroid nodules
Transition from iodine deficiency to sufficiency	+		Transition from iodine deficiency to sufficiency was associated with an increase in TPO antibodies from 14.3% and 23.8% in one study ¹³⁵ . As a result, the incidence of overt hypothyroidism increased almost 20% from 38.3/100.000 per year at baseline to 47.2/100.000 per year ¹³⁶ .
Other autoimmune conditions	+	+	One study reported that another auto-immune disease was present in almost 10% of patients with Graves' disease and in 15% of patients with Hashimoto's thyroiditis with rheumatoid arthritis being the most common ¹⁶ .
Genetic risk factors			Both Graves' disease and Hashimoto's thyroiditis have genetic predispositions. Genome wide association data have identified regions associated with TPO antibody positivity ¹⁵⁹ and thyroid disease ^{159, 160} . Whole genome sequence may reveal novel insights ¹⁵¹ .
Smoking	—	+	Current smoking increases the odds of Graves' hyperthyroidism almost 2 fold and increases the risk of Graves' ophthalmopathy almost 8 fold ¹⁶¹ . Smokers also have a slower response during antithyroid drug treatment ¹⁶² . Smoking may protect against hypothyroidism as smokers have a 30-45% reduction in the odds of being TPO antibody positive ^{163,164} . Current smokers had a 50% lower prevalence of subclinical hypothyroidism and a 40% lower prevalence of overt hypothyroidism with smokers ¹⁶⁵ .
Alcohol	—		Moderate alcohol intake may be associated with a reduced risk of hypothyroidism ¹⁶⁶
Selenium deficiency	+	+	One study reported that patients with newly diagnosed Graves' disease and hypothyroidism had lower selenium levels than the normal population, particularly in patients with Graves' disease ¹⁵
Drugs	+	+	Examples include Amiodarone ¹⁸ ,Lithium ¹⁹ , interferon gamma
Infections			Infectious agents have been associated with both auto-immune diseases and Graves' disease ¹⁶⁷ . The most well studied is Yersinia enterocolitica although retroviruses have been identified a ^{13,167} .
Syndromic Conditions	+		In Down's syndrome almost 25% of patients in a large registry had thyroid disease, the commonest being primary hypothyroidism ¹⁷ . The prevalence of hypothyroidism in Turner's syndrome is approximately 13% ¹⁶⁰ but the incidence increases substantially by the third decade.

Table 2: Incidence and prevalence of hyperthyroidism in iodine sufficient and iodine deficient countries

Author, country, publication year	Study date	Sample no	Age, years	Female, %	Iodine intake/UIC	Incidence per 10 ⁵ /year			Prevalence, %		
						M	F	Total	M	F	Total
IODINE SUFFICIENT											
Tunbridge, UK, 1977 ²⁵	1972-1974	2,779	>18	54	811 nmol/24h				0.2	1.9	1.1
Mogensen, Denmark, 1980 ¹⁶⁸	1972-1974	439,756	>0	50		8.7	46.5	27.6			
Berglund, Sweden, 1990 ¹⁶⁹	1970-1974	258,000	>0	52		10.1	40.6	25.8			
Konno, Japan, 1993 ³²	1990-1991	4,110	Adult	29					0.3	0.5	0.3
Galofre, Spain, 1994 ¹⁷⁰	1990-1992	103,098	15–85	57		6.5	89.1	52.4			
Berglund, Sweden, 1996 ²⁸	1988-1990	231,774	>0	53		10.9	72.0	43			
Vanderpump, UK, 1995 ²⁷	1975-1994	1,877	38-93	56	102 µg/g cr	0	80	53	0.2	3.9	2.5
Bjoro, Norway, 2000 ³¹	1995-1997	94,009	>20	50					0.1	0.3	0.2
Canaris, USA, 2000 ⁹⁵	1995	24,337	>18	56							0.1
Hollowell, USA, 2002 ²⁴	1988-1994	13,344	>12		145 µg/l						0.2
Volzke, Germany, 2003 ¹⁷¹	1997-2001	3,941	20-79	48	12 µg/dL						0.4
Flynn, UK, 2004 ⁹⁶	1993-1997	369,885	>0			14	77	46			0.6
O' Leary 2006 ¹⁷²	1981	2,115	16-89	50			16-89		0.1	0.2	50 0.1
Leese, UK, 2007 ¹⁷³	1994-2001	388,750	>0	52		14	87		0.2	1.3	0.8
Lucas, Spain, 2010 ¹⁷⁴	2002	1,124	18-74	56	150 µg/l				0.2	0.2	0.2
Asvold, Norway, 2012 ⁹³	1995-2008	15,106	>20	67		49.6	97.3	81.6			
Delshad, Iran, 2012 ¹⁷⁵	1999-2005	1,999	>20	61		21	140				
Unnikrishnan, India, 2013† ¹⁰⁹	2011	5376	18-100	53.7					0.62	0.72	0.67
Sriphrapadang, Thailand, 2014 ¹⁷⁶	2009	2545	≥14	46							0.94
Nystrom, Sweden, 2013 ²⁹	2003-2005	631, 239	>0		125 µg/l			27.6			
Valdes, Spain, 2017 ⁹⁷	2009-2010	4,554	18-93	58	117 µg/l						0.4
IODINE DEFICIENT											
Kalk, South Africa, 1981 ⁴³	1974-1984	1,246,294	>15	48		0.7	8.8	5.5			
Aghini-Lombardi, Italy, 1999 ³⁷	1995	992	>15	58	55µg/l				2.9	3.0	2.9
Knudsen, 1999, Denmark ¹⁰⁴	1993-1994	2,613	41-71	49	70µg/l				0	1.2	0.6

Knudsen, 2000, Denmark ³⁰	1997-1998	2,293	18-65	79	45µg/l						0.4
Knudsen, 2000, Denmark ³⁰	1997-1998	2,067	18-65	79	61µg/l						0.8
Hoogendoorn, 2006, Netherlands ¹⁷⁷	2002-2003	5,167	>18	54					0.2	0.6	0.4
Laurberg, 2006, Denmark ³⁶	1997-1998	310,124	18-65	50	68µg/l	36	149.1	92.9			
Laurberg, 2006, Denmark ³⁶	1997-1998	225,707	18-65	53	53µg/l	26.8	101.7	65.4			

Data is for cases of overt hyperthyroidism except where otherwise stated. Iodine status is based on reported status by authors; spaces are left blank where there is no data on incidence or prevalence or where the data is unclear from the report. †same study population, studied at 5 and 11 year intervals post iodization.

†Study from 8 cities with a wide mix of iodine status ranging from sufficient to deficient. Studies in specific population groups such as children, pregnant women, specified co-morbid states, and unstable iodine nutrition are excluded

IODINE DEFICIENT

Laurberg, Denmark, 1999 ¹⁷⁹	24 months	569,108	>0	51	60 µg/day	3.6	22.9	13.5			
Aghini-Lombardi, Italy, 1999 ³⁷	1995	992	>15	58	55 µg/l				0	0.3	0.2
Knudsen, 1999, Denmark ¹⁰⁴	1993-1994	2,613	41-71	49	70 µg/l				0.2	0.5	0.3
Knudsen, 2000, Denmark ³⁰	1997-1998	2,293	18-65	79	45 µg/l						0.2
Knudsen, 2000, Denmark ³⁰	1997-1998	2,067	18-65	79	61 µg/l						0.6
Hoogendoorn, 2006, Netherlands ¹⁷⁷	2002-2003	5,167	>18	54					0.2	0.6	0.4
Laurberg, 2006, Denmark ³⁶	1997-1998	310,124	18-65	50	68 µg/l	9.4	43.5	26.5			
Laurberg, 2006, Denmark ³⁶	1997-1998	225,707	18-65	53	53 µg/l	17.3	60.6	40.1			
Teng†, China, 2006 (deficient) ¹⁰⁸	1999	1103	≥18								0.3
Du, China, 2014 (mildly deficient) ³⁸		667	≥18	71					0.15	0.90	1.05

Data is for cases of overt hypothyroidism except where otherwise stated. Iodine status is based on reported status by authors; spaces are left blank where there is no data on incidence or prevalence or where the data is unclear from the report. †same study population, studied at 5 and 11 year intervals post iodization. †Data from 8 cities with a wide mix of iodine status from sufficient to deficient. Studies in specific population groups such as children, pregnant women, specified co-morbid states, and unstable iodine nutrition are excluded

Table 4: Longitudinal studies of iodine supplementation and frequency of hyperthyroidism and hypothyroidism

Author, year, Country	Sample number	Age, years	Female, %	Iodisation year	Form of iodisation	MUI, mcg/L	Hypothyroidism		Hyperthyroidism	
							Pre-iodine	Post-iodine	Pre-iodine	Post-iodine
Galofre, 1994, Spain ¹⁸⁰	103,098	15-85	57	1985	KI 60 mg/kg salt	—	—	—	3.10/10 ⁵	7.68/10 ⁵
Yang, 2002, China ¹⁸¹										
Panshan	1103	14-88	65	1996	USI	84	—	—	28/10 ⁵	81/10 ⁵
Zhangwu	1584	14-95	69	1996	USI	243	—	—	23/10 ⁵	36/10 ⁵
Huanghua	1074	14-79	66	1996	USI	651	—	—	35/10 ⁵	37/10 ⁵
Teng, 2006, China ¹⁰⁸										
Panshan	884	19-80	68	1996	USI	88	—	1.2%	—	5.3%
Zhangwu	1270	19-84	70	1996	USI	214	—	3.8%	—	5.9%
Huanghua	1074	19-83	69	1996	USI	634	—	8.1%	—	2.3%
Golkowski, 2007, Poland ¹⁸²	1424	16+	66	1997	KI 30 mg/kg salt	112	—	—	4.8%	6.5%
Pedersen, 2007, Denmark ¹³⁶										
Aalborg	310124	>0	NS	1998	8-13 ppm	53	—	—	30/10 ⁵	40/10 ⁵
Copenhagen	225707	>0	NS	1998	8-13 ppm	68	—	—	52/10 ⁵	57/10 ⁵
Heydarian, 2007, Iran ¹⁸³	1891	>20		1994	KI 40 mg/kg salt		328/10 ⁵	25.2/10 ⁵	88/10 ⁵	63/10 ⁵
Cerqueira, 2011, Denmark ¹⁸⁴	5,300,000									
Western region	2,920,000	>0	NS	1998	8-13 ppm	53	72/10 ⁵	126/10 ⁵		
Eastern region	2,380,000	>0	NS	1998	8-13 ppm	68	87/10 ⁵	163/10 ⁵		
A-Lombardi, 2013, Italy ¹⁸⁵	2289	>1	64	2005	KI 30 mg/kg salt	55	2.8%	5.0%	2.1%	1.6%
Tammaro, 2016, Italy ¹⁴²	7976		85	2005					2.5%	2.1%
Hong, 2017, Australia ¹⁴⁰	389910	45±20	59	2001	Iodised bread	75	—	60% fall*	—	62% fall*

Prevalence figures are in % and incidence rates are in cases/10⁵, Figures represent overt and subclinical thyroid dysfunction. Age is in range or mean ± standard deviation. KI, potassium iodide, USI, universal salt iodisation, ppm, parts per million, NS, not stated, MUI, median urinary iodine concentration at onset of programme. *fall in the incidence of overt thyroid dysfunction from 1995-2013.

Figure 1 Causes of Hypothyroidism and Hyperthyroidism

Hypothyroidism

Primary

- Chronic auto-immune (Hashimoto thyroiditis)
- Iodine status – severe iodine deficiency or mild to severe iodine excess
- Iatrogenic – radioiodine or surgery (usually to treat hyperthyroidism, goitre or thyroid cancer)
- Genetic (including variations causing congenital hypothyroidism)
- Pharmacological including amiodarone, lithium, monoclonal antibodies, anti-epileptic (Na Valproate), tyrosine kinase inhibitors), immune checkpoint inhibitors
- Transient thyroiditis post-partum, viral (De Quervain's syndrome),
- Thyroid infiltration – infectious, malignant (primary thyroid or metastatic) other autoimmune conditions such as sarcoidosis

Secondary (central)

- Hypothalamic failure/dysfunction
- Pituitary (macroadenoma/apoplexy)
- Resistance to TSH or TRH
- Pharmacological (e.g. dopamine, somatostatins)

Extra-thyroidal

- Consumptive hypothyroidism
- Tissue specific secondary to genetic mutations (e.g. *THR α* , *THR β* and *MCT ρ*)

Hyperthyroidism

Primary

- Increased stimulation - secondary to TSH receptor antibodies (Graves' disease), excess HCG secretion (hyperemesis gravidarum and trophoblastic tumours such as choriocarcinoma or hydatidiform mole)
- Autonomous thyroid function -(toxic multinodular goitre, solitary toxic nodule, familial non-auto immune hyperthyroidism)
- Excess release of stored thyroid hormone - autoimmune (silent or postpartum thyroiditis) infective (viral - De Quervain thyroiditis, bacterial or fungal), pharmacological (amiodarone interferon α), radiation
- Exposure to excess iodine known as the Jod Basedow effect (from excess iodine intake including radiographic contrast)

Secondary (central)

- Inappropriate TSH secretion (TSH secreting pituitary adenoma, pituitary resistance to thyroid hormone)

Extra-thyroidal

- Excess intake of thyroid hormone (iatrogenic or factitious)
- Ectopic thyroid hormone secretion (Struma ovarii; functional thyroid cancer metastases)

References

- 1 Dumont, J. *et al.* Ontogeny, Anatomy, Metabolism and Physiology of the Thyroid. *Thyroid Disease Manager*. Available at: <http://www.thyroidmanager.org/chapter/ontogeny-anatomy-metabolism-and-physiology-of-the-thyroid> (2011).
- 2 De Leo, S., Lee, S. Y. & Braverman, L. E. Hyperthyroidism. *Lancet* **388**, 906-918, doi:10.1016/s0140-6736(16)00278-6 (2016).
- 3 Chaker, L., Bianco, A. C., Jonklaas, J. & Peeters, R. P. Hypothyroidism. *Lancet*, doi:10.1016/s0140-6736(17)30703-1 (2017).
- 4 Rice, S. P., Boregowda, K., Williams, M. T., Morris, G. C. & Okosieme, O. E. A Welsh-speaking dysphasia. *Lancet* **382**, 1608, doi:10.1016/s0140-6736(13)61837-1 (2013).
- 5 Taylor, P. N. *et al.* Weekly Intramuscular Injection of Levothyroxine following Myxoedema: A Practical Solution to an Old Crisis. *Case reports in endocrinology* **2015**, 169194, doi:10.1155/2015/169194 (2015).
- 6 Persani, L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *J Clin Endocrinol Metab* **97**, 3068-3078, doi:10.1210/jc.2012-1616 (2012).
- 7 Hadlow, N. C. *et al.* The relationship between TSH and free T4 in a large population is complex and nonlinear and differs by age and sex. *J Clin Endocrinol Metab* **98**, 2936-2943, doi:10.1210/jc.2012-4223 (2013).
- 8 Pearce, S. H. *et al.* 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J* **2**, 215-228, doi:10.1159/000356507 (2013).
- 9 Zimmermann, M. B. Iodine deficiency. *Endocr Rev* **30**, 376-408, doi:10.1210/er.2009-0011 (2009).
- 10 Vanderpump, M. P. The epidemiology of thyroid disease. *British medical bulletin* **99**, 39-51, doi:10.1093/bmb/ldr030 (2011).
- 11 De Groot, L. *et al.* Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* **97**, 2543-2565, doi:10.1210/jc.2011-2803 (2012).
- 12 Wiersinga, W. M. Smoking and thyroid. *Clin Endocrinol (Oxf)* **79**, 145-151, doi:10.1111/cen.12222 (2013).
- 13 Wiersinga, W. M. Clinical Relevance of Environmental Factors in the Pathogenesis of Autoimmune Thyroid Disease. *Endocrinology and metabolism (Seoul, Korea)* **31**, 213-222, doi:10.3803/EnM.2016.31.2.213 (2016).
- 14 Preau, L., Fini, J. B., Morvan-Dubois, G. & Demeneix, B. Thyroid hormone signaling during early neurogenesis and its significance as a vulnerable window for endocrine disruption. *Biochimica et biophysica acta* **1849**, 112-121, doi:10.1016/j.bbagr.2014.06.015 (2015).
- 15 Bulow Pedersen, I. *et al.* Serum selenium is low in newly diagnosed Graves' disease: a population-based study. *Clin Endocrinol (Oxf)* **79**, 584-590, doi:10.1111/cen.12185 (2013).
- 16 Boelaert, K. *et al.* Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* **123**, 183.e181-189, doi:10.1016/j.amjmed.2009.06.030 (2010).

- 17 Pierce, M. J., LaFranchi, S. H. & Pinter, J. D. Characterization of Thyroid Abnormalities in a Large Cohort of Children with Down Syndrome. *Hormone research in paediatrics* **87**, 170-178, doi:10.1159/000457952 (2017).
- 18 Bartalena, L. *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clinical Endocrinology* **61**, 494-502 (2004).
- 19 Shine, B., McKnight, R. F., Leaver, L. & Geddes, J. R. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet* **386**, 461-468, doi:10.1016/s0140-6736(14)61842-0 (2015).
- 20 Laurberg, P. *et al.* Iodine intake as a determinant of thyroid disorders in populations. *Best practice & research. Clinical endocrinology & metabolism* **24**, 13-27, doi:10.1016/j.beem.2009.08.013 (2010).
- 21 Bould, H. *et al.* Investigation of thyroid dysfunction is more likely in patients with high psychological morbidity. *Fam Pract* **29**, 163-167, doi:10.1093/fampra/cm059 (2012).
- 22 Taylor, P. N. *et al.* Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. *JAMA Intern Med* **174**, 32-39, doi:10.1001/jamainternmed.2013.11312 (2014).
- 23 Garmendia Madariaga, A., Santos Palacios, S., Guillen-Grima, F. & Galofre, J. C. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab* **99**, 923-931, doi:10.1210/jc.2013-2409 (2014).
- 24 Hollowell, J. G. *et al.* Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* **87**, 489-499 (2002).
- 25 Tunbridge, W. M. *et al.* The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf)* **7**, 481-493 (1977).
- 26 Furszyfer, J., Kurland, L. T., McConahey, W. M. & Eiveback, L. R. Graves' disease in Olmsted County, Minnesota, 1935 through 1967. *Mayo Clinic proceedings* **45**, 636-644 (1970).
- 27 Vanderpump, M. P. *et al.* The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)* **43**, 55-68 (1995).
- 28 Berglund, J., Ericsson, U. B. & Hallengren, B. Increased incidence of thyrotoxicosis in Malmo during the years 1988-1990 as compared to the years 1970-1974. *Journal of internal medicine* **239**, 57-62 (1996).
- 29 Nystrom, H. F., Jansson, S. & Berg, G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003-2005. *Clin Endocrinol (Oxf)* **78**, 768-776, doi:10.1111/cen.12060 (2013).
- 30 Knudsen, N. *et al.* Comparative study of thyroid function and types of thyroid dysfunction in two areas in Denmark with slightly different iodine status. *European journal of endocrinology / European Federation of Endocrine Societies* **143**, 485-491 (2000).
- 31 Bjoro, T. *et al.* Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). *European journal of endocrinology / European Federation of Endocrine Societies* **143**, 639-647 (2000).

- 32 Konno, N. *et al.* Screening for thyroid diseases in an iodine sufficient area with sensitive thyrotrophin assays, and serum thyroid autoantibody and urinary iodide determinations. *Clin Endocrinol (Oxf)* **38**, 273-281 (1993).
- 33 Walsh, J. P. Managing thyroid disease in general practice. *The Medical journal of Australia* **205**, 179-184 (2016).
- 34 Gopinath, B. *et al.* Five-year incidence and progression of thyroid dysfunction in an older population. *Internal medicine journal* **40**, 642-649, doi:10.1111/j.1445-5994.2009.02156.x (2010).
- 35 Laurberg, P., Pedersen, K. M., Vestergaard, H. & Sigurdsson, G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. *Journal of internal medicine* **229**, 415-420 (1991).
- 36 Laurberg, P. *et al.* The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *European journal of endocrinology / European Federation of Endocrine Societies* **155**, 219-228, doi:10.1530/eje.1.02210 (2006).
- 37 Aghini-Lombardi, F. *et al.* The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J Clin Endocrinol Metab* **84**, 561-566 (1999).
- 38 Du, Y. *et al.* Iodine deficiency and excess coexist in china and induce thyroid dysfunction and disease: a cross-sectional study. *PloS one* **9**, e111937, doi:10.1371/journal.pone.0111937 (2014).
- 39 Tan, L. *et al.* Prevalence of thyroid dysfunction with adequate and excessive iodine intake in Hebei Province, People's Republic of China. *Public health nutrition* **18**, 1692-1697, doi:10.1017/s1368980014002237 (2015).
- 40 Okosieme, O. E. Impact of iodination on thyroid pathology in Africa. *Journal of the Royal Society of Medicine* **99**, 396-401, doi:10.1258/jrsm.99.8.396 (2006).
- 41 Ogbera, A. O. & Kuku, S. F. Epidemiology of thyroid diseases in Africa. *Indian Journal of Endocrinology and Metabolism* **15**, S82-S88, doi:10.4103/2230-8210.83331 (2011).
- 42 Muller, G. M., Levitt, N. S. & Louw, S. J. Thyroid dysfunction in the elderly. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* **87**, 1119-1123 (1997).
- 43 Kalk, W. J. Thyrotoxicosis in urban black Africans: a rising incidence. *East African medical journal* **58**, 109-116 (1981).
- 44 Sarfo-Kantanka, O., Sarfo, F. S., Ansah, E. O. & Kyei, I. Spectrum of Endocrine Disorders in Central Ghana. *International Journal of Endocrinology* **2017**, 7, doi:10.1155/2017/5470731 (2017).
- 45 Sarfo-Kantanka, O., Kyei, I., Sarfo, F. S. & Ansah, E. O. Thyroid Disorders in Central Ghana: The Influence of 20 Years of Iodization. *Journal of thyroid research* **2017**, 8, doi:10.1155/2017/7843972 (2017).
- 46 Ogbera, A. O., Fasanmade, O. & Adediran, O. Pattern of thyroid disorders in the southwestern region of Nigeria. *Ethnicity and Disease* **17** (2007).
- 47 Tellez, M., Cooper, J. & Edmonds, C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. *Clin Endocrinol (Oxf)* **36**, 291-294 (1992).
- 48 Okinaka, S. *et al.* The association of periodic paralysis and hyperthyroidism in Japan. *J Clin Endocrinol Metab* **17**, 1454-1459, doi:10.1210/jcem-17-12-1454 (1957).

- 49 Kelley, D. E., Gharib, H., Kennedy, F. P., Duda, R. J., Jr. & McManis, P. G. Thyrotoxic periodic paralysis. Report of 10 cases and review of electromyographic findings. *Arch Intern Med* **149**, 2597-2600 (1989).
- 50 Tamai, H. *et al.* HLA and thyrotoxic periodic paralysis in Japanese patients. *J Clin Endocrinol Metab* **64**, 1075-1078, doi:10.1210/jcem-64-5-1075 (1987).
- 51 Bartalena, L. *et al.* The phenotype of newly diagnosed Graves' disease in Italy in recent years is milder than in the past: results of a large observational longitudinal study. *J Endocrinol Invest* **39**, 1445-1451, doi:10.1007/s40618-016-0516-7 (2016).
- 52 Bartalena, L. & Fatourech, V. Extrathyroidal manifestations of Graves' disease: a 2014 update. *J Endocrinol Invest* **37**, 691-700, doi:10.1007/s40618-014-0097-2 (2014).
- 53 Perros, P. *et al.* PREGO (presentation of Graves' orbitopathy) study: changes in referral patterns to European Group On Graves' Orbitopathy (EUGOGO) centres over the period from 2000 to 2012. *The British journal of ophthalmology* **99**, 1531-1535, doi:10.1136/bjophthalmol-2015-306733 (2015).
- 54 Vitti, P., Rago, T., Tonacchera, M. & Pinchera, A. Toxic multinodular goiter in the elderly. *J Endocrinol Invest* **25**, 16-18 (2002).
- 55 Horst, W., Rosler, H., Schneider, C. & Labhart, A. 306 cases of toxic adenoma: clinical aspects, findings in radioiodine diagnostics, radiochromatography and histology; results of 131-I and surgical treatment. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* **8**, 515-528 (1967).
- 56 Pearce, E. N., Farwell, A. P. & Braverman, L. E. Thyroiditis. *N Engl J Med* **348**, 2646-2655, doi:10.1056/NEJMra021194 (2003).
- 57 Nikolai, T. F., Brosseau, J., Kettrick, M. A., Roberts, R. & Beltaos, E. Lymphocytic thyroiditis with spontaneously resolving hyperthyroidism (silent thyroiditis). *Arch Intern Med* **140**, 478-482 (1980).
- 58 Ross, D. S. Syndromes of thyrotoxicosis with low radioactive iodine uptake. *Endocrinology and metabolism clinics of North America* **27**, 169-185 (1998).
- 59 Fatourech, V., Aniszewski, J. P., Fatourech, G. Z., Atkinson, E. J. & Jacobsen, S. J. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. *J Clin Endocrinol Metab* **88**, 2100-2105, doi:10.1210/jc.2002-021799 (2003).
- 60 Schwartz, F., Bergmann, N., Zerahn, B. & Faber, J. Incidence rate of symptomatic painless thyroiditis presenting with thyrotoxicosis in Denmark as evaluated by consecutive thyroid scintigraphies. *Scandinavian journal of clinical and laboratory investigation* **73**, 240-244, doi:10.3109/00365513.2013.769623 (2013).
- 61 Vitug, A. C. & Goldman, J. M. Silent (painless) thyroiditis. Evidence of a geographic variation in frequency. *Arch Intern Med* **145**, 473-475 (1985).
- 62 Schneeberg, N. G. Silent thyroiditis. *Archives of internal medicine* **143**, 2214 (1983).
- 63 Martino, E., Bartalena, L., Bogazzi, F. & Braverman, L. E. Vol. 22 240-254 (2001).
- 64 Bogazzi, F., Tomisti, L., Bartalena, L., Aghini-Lombardi, F. & Martino, E. Amiodarone and the thyroid: a 2012 update. *J Endocrinol Invest*, doi:10.3275/8298 (2012).
- 65 Zosin, I. & Balas, M. Amiodarone-induced thyroid dysfunction in an iodine-replete area: epidemiological and clinical data. *Endokrynologia Polska* **63**, 2-9 (2012).
- 66 Tsang, W. & Houlden, R. L. Amiodarone-induced thyrotoxicosis: A review. *The Canadian Journal of Cardiology* **25**, 421-424 (2009).

- 67 Uchida, T. *et al.* Prevalence of Amiodarone-Induced Thyrotoxicosis and Associated Risk Factors in Japanese Patients. *International Journal of Endocrinology* **2014**, 534904, doi:10.1155/2014/534904 (2014).
- 68 Carle, A., Andersen, S. L., Boelaert, K. & Laurberg, P. MANAGEMENT OF ENDOCRINE DISEASE: Subclinical thyrotoxicosis: prevalence, causes and choice of therapy. *Eur J Endocrinol* **176**, R325-r337, doi:10.1530/eje-16-0276 (2017).
- 69 Vadiveloo, T., Donnan, P. T., Cochrane, L. & Leese, G. P. The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab* **96**, E1-8, doi:10.1210/jc.2010-0854 (2011).
- 70 Das, G. *et al.* Serum thyrotrophin at baseline predicts the natural course of subclinical hyperthyroidism. *Clin Endocrinol (Oxf)* **77**, 146-151, doi:10.1111/j.1365-2265.2012.04345.x (2012).
- 71 Rosario, P. W. Natural history of subclinical hyperthyroidism in elderly patients with TSH between 0.1 and 0.4 mIU/l: a prospective study. *Clin Endocrinol (Oxf)* **72**, 685-688, doi:10.1111/j.1365-2265.2009.03696.x (2010).
- 72 Stanbury, J. B. *et al.* Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid* **8**, 83-100, doi:10.1089/thy.1998.8.83 (1998).
- 73 Roti, E. & Uberti, E. D. Iodine excess and hyperthyroidism. *Thyroid* **11**, 493-500 (2001).
- 74 Lee, S. Y. *et al.* A review: Radiographic iodinated contrast media-induced thyroid dysfunction. *J Clin Endocrinol Metab* **100**, 376-383, doi:10.1210/jc.2014-3292 (2015).
- 75 Korelitz, J. J. *et al.* Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. *Thyroid* **23**, 758-765, doi:10.1089/thy.2012.0488 (2013).
- 76 Andersen, S. L., Olsen, J., Carle, A. & Laurberg, P. Hyperthyroidism incidence fluctuates widely in and around pregnancy and is at variance with some other autoimmune diseases: a Danish population-based study. *J Clin Endocrinol Metab* **100**, 1164-1171, doi:10.1210/jc.2014-3588 (2015).
- 77 Okosieme, O. E. & Lazarus, J. H. Important considerations in the management of Graves' disease in pregnant women. *Expert review of clinical immunology* **11**, 947-957, doi:10.1586/1744666x.2015.1054375 (2015).
- 78 Taylor, P. N. & Vaidya, B. Side effects of anti-thyroid drugs and their impact on the choice of treatment for thyrotoxicosis in pregnancy. *European Thyroid Journal* **1**, 176-185 (2012).
- 79 Vaidya, B., Williams, G. R., Abraham, P. & Pearce, S. H. Radioiodine treatment for benign thyroid disorders: results of a nationwide survey of UK endocrinologists. *Clin Endocrinol (Oxf)* **68**, 814-820, doi:10.1111/j.1365-2265.2007.03097.x (2008).
- 80 Agboola-Abu, C. F. & Kuku, S. F. Experience in the use of radioactive iodine therapy for hyperthyroidism in Nigerian patients. A study of twenty-two patients. *West African journal of medicine* **22**, 324-328 (2003).
- 81 Bath, S. C., Steer, C. D., Golding, J., Emmett, P. & Rayman, M. P. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* **382**, 331-337, doi:10.1016/s0140-6736(13)60436-5 (2013).
- 82 Taylor, P. N., Okosieme, O. E., Dayan, C. M. & Lazarus, J. H. Therapy of endocrine disease: Impact of iodine supplementation in mild-to-moderate iodine deficiency:

- systematic review and meta-analysis. *European journal of endocrinology / European Federation of Endocrine Societies* **170**, R1-R15, doi:10.1530/eje-13-0651 (2014).
- 83 Vanderpump, M. P. *et al.* Iodine status of UK schoolgirls: a cross-sectional survey. *Lancet* **377**, 2007-2012, doi:10.1016/s0140-6736(11)60693-4 (2011).
- 84 Bath, S., Walter, A., Taylor, A. & Rayman, M. Iodine status of UK women of childbearing age. *Journal of Human Nutrition and Dietetics* **21**, 379-380, doi:10.1111/j.1365-277X.2008.00881_9.x (2008).
- 85 Pearce, E. N. *et al.* Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. *J Clin Endocrinol Metab* **95**, 3207-3215, doi:10.1210/jc.2010-0014 (2010).
- 86 Lazarus, J. H. & Smyth, P. P. Iodine deficiency in the UK and Ireland. *Lancet* **372**, 888, doi:10.1016/s0140-6736(08)61390-2 (2008).
- 87 Delange, F. Iodine deficiency in Europe anno 2002. *Thyroid International* **5**, 3-18 (2002).
- 88 Mazzarella, C. *et al.* Iodine status assessment in Campania (Italy) as determined by urinary iodine excretion. *Nutrition (Burbank, Los Angeles County, Calif.)* **25**, 926-929, doi:10.1016/j.nut.2009.01.020 (2009).
- 89 Vitti, P., Delange, F., Pinchera, A., Zimmermann, M. & Dunn, J. T. Europe is iodine deficient. *Lancet* **361**, 1226, doi:10.1016/s0140-6736(03)12935-2 (2003).
- 90 Pearce, E. N., Andersson, M. & Zimmermann, M. B. Global iodine nutrition: where do we stand in 2013? *Thyroid* **23**, 523-528, doi:10.1089/thy.2013.0128 (2013).
- 91 Parle, J. V., Franklyn, J. A., Cross, K. W., Jones, S. C. & Sheppard, M. C. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol* **34**, 77-83 (1991).
- 92 Gussekloo, J. *et al.* Thyroid status, disability and cognitive function, and survival in old age. *Jama* **292**, 2591-2599 (2004).
- 93 Asvold, B. O., Vatten, L. J. & Bjoro, T. Changes in the prevalence of hypothyroidism: the HUNT Study in Norway. *European journal of endocrinology / European Federation of Endocrine Societies* **169**, 613-620, doi:10.1530/eje-13-0459 (2013).
- 94 McGrogan, A., Seaman, H. E., Wright, J. W. & de Vries, C. S. The incidence of autoimmune thyroid disease: a systematic review of the literature. *Clin Endocrinol (Oxf)* **69**, 687-696, doi:10.1111/j.1365-2265.2008.03338.x (2008).
- 95 Canaris, G. J., Manowitz, N. R., Mayor, G. & Ridgway, E. C. The Colorado thyroid disease prevalence study. *Arch Intern Med* **160**, 526-534 (2000).
- 96 Flynn, R. W., MacDonald, T. M., Morris, A. D., Jung, R. T. & Leese, G. P. The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. *J Clin Endocrinol Metab* **89**, 3879-3884 (2004).
- 97 Valdes, S. *et al.* Population-Based National Prevalence of Thyroid Dysfunction in Spain and Associated Factors: Di@bet.es Study. *Thyroid* **27**, 156-166, doi:10.1089/thy.2016.0353 (2017).
- 98 Sichieri, R. *et al.* Low prevalence of hypothyroidism among black and Mulatto people in a population-based study of Brazilian women. *Clin Endocrinol (Oxf)* **66**, 803-807, doi:10.1111/j.1365-2265.2007.02816.x (2007).
- 99 Sgarbi, J. A., Matsumura, L. K., Kasamatsu, T. S., Ferreira, S. R. & Maciel, R. M. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. *Eur J Endocrinol* **162**, 569-577, doi:10.1530/eje-09-0845 (2010).

- 100 Kasagi, K. *et al.* Thyroid function in Japanese adults as assessed by a general health checkup system in relation with thyroid-related antibodies and other clinical parameters. *Thyroid* **19**, 937-944, doi:10.1089/thy.2009.0205 (2009).
- 101 Awad Saad Al Shahrani *et al.* The epidemiology of thyroid diseases in the Arab world: A systematic review. *Journal of Public Health and Epidemiology* **8**, 17-26 (2016).
- 102 Amouzegar, A. *et al.* Natural Course of Euthyroidism and Clues for Early Diagnosis of Thyroid Dysfunction: Tehran Thyroid Study. *Thyroid* **27**, 616-625, doi:10.1089/thy.2016.0409 (2017).
- 103 Amouzegar, A. *et al.* The Prevalence, Incidence and Natural Course of Positive Antithyroperoxidase Antibodies in a Population-Based Study: Tehran Thyroid Study. *PloS one* **12**, e0169283, doi:10.1371/journal.pone.0169283 (2017).
- 104 Knudsen, N., Jorgensen, T., Rasmussen, S., Christiansen, E. & Perrild, H. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. *Clin Endocrinol (Oxf)* **51**, 361-367 (1999).
- 105 Okosieme, O. E., Taylor, R. C., Ohwovoriole, A. E., Parkes, A. B. & Lazarus, J. H. Prevalence of thyroid antibodies in Nigerian patients. *QJM* **100**, 107-112, doi:10.1093/qjmed/hcl137 (2007).
- 106 Satti, H. *et al.* High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* **16**, 468-472, doi:10.5588/ijtld.11.0615 (2012).
- 107 Shan, Z. *et al.* Iodine Status and Prevalence of Thyroid Disorders After Introduction of Mandatory Universal Salt Iodization for 16 Years in China: A Cross-Sectional Study in 10 Cities. *Thyroid* **26**, 1125-1130, doi:10.1089/thy.2015.0613 (2016).
- 108 Teng, W. *et al.* Effect of iodine intake on thyroid diseases in China. *The New England journal of medicine* **354**, 2783-2793, doi:10.1056/NEJMoa054022 (2006).
- 109 Unnikrishnan, A. G. *et al.* Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. *Indian J Endocrinol Metab* **17**, 647-652, doi:10.4103/2230-8210.113755 (2013).
- 110 Bagcchi, S. Hypothyroidism in India: more to be done. *The lancet. Diabetes & endocrinology* **2**, 778, doi:10.1016/s2213-8587(14)70208-6 (2014).
- 111 Taylor, P. N., Okosieme, O. E., Premawardhana, L. & Lazarus, J. H. Should all women be screened for thyroid dysfunction in pregnancy? *Women's health (London, England)* **11**, 295-307, doi:10.2217/whe.15.7 (2015).
- 112 Krassas, G. E., Poppe, K. & Glinioer, D. Thyroid Function and Human Reproductive Health. *Endocrine Reviews* **31**, 702-755, doi:10.1210/er.2009-0041 (2010).
- 113 Stagnaro-Green, A. *et al.* Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. *Thyroid* **21**, 1081-1125, doi:10.1089/thy.2011.0087 (2011).
- 114 Zhang, Y., Wang, H., Pan, X., Teng, W. & Shan, Z. Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: A systematic review and meta-analysis. *PloS one* **12**, e0175708, doi:10.1371/journal.pone.0175708 (2017).
- 115 Korevaar, T. I. *et al.* Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. *J Clin Endocrinol Metab* **98**, 4382-4390, doi:10.1210/jc.2013-2855 (2013).

- 116 Lazarus, J. H. *et al.* Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* **366**, 493-501, doi:10.1056/NEJMoa1106104 (2012).
- 117 Casey, B. M. *et al.* Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. *New England Journal of Medicine* **376**, 815-825, doi:10.1056/NEJMoa1606205 (2017).
- 118 Dosiou, C. *et al.* Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J Clin Endocrinol Metab* **97**, 1536-1546, doi:10.1210/jc.2011-2884 (2012).
- 119 Gruters, A. & Krude, H. Update on the management of congenital hypothyroidism. *Horm Res* **68 Suppl 5**, 107-111, doi:10.1159/000110591 (2007).
- 120 Fisher, D. A. Second International Conference on Neonatal Thyroid Screening: progress report. *The Journal of pediatrics* **102**, 653-654 (1983).
- 121 Harris, K. B. & Pass, K. A. Increase in congenital hypothyroidism in New York State and in the United States. *Molecular genetics and metabolism* **91**, 268-277, doi:10.1016/j.ymgme.2007.03.012 (2007).
- 122 Albert, B. B. *et al.* Etiology of increasing incidence of congenital hypothyroidism in New Zealand from 1993-2010. *J Clin Endocrinol Metab* **97**, 3155-3160, doi:10.1210/jc.2012-1562 (2012).
- 123 Ford, G. & LaFranchi, S. H. Screening for congenital hypothyroidism: A worldwide view of strategies. *Best Practice & Research Clinical Endocrinology & Metabolism* **28**, 175-187, doi:<http://dx.doi.org/10.1016/j.beem.2013.05.008> (2014).
- 124 Gittoes, N. J. L. & Franklyn, J. A. Drug-Induced Thyroid Disorders. *Drug Safety* **13**, 46-55, doi:10.2165/00002018-199513010-00006 (1995).
- 125 Martino, E. *et al.* Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. *Ann Intern Med* **101**, 28-34 (1984).
- 126 Cukier, P., Santini, F. C., Scaranti, M. & Hoff, A. O. Endocrine side effects of cancer immunotherapy. *Endocrine-related cancer* **24**, T331-t347, doi:10.1530/erc-17-0358 (2017).
- 127 Barroso-Sousa, R., Barry, W. T., Garrido-Castro, A. C. & *et al.* Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. *JAMA Oncology*, doi:10.1001/jamaoncol.2017.3064 (2017).
- 128 Mahzari, M., Arnaout, A. & Freedman, M. S. Alemtuzumab Induced Thyroid Disease in Multiple Sclerosis: A Review and Approach to Management. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques* **42**, 284-291, doi:10.1017/cjn.2015.48 (2015).
- 129 Wolter, P. *et al.* The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. *British journal of cancer* **99**, 448-454, doi:10.1038/sj.bjc.6604497 (2008).
- 130 Network, I. G. in *2016 Annual report* (2016).
- 131 Dasgupta, P. K., Liu, Y. & Dyke, J. V. Iodine nutrition: iodine content of iodized salt in the United States. *Environmental science & technology* **42**, 1315-1323 (2008).
- 132 Premawardhana, L. D. *et al.* Increased prevalence of thyroglobulin antibodies in Sri Lankan schoolgirls--is iodine the cause? *Eur J Endocrinol* **143**, 185-188 (2000).
- 133 Sundick, R. S., Bagchi, N. & Brown, T. R. The role of iodine in thyroid autoimmunity: from chickens to humans: a review. *Autoimmunity* **13**, 61-68 (1992).

- 134 Okosieme, O. E. *et al.* Thyroglobulin epitope recognition in a post iodine-supplemented Sri Lankan population. *Clin Endocrinol (Oxf)* **59**, 190-197 (2003).
- 135 Bulow Pedersen, I. *et al.* A cautious iodization program bringing iodine intake to a low recommended level is associated with an increase in the prevalence of thyroid autoantibodies in the population. *Clin Endocrinol (Oxf)*, doi:10.1111/j.1365-2265.2011.04008.x (2011).
- 136 Pedersen, I. B. *et al.* An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. *J Clin Endocrinol Metab* **92**, 3122-3127, doi:10.1210/jc.2007-0732 (2007).
- 137 Buziak-Bereza, M., Golkowski, F. & Szybinski, Z. [Disturbances of thyroid function in adult population of the city of Cracow followed up for ten years observation]. *Przegląd lekarski* **62**, 676-679 (2005).
- 138 Laurberg, P. *et al.* Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. *J Clin Endocrinol Metab* **83**, 765-769, doi:10.1210/jcem.83.3.4624 (1998).
- 139 Konno, N., Makita, H., Yuri, K., Iizuka, N. & Kawasaki, K. Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. *J Clin Endocrinol Metab* **78**, 393-397, doi:10.1210/jcem.78.2.8106628 (1994).
- 140 Hong, A., Stokes, B., Otahal, P., Owens, D. & Burgess, J. R. Temporal trends in thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (ATPO) testing across two phases of iodine fortification in Tasmania (1995-2013). *Clin Endocrinol (Oxf)* **87**, 386-393, doi:10.1111/cen.13371 (2017).
- 141 Parveen, S., Latif, S. A., Kamal, M. M. & Uddin, M. M. Effects of long term iodized table salt consumption on serum T3, T4 and TSH in an iodine deficient area of Bangladesh. *Mymensingh medical journal : MMJ* **16**, 57-60 (2007).
- 142 Tamaro, A., Pigliacelli, F., Fumarola, A. & Persechino, S. Trends of thyroid function and autoimmunity to 5 years after the introduction of mandatory iodization in Italy. *European annals of allergy and clinical immunology* **48**, 77-81 (2016).
- 143 Bourdoux, P. P., Ermans, A. M., Mukalay wa Mukalay, A., Filetti, S. & Vigneri, R. Iodine-induced thyrotoxicosis in Kivu, Zaire. *Lancet* **347**, 552-553 (1996).
- 144 Todd, C. H. *et al.* in *Lancet* Vol. 346 1563-1564 (1995).
- 145 Connolly, R. J. An increase in thyrotoxicosis in southern Tasmania after an increase in dietary iodine. *The Medical journal of Australia* **1**, 1268-1271 (1971).
- 146 Elnagar, B. *et al.* The effects of different doses of oral iodized oil on goiter size, urinary iodine, and thyroid-related hormones. *J Clin Endocrinol Metab* **80**, 891-897, doi:10.1210/jcem.80.3.7883848 (1995).
- 147 Okosieme, O. E. Iodisation in displaced African populations. *Lancet* **373**, 214, doi:10.1016/S0140-6736(09)60069-6 (2009).
- 148 Aakre, I. *et al.* Development of thyroid dysfunction among women with excessive iodine intake--A 3-year follow-up. *J Trace Elem Med Biol* **31**, 61-66, doi:10.1016/j.jtemb.2015.03.004 (2015).
- 149 Aoki, Y. *et al.* Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). *Thyroid* **17**, 1211-1223, doi:10.1089/thy.2006.0235 (2007).

- 150 Medici, M. *et al.* Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. *PLoS Genet* **10**, e1004123, doi:10.1371/journal.pgen.1004123 (2014).
- 151 Taylor, P. N. *et al.* Whole genome sequence based analysis of thyroid function. *Nature Communications (in press)* (2015).
- 152 Kus, A. *et al.* The association of thyroid peroxidase antibody risk loci with susceptibility to and phenotype of Graves' disease. *Clin Endocrinol (Oxf)* **83**, 556-562, doi:10.1111/cen.12640 (2015).
- 153 Meyerovitch, J. *et al.* Vol. 167 1533-1538 (2007).
- 154 Stott, D. J. *et al.* Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. *New England Journal of Medicine* **376**, 2534-2544, doi:10.1056/NEJMoa1603825 (2017).
- 155 Collet, T. H. *et al.* Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. *J Clin Endocrinol Metab* **99**, 3353-3362, doi:10.1210/jc.2014-1250 (2014).
- 156 Cooper, D. S. & Biondi, B. Subclinical thyroid disease. *Lancet* **379**, 1142-1154, doi:10.1016/s0140-6736(11)60276-6 (2012).
- 157 Taylor, P. N., Razvi, S., Pearce, S. H. & Dayan, C. M. Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab* **98**, 3562-3571, doi:10.1210/jc.2013-1315 (2013).
- 158 Rieben, C. *et al.* Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies. *J Clin Endocrinol Metab* **101**, 4945-4954, doi:10.1210/jc.2016-2129 (2016).
- 159 Schultheiss, U. T. *et al.* A genetic risk score for thyroid peroxidase antibodies associates with clinical thyroid disease in community-based populations. *J Clin Endocrinol Metab* **100**, E799-807, doi:10.1210/jc.2014-4352 (2015).
- 160 Marinò, M., Latrofa, F., Menconi, F., Chiovato, L. & Vitti, P. Role of genetic and non-genetic factors in the etiology of Graves' disease. *Journal of Endocrinological Investigation* **38**, 283-294, doi:10.1007/s40618-014-0214-2 (2015).
- 161 Prummel, M. F. & Wiersinga, W. M. Smoking and risk of Graves' disease. *Jama* **269**, 479-482 (1993).
- 162 Nyirenda, M. J., Taylor, P. N., Stoddart, M., Beckett, G. J. & Toft, A. D. Thyroid-stimulating hormone-receptor antibody and thyroid hormone concentrations in smokers vs nonsmokers with Graves disease treated with carbimazole. *JAMA* **301**, 162-164, doi:10.1001/jama.2008.931 (2009).
- 163 Strieder, T. G., Prummel, M. F., Tijssen, J. G., Endert, E. & Wiersinga, W. M. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. *Clin Endocrinol (Oxf)* **59**, 396-401 (2003).
- 164 Belin, R. M., Astor, B. C., Powe, N. R. & Ladenson, P. W. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* **89**, 6077-6086 (2004).
- 165 Asvold, B. O., Bjoro, T., Nilsen, T. I. & Vatten, L. J. Tobacco smoking and thyroid function: a population-based study. *Arch Intern Med* **167**, 1428-1432 (2007).

- 166 Carlé, A. *et al.* Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study. *European Journal of Endocrinology* **167**, 483-490, doi:10.1530/eje-12-0356 (2012).
- 167 Tomer, Y. & Davies, T. F. Infection, thyroid disease, and autoimmunity. *Endocr Rev* **14**, 107-120, doi:10.1210/edrv-14-1-107 (1993).
- 168 Mogensen, E. F. & Green, A. The epidemiology of thyrotoxicosis in Denmark. Incidence and geographical variation in the Funen region 1972-1974. *Acta medica Scandinavica* **208**, 183-186 (1980).
- 169 Berglund, J., Christensen, S. B. & Hallengren, B. Total and age-specific incidence of Graves' thyrotoxicosis, toxic nodular goitre and solitary toxic adenoma in Malmo 1970-74. *Journal of internal medicine* **227**, 137-141 (1990).
- 170 Galofre, J. C. *et al.* Incidence of different forms of thyroid dysfunction and its degrees in an iodine sufficient area. *Thyroidology* **6**, 49-54 (1994).
- 171 Volzke, H. *et al.* The prevalence of undiagnosed thyroid disorders in a previously iodine-deficient area. *Thyroid* **13**, 803-810, doi:10.1089/105072503768499680 (2003).
- 172 O'Leary, P. C. *et al.* Investigations of thyroid hormones and antibodies based on a community health survey: the Busselton thyroid study. *Clin Endocrinol (Oxf)* **64**, 97-104 (2006).
- 173 Leese, G. P. *et al.* Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS). *Clin Endocrinol (Oxf)* **68**, 311-316 (2008).
- 174 Lucas, A. *et al.* Undiagnosed thyroid dysfunction, thyroid antibodies, and iodine excretion in a Mediterranean population. *Endocrine* **38**, 391-396, doi:10.1007/s12020-010-9397-2 (2010).
- 175 Delshad, H., Mehran, L., Tohidi, M., Assadi, M. & Azizi, F. The incidence of thyroid function abnormalities and natural course of subclinical thyroid disorders, Tehran, I.R. Iran. *J Endocrinol Invest* **35**, 516-521, doi:10.3275/7968 (2012).
- 176 Sriphrapadang, C. *et al.* Reference ranges of serum TSH, FT4 and thyroid autoantibodies in the Thai population: the national health examination survey. *Clin Endocrinol (Oxf)* **80**, 751-756, doi:10.1111/cen.12371 (2014).
- 177 Hoogendoorn, E. H. *et al.* Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. *Clinical chemistry* **52**, 104-111, doi:10.1373/clinchem.2005.055194 (2006).
- 178 Marwaha, R. K. *et al.* The evolution of thyroid function with puberty. *Clin Endocrinol (Oxf)* **76**, 899-904, doi:10.1111/j.1365-2265.2011.04305.x (2012).
- 179 Laurberg, P., Bulow Pedersen, I., Pedersen, K. M. & Vestergaard, H. Low incidence rate of overt hypothyroidism compared with hyperthyroidism in an area with moderately low iodine intake. *Thyroid* **9**, 33-38, doi:10.1089/thy.1999.9.33 (1999).
- 180 Galofre, J. C., Fernandez-Calvet, L., Rios, M. & Garcia-Mayor, R. V. Increased incidence of thyrotoxicosis after iodine supplementation in an iodine sufficient area. *J Endocrinol Invest* **17**, 23-27, doi:10.1007/bf03344958 (1994).
- 181 Yang, F. *et al.* Epidemiological survey on the relationship between different iodine intakes and the prevalence of hyperthyroidism. *European journal of endocrinology / European Federation of Endocrine Societies* **146**, 613-618 (2002).

- 182 Golkowski, F. *et al.* Increased prevalence of hyperthyroidism as an early and transient side-effect of implementing iodine prophylaxis. *Public health nutrition* **10**, 799-802, doi:10.1017/s1368980007585939 (2007).
- 183 Heydarian, P., Ordookhani, A. & Azizi, F. Goiter rate, serum thyrotropin, thyroid autoantibodies and urinary iodine concentration in Tehranian adults before and after national salt iodization. *J Endocrinol Invest* **30**, 404-410, doi:10.1007/bf03346318 (2007).
- 184 Cerqueira, C. *et al.* Doubling in the use of thyroid hormone replacement therapy in Denmark: association to iodization of salt? *European journal of epidemiology* **26**, 629-635, doi:10.1007/s10654-011-9590-5 (2011).
- 185 Aghini Lombardi, F. *et al.* The effect of voluntary iodine prophylaxis in a small rural community: the Pescopagano survey 15 years later. *J Clin Endocrinol Metab* **98**, 1031-1039, doi:10.1210/jc.2012-2960 (2013).