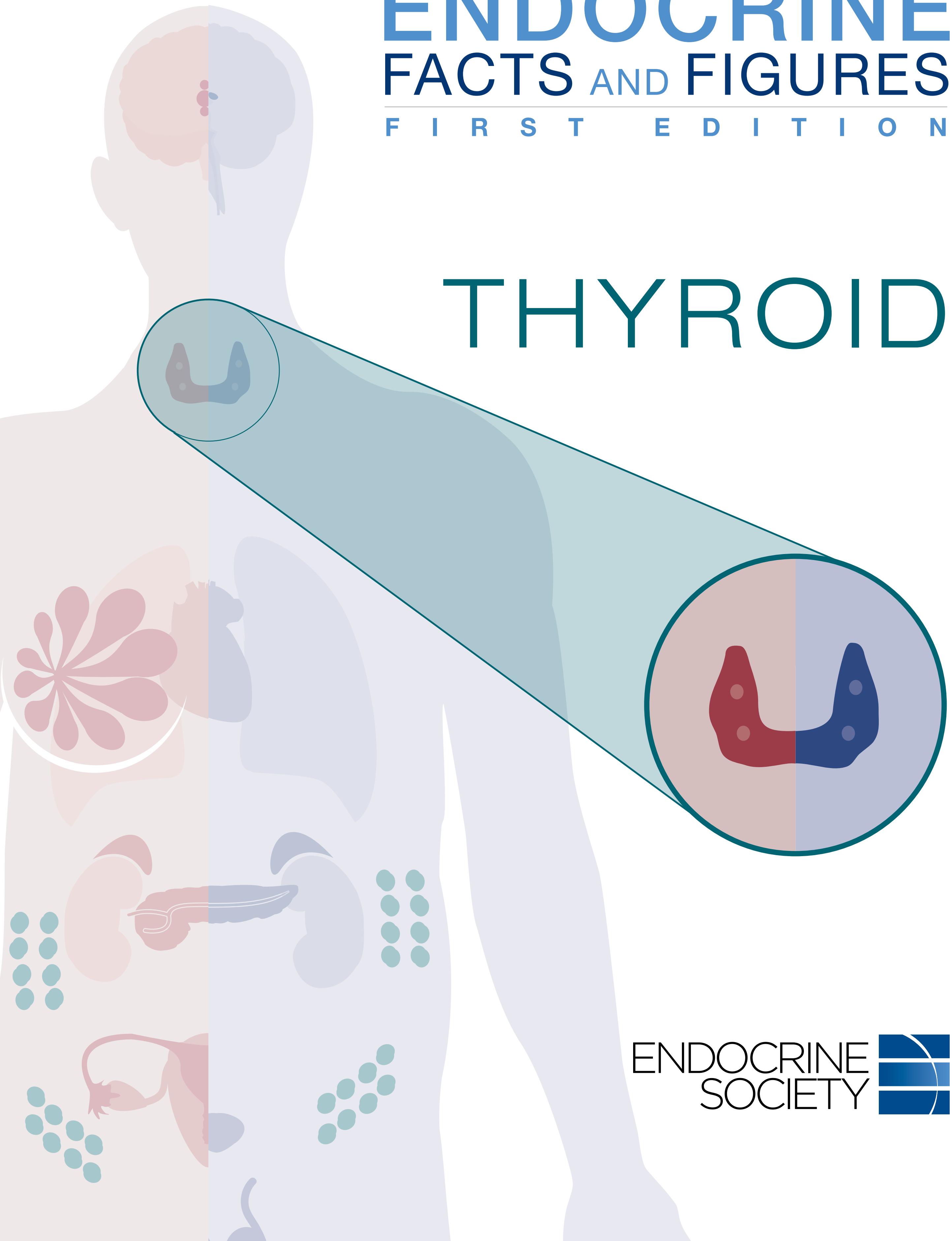
ENDOCRINE FACTS AND FIGURES

FIRST EDITION

THYROID



ENDOCRINE SOCIETY

FOR EVERY **1,000 AMERICANS**, UP TO

8 HAVE OVERT HYPOTHYROIDISM

130 HAVE SUBCLINICAL HYPOTHYROIDISM

5 HAVE OVERT HYPERTHYROIDISM

4 HAVE SUBCLINICAL HYPERTHYROIDISM

THYROID CONDITIONS

5 TO **10x**
MORE COMMON IN WOMEN
COMPARED TO MEN[2]

IN 2008, THYROID DISEASE
TREATMENT COSTS
FOR US WOMEN OVER AGE 18 TOTALED
$4.3 BILLION *OR*
$343.00 / WOMAN RECEIVING TREATMENT[3]

92,931
THYROIDECTOMIES
WERE PERFORMED
IN THE US IN 2006[4]

UP
39%
FROM 1996

1 Source: Hollowell et al. 2002
2 Source: Wang et al. 1997
3 Source: Soni. 2011
4 Source: Sun et al. 2013

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Mission Statement of the Endocrine Society

The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

About Endocrine Facts and Figures

Endocrine Facts and Figures is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Calcium, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of **Endocrine Facts and Figures** emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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For More Information

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Disclaimer

This publication summarizes current scientific information about epidemiology and trends data related to a spectrum of endocrine diseases. It is not a practice guideline or systematic review. Except when specified, this publication does not represent the official policy of the Endocrine Society.

I OVERVIEW

The thyroid is a component of the hypothalamic-pituitary-thyroid axis, which is responsible for maintaining normal levels of thyroid hormones (Figure 1).[1] Thyroid hormones, T_3 and T_4, play an essential role in the regulation of many aspects of metabolism[2,3,4], with T_4 being the predominant thyroid hormone in circulation and T_3 being the most active form.[5] Interestingly, approximately 80% of T_4 is converted to T_3 in liver and other target organs, whereas 20% of T_3 is synthesized in the thyroid.[1]

Thyroid disease or dysfunction may result from structural or functional abnormalities along any part of this complex network. This chapter presents epidemiological data on the following thyroid conditions: thyroid nodules and goiter; hypothyroidism; hyperthyroidism; thyroiditis; autoimmune thyroiditis (Hashimoto's thyroiditis); and iodine deficiency — hereinafter collectively referred to as thyroid disease.

1.1
EPIDEMIOLOGY

Table 1 summarizes recently published data on the prevalence of thyroid disease, by condition, conducted in United States (US) and international-based studies.There are significant differences in the prevalence of thyroid disease based on factors that include sex, race and ethnicity. Differences in thyroid disease prevalence among major ethnic/racial groups in the US are summarized below (Table 2).

As a group, thyroid conditions affect 5-10 times more females than males.[17,18] Table 3 provides an example of this sex difference as observed in the incidence of Graves' disease and Hashimoto's thyroiditis.

1.2
COST BURDEN OF DISEASE

National surveillance data report a steady rise in case volume of endocrine procedures in the US over the last decade, mainly attributable to new and improved imaging and surgical techniques.[20] It is estimated that the number of endocrine procedures performed in the US in 2020 may be as high as 173,509.[20]

In 2008, overall thyroid disease treatment costs in the US for females over age 18 totaled $4.3 billion, including $2.2 billion for ambulatory visits, and $1.4 billion for prescription medications. In 2008, among females with any expenses for thyroid disease treatment, the average expenditure per female for the treatment of thyroid disease was $343; the mean expenditure for ambulatory care visits was $409, and the mean expenditure for prescription medications was $116.[21]

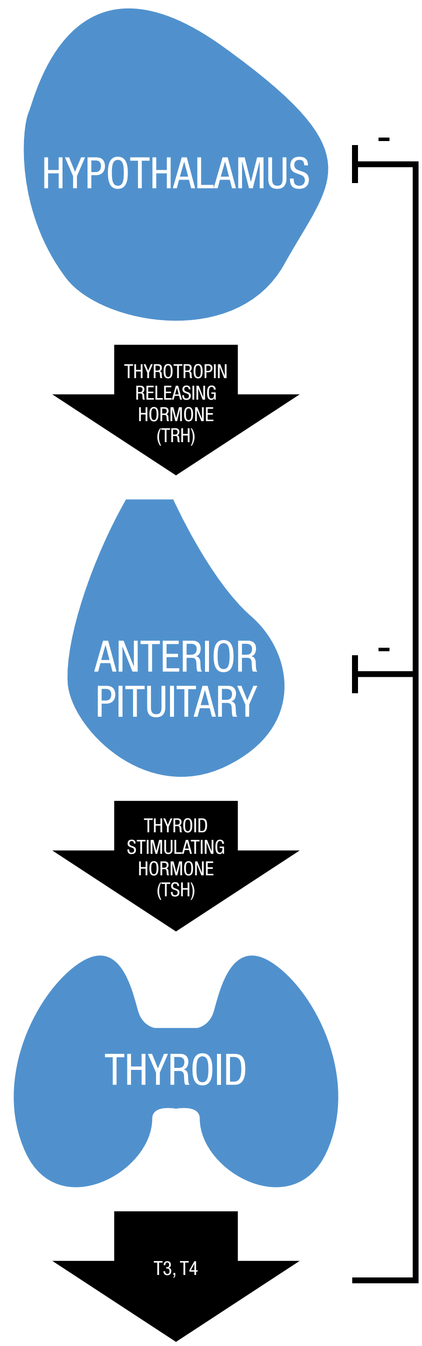

Figure 1. Hypothalamic-pituitary-thyroid axis feedback loop.

Table 1

Estimated prevalence of thyroid disease by condition.					
CONDITION	METHOD	DATA SOURCE	POPULATION	PREVALENCE	REFERENCE
Thyroid nodules	Autopsy	Review article	International population	13% – 60%	Stanicic et al, 2009[6]
	Palpation	Whickham Survey (1972)	Adults, Whickham, UK	0.5% – 26%	Vanderpump et al, 1995[7]
	Ultrasonography	Review article	International population	13.4% – 46%	Stanicic et al, 2009[6]
	Enhanced chest radiography	Johns Hopkins Hospital	Adult outpatients, US	25.1%	Ahmed et al, 2012[8]
Hyperthyroidism	Overt	NHANES III (1988-1994)	Subjects age 12 years and older, US (n=17,353)	0.1% – 0.5%	Hollowell et al, 2002[9]
	Subclinical	NHANES III (1988-1994)	Subjects age 12 years and older, US (n=17,353)	0.75% – 4.3%	Hollowell et al, 2002[9]
	Graves' disease	Literature review	US population	0.63% – 1.49%	Hayter et al, 2012[10]
Hypothyroidism	Overt	NHANES III (1988–1994)	Subjects age 12 years and older, US (n=17,353)	0.3% – 0.8%	Hollowell et al, 2002[9]
	Subclinical	NHANESIII (1988-1994)	Subjects age 12 years and older, US (n=17,353)	0.7% – 13%	Hollowell et al, 2002[9]
	Gestational	Quest diagnostics data (2005-2008)	Pregnant women, US (n=117,892)	15.5%	Blatt et al, 2012[11]
	Congenital (incidence)	NNSGRC dataset (1991-2000)	Newborns, US	0.04%	Hinton et al, 2010[12]
Autoimmune thyroiditis	Hashimoto's thyroiditis	Thyroid Multidisciplinary Clinic, Wisconsin (2006-2008)	811 consecutive patients who received fine needle application biopsies, US	4.6% – 13.4%	Staii et al, 2010[13]
Goiter	Sporadic diffuse	Literature review	International population	1% – 10%	Lind et al, 1998[14]
	Sporadic nodular	Literature review	International population	5% – 9%	Lind et al, 1998[14]
	School-aged children	Research study	Children age 9-16 years, US (n=7,785)	6.8%	Trowbridge et al, 1975[15]
Iodine deficiency	Low urinary iodine concentrations (<50 mcg/L)	NHANES (2001-2006)	Non-pregnant, non-lactating women age 15-44 years, US	17%	Perrine et al, 2010[16]

Note: Differences in diagnostic criteria and analytical techniques account for ranges of prevalence of thyroid disease reported in the literature.

Importantly, in the time period reported in Table 4 (1996 to 2006), there was only a 19.5% increase in inpatient thyroidectomies, whereas outpatient thyroidectomies increased 60.9%. In 2006, the difference in unit charge between inpatient and outpatient (i.e. length of stay in hospital <24 hours) thyroidectomy ($15,315) yielded estimated yearly savings of $63.6 million by reducing length of stay to less than 24 hours.[22]

In addition to costs related to treatment expenses and hospitalization, costs also involve work absence, and unemployment. Indeed, certain forms of disease have a higher cost in terms of work disability. For example, a recent Danish study found that patients with Graves' orbitopathy had the highest risk of work disability, with this being most pronounced in the first year after diagnosis.[23]

Table 2

Prevalence of thyroid disease by race/ethnicity in the US.						
	HYPOTHYROIDISM			HYPERTHYROIDISM		
RACE/ETHNICITY	OVERALL	OVERT	SUBCLINICAL	OVERALL	OVERT	SUBCLINICAL
All	4.6%	0.3%	4.3%	1.3%	0.55%	0.75%
White, non-Hispanic	5.1%	0.4%	4.8%	1.4%	0.6%	0.8%
Black, non-Hispanic	1.7%	0.1%	1.6%	1.1%	0.5%	0.6%
Mexican American	4.1%	0.2%	3.9%	0.7%	0.2%	0.5%
All other races/ ethnicities	4.2%	0.2%	4.0%	0.7%	0.4%	0.3%
Source: Hollowell et al. 2002[9]						

Table 3

Sex differences in incidence of thyroid disease (per 1000 person-years).				
DATA SOURCE	POPULATION	CONDITION	MALES	FEMALES
Comprehensive analysis of medical diagnoses of active US Military Personnel (1997-2011)	US adults age 20-57 years	Hashimoto's thyroiditis	0.03	0.26
		Graves' disease	0.08	0.47
Source: McLeod et al. 2014[19]				

Table 4

Estimated cost for inpatient thyroidectomies in US adults.				
DATA SOURCE	POPULATION	MEASURE	1996	2006
Nationwide Inpatient Sample (NIS) and National Survey of Ambulatory Surgery (NSAS)	52,062 hospital patients with ICD-9 code undergoing thyroidectomies	Inflation-adjusted per capita charges	$9,934	$22,537
		Aggregate national inpatient charges	$464 Million	$1.37 Billion
Source: Sun et al. 2013[22]				

1.3

RECENT SCIENTIFIC BREAKTHROUGHS

1.3.1

Epigenetics

The pathophysiology of Graves' disease involves genetic and environmental factors that interact in as-yet-unknown ways to trigger the disease. Recent research reports a previously unidentified genetic–epigenetic interaction. Using human thyroid cells exposed to interferon-alpha, meant to mimic the immune response produced by exposure to a virus (environmental trigger), researchers found that a noncoding single-nucleotide polymorphism in the thyroid stimulating hormone receptor (*TSHR*) gene interacts epigenetically with the transcriptional repressor PLZF. This interaction resulted in decreased thymic expression of *TSHR,* enabling TSH receptor-reactive T cells to escape central tolerance mechanisms, thereby triggering thyroid autoimmunity and Graves' disease.[24]

1.3.2

Selenium Supplementation

Given its pivotal role in the thyroid, selenium supplementation is being evaluated in several clinical trials in patients with thyroid disorders. The Danish GRASS study (NCT01611896) is currently investigating whether adding dietary selenium supplementation to the standard treatment regimen of antithyroid drugs (ATDs) for 24-30 months — with ATD withdrawn and selenium continued 12-18 months after randomization — may lead to fewer treatment failures and faster and longer-lasting remissions in patients with Graves' disease.[25] Similarly, the CATALYST trial (NCT02013479) aims to compare selenium supplementation versus placebo, both adjuvant to the standard treatment with T_4, in patients with chronic autoimmune thyroiditis.[26] A 2013 Cochrane review concluded that studies published to date are highly heterogeneous and had little clinical relevance. Indeed, they have failed to confirm or refute the efficacy of selenium supplementation for symptom management in patients with Hashimoto's thyroiditis.[27] Results of ongoing trials for the aforementioned thyroid conditions may provide further insight into the value of selenium supplementation in thyroid condition-specific cases.

1.3.3

Use of Genetic/Genomic Markers to Assess Risk of Thyroid Nodules Prior to Surgery

Since its inception as a diagnostic technique about 35-40 years ago, fine-needle aspiration (FNA) has become the gold standard for determining the malignancy of thyroid nodules.[28] However, in cases where FNA yields indeterminate results, the use of molecular markers may be an effective diagnostic strategy. In 265 lesions shown to be cytologically indeterminate by FNA, the negative predictive values for "atypia (or follicular lesion) of undetermined clinical significance," "follicular neoplasm or lesion suspicious for follicular neoplasm," or "suspicious cytologic findings" were 95%, 94%, and 85%, respectively.[29] In a recent study, Eszlinger and colleagues assessed the presence of point mutations and rearrangements in samples extracted by FNA as predictors of follicular thyroid carcinoma. In this study, BRAF mutations and RET/PTC rearrangements mutations were associated with thyroid cancer in 100% of the samples, while RAS and PAX8/PPARG rearrangements were a positive indicator of malignancy in 12% and 50% of samples, respectively.[30]

Similarly, Rossi and colleagues evaluated the diagnostic utility of molecular screening, specifically the presence of BRAF and RAS mutations, as well as RET/PTC1 and RET/PTC2 rearrangements, in the pre-surgical assessment of thyroid nodules. Parallel cytological examination and molecular testing in 940 specimens collected by FNA showed that BRAF mutations were the best molecular marker for cancer diagnosis, including cytologically indeterminate lesions, whereas RAS and RET/PTC analysis did not improve diagnostic sensitivity.[31] In addition, the biomolecular analysis of the BRAF V600E mutation has been reported to increase the accuracy of FNA diagnosis for papillary thyroid carcinoma from 43.9% to 73.25%.[32] To date, the presence of the aforementioned markers has not been unanimously correlated to specific prognostic values.[33]

1.3.4

TSH Receptor Antagonist for Graves' Disease

Graves' disease is caused by persistent, unregulated stimulation of thyrocytes by thyroid-stimulating antibodies (TSAbs) that activate the TSH receptor. In recent years, TSH receptor antagonists and reverse agonists have been pursued as a way of reversing this pathogenic process. Researchers from the National Institute of Diabetes and Digestive and Kidney Diseases synthesized a small-molecule antagonist of TSH receptor signaling and demonstrated its efficacy in decreasing serum free T_4 levels and thyroid gene expression in female mice.[34] Although not the first compound with this mechanism of action,[35] this is the first TSH receptor antagonist to be successfully tested *in vivo*.

1.3.5

Effect of Low Maternal Thyroid Hormone on Childhood Cognitive Function

Low maternal thyroid hormone levels during pregnancy have been linked to poor cognitive function in offspring,[36] contributing to the opinion that timely diagnosis and treatment of maternal hypothyroidism may improve infant outcomes. An antenatal screening program was conducted in the United Kingdom (UK) and Italy to identify women with thyrotropin levels above the 97.5th percentile, free T_4 levels below the 2.5th percentile, or both, in blood samples obtained during the first 16 weeks of gestation.[37] Blood samples were obtained, but not tested until after delivery, for a control group. Women in the screening group who tested positive for hypothyroidism and received T_4 supplementation throughout their pregnancy, and offspring from both the screening and control groups were followed for the first 3 years of life. At the end of this period, there was no difference in cognitive function (measured as IQ levels) in children born to mothers diagnosed with and treated for hypothyroidism, as compared to those born to mothers in the control group with untreated hypothyroidism.[37] A trial comparing 390 children of women treated for isolated high TSH or isolated low free T_4, with 404 children of untreated mothers showed no improvement in the cognitive ability of the former group of children. Currently, a trial is being conducted to further clarify this issue (NCT00388297); however, at present there is no consensus regarding the need for routine screening for subclinical thyroid dysfunction during pregnancy. In addition, the threshold level of TSH used as an indicator of possible fetal damage is a topic of ongoing discussion.[38]

II THYROID NODULES AND GOITER

A thyroid nodule is a discrete lesion within the thyroid gland that is palpably and/or sonographically distinct from the surrounding thyroid parenchyma.[39] Thyroid nodules may be solid or fluid-filled cysts and may develop as a result of various conditions, including iodine deficiency and Hashimoto's thyroiditis. In addition, depending on the method of detection, thyroid nodules are found in up to 50% of the general population, and are frequently asymptomatic and benign.[40]

Thyroid nodule classification is used to determine when a FNA should be performed in order to evaluate the composition of the nodule. The Bethesda System for Reporting Thyroid Cytopathology is a standardized reporting system for classifying FNA results comprising 6 diagnostic categories unique characteristics of malignancy and recommendations for clinical management.[41]

Table 5 shows the risk of malignancy as cited in a recent systematic review and meta-analysis of 41 studies that characterized 29,678 thyroid nodules in total. This study verified and weighted each suspicious and clinical feature of the thyroid nodules.[42]

A goiter is an enlargement of the thyroid gland itself that may result from a variety of conditions, including hypothyroidism, hyperthyroidism, iodine deficiency, or thyroid tumors; all of which may require specific treatment.[43] In addition, a goiter might present itself as a sporadic non-toxic goiter, a benign enlargement of the thyroid in a euthyroid subject living in an iodine-sufficient area, or as either a solitary thyroid nodule or a multi-nodular goiter (MNG), both of which may be toxic or non-toxic, depending on whether they produce an excess of thyroid hormone.[44]

Table 5

Risk of malignancy by nodule characteristic and patient history (meta-analysis of 41 studies).

NODULE CHARACTERISTIC OR PATIENT HISTORY	INCREASED RISK OF MALIGNANCY (VS. NON-MALIGNANT NODULE)
Height > Width	>10 times
Absent halo sign	>7 times
Presence of microcalcifications or irregular margins	>6 times
Hypoechogenicity or solid structure	>5 times
Intranodular vascularization	>3 times
Family history of thyroid carcinoma	>2 times
Nodule size ≥ 4cm	>1.6 times
Single nodule	>4 times
History of head/neck irradiation	>1.3 times
Male gender	>1.2 times

Source: Campanella et al. 2014[42]

2.1
PREVALENCE AND INCIDENCE

2.1.1
Thyroid Nodules

Table 6 summarizes the prevalence of thyroid nodules and goiter reported by US- and international-based studies. Importantly, reported prevalence values depend on the population studied, for example in iodine-sufficient versus iodine-deficient regions, and the diagnostic method used.[45]

2.2
DEMOGRAPHIC DIFFERENCES

Overall, palpable thyroid nodules are more prevalent in women than men. The results of two large epidemiological studies illustrating these differences are summarized in Table 7.

In studies in different US locations, prevalence of nodules detected by microscopic examination at autopsy ranged from 8.2% to 64.5%.[17]

In a meta-analysis of trials between 1965 and 2012 conducted in 27 countries, the authors chose 143 eligible articles to calculate the effect of gender on goiter prevalence in different age groups and with differing iodine status. They found that goiter is more frequent in females, and the difference is more prominent in iodine-deficient areas. For countries that used the WHO definition for the palpation group, goiter was classified according to WHO criteria. Grade 0: no goiter is found (the thyroid impalpable and not visible on clinical inspection); grade 1: neck thickening is present from enlarged thyroid and palpable, however, not visible in normal position of neck; grade 2: neck swelling, visible when the neck is in normal position, corresponding to enlarged thyroid found in palpation.[49]

The International Classification of Diseases 9th edition (ICD-9) codes non-toxic uninodular goiter using ICD-9 code 241.0. In 2010, 123,274 US outpatient hospital visits reported ICD code 241.0 as the primary diagnosis and 162,141 visits reported this code as part of any recorded diagnoses, including both primary and secondary cases.[50] Similarly, 864,980 physician office visits listed this ICD code as the primary diagnosis, and 1,074,393 visits reported in conjunction with other diagnoses.[51] Table 9 presents selected US demographic and clinical breakouts for 2010.[50] Similar demographic data based on physician office visits were not available for multinodular goiter.

2.3
LIFE EXPECTANCY AND MORTALITY

A study of re-biopsy of 66 (11.4%) of 578 patients with initially benign nodules over an 8-year follow-up reported that only one patient was subsequently diagnosed with thyroid malignancy.[52] Moreover, evaluation of the long-term status of patients with initially benign FNA cytology, evaluated in the Brigham and Women's Hospital and Harvard Medical School thyroid nodule clinic between 1995 and 2003, documented only 30 (2.2%) deaths among 1,369 patients, with no deaths attributed to thyroid cancer.[53] A recent study that evaluated the diagnostic efficacy of FNA utilizing histological evaluations of tissue samples, found a high correlation between malignancy rates and the predictive results of FNA.[54]

2.4
DIAGNOSIS, TREATMENT, AND PRESCRIPTION TRENDS

Use of imaging technologies, such as ultrasound, CT, and magnetic resonance imaging (MRI), has led to more thyroid nodule diagnosis than in the past, when physical examination was the primary mode of diagnosis. Indeed, studies have reported that nodules are up to 10 times as likely to be detected with ultrasound as compared with physical examination.[55]

Similarly, from 2006 to 2011, the use of FNA more than doubled, with a 16% annual growth.[28] Interestingly, while indeterminate cytology can be found in 15-30% of FNA specimens, retrospective studies have reported that ultrasound-guided FNA procedures yield lower rates of both non-diagnostic and false-negative cytology specimens.[61] Moreover, some sources credit FNA biopsies with an increase in the diagnostic yield of cancers at thyroidectomy.[55]

A retrospective study of patients with FNA biopsy results classified as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) found that 62% of patients were sent directly to surgery, 25% had the FNA biopsy repeated and 13% had neither but remained under observation.[56]

Table 10 presents data from the Nationwide Inpatient Sample (NIS) and National Survey of Ambulatory Surgery (NSAS) showing an overall increase in thyroidectomies between 1996 and 2006.[22]

Table 11 summarizes data from a recent study using multiple claims data, reporting an increase in the total

Table 6

Estimated prevalence of thyroid nodules and goiter.						
CONDITION	DATA SOURCE	POPULATION	METHOD	INCIDENCE RATE	PREVALENCE	REFERENCE
Thyroid nodules	Framingham Heart Study (1948), US	5,127 subjects free of coronary heart disease: 2,845 women, 2,282 men	Palpation or previous surgery for thyroid nodules	Not reported	4.2% overall; 6.4% in women, 1.5% in men	Vander et al. 1968[46]
	Framingham Heart Study, 15 year follow-up (1948-1953), US	4,909 survivors of original cohort, initially free of thyroid disease: 2,262 women, 2,247 men	Palpation	15-year incidence: 1.4% (1.7% in women, 0.9% in men)	1%, multinodular goiters	
	Whickham Survey, UK, 20-year follow-up (1972-1992)	1802 survivors of Whickham Survey	Antibody assay	Not reported	15.5% overall; 8.6% small goiter, 5.9% large goiter	Vanderpump et al. 1995[7]
	Review (2008), US, 1965	8,641 subjects, age 0-70 years	Palpation	Not reported	0.47%	Dean et al. 2008[45]
	Review (2008), US, 1968	5,127 subjects, age 30-59 years	Palpation	Not reported	4.2%	
	Review (2008), US, 1975	2,271 subjects, age 11-18 years	Palpation	Not reported	1.5%	
	Review (2008), US, 1977	7,785 subjects, 9-16 years	Palpation	Not reported	0.2%	
	Review (2008), England, 1977	2,979 subjects, age 18-75 years	Palpation	Not reported	3.2%	
	Review (2008), Finland, 1991	253 subjects, age 19-50 years	Palpation	Not reported	5.1%	
	Review (2008), Belgium, 1985	300 subjects, age 0-90 years	Ultrasonography	Not reported	19%	
	Review (2008), Finland, 1991	253 subjects, age 19-50 years	Ultrasonography	Not reported	27.3%	
	Review (2008), France, 1994	1000 adult subjects	Ultrasonography	Not reported	34.7%	
	Retrospective review of adult outpatients (2008-2009), US	3077 adults imaged for non-thyroid indications	Incidental, contrast-enhanced chest CT	Not reported	25.1%	Ahmed et al. 2012[8]
Goiter	Study of thyroid diseases in iodine-sufficient areas (1998)	Adults with sporadic diffuse goiter, in iodine sufficient areas	Ultrasonography	Not reported	1% to <10%	Lind et al. 1998[14]
		Adult females with sporadic diffuse goiter, in iodine sufficient areas	Ultrasonography	Not reported	5% to 9%	
	Study of goiter in children (1975), Michigan, Kentucky, Texas and Georgia, US	7,785 children age 9-16 years examined, 377 goitrous children matched with equal number non-goitrous	Urinary iodine and creatinine, T_4, protein-bound iodine, and plasma inorganic iodide determinations	Not reported	6.8%	Trowbridge et al. 1975[15]

Table 7

Incidence and prevalence of palpable thyroid nodules by sex.							
DATA SOURCE	POPULATION	METHOD	PREVALENCE		INCIDENCE		REFERENCE
			MALES	FEMALES	MALES	FEMALES	
Framingham Heart Study (1948), US	5,127 subjects free of coronary heart disease: 2,845 women, 2,282 men	Palpation	1.5%	6.4%	NA	NA	Vander et al. 1968[46]; Dawber et al. 1951[47]
Framingham Heart Study, 15-year follow-up (1948-1953), US	4,909 surviving subjects	Palpation	0.5%	4.7%	0.06%	0.11%	Vander et al. 1968[46]
Whickham Survey (1972), UK	2779 subjects	Palpation	5%	26%	NA	NA	Tunbridge et al. 1977[48]
Whickham Survey, 20-year follow-up (1972-1992), UK	1802 survivors of Whickham Survey	Palpation, Serum TSH, free T_4	2%	10.0%	NR	NR	Vanderpump et al. 1995[7]

Abbreviation: NA, not applicable; NR, not reported.

Table 8

Prevalence of goiter by gender and age group (values given as proportion of total).				
DATA SOURCE	METHOD	POPULATION	MALES	FEMALES
Systematic review and meta-analysis for 27 countries (1965-2012)	**Palpation**			
	All studies, all countries, all levels of iodine status	470,066 patients, approximately equal males and females, 1-80 years	0.46	0.54
	Grade 1		0.46	0.54
	Grade 2		0.37	0.63
	United States	US total	0.20	0.80
	Grade 1		0.21	0.79
	Grade 2		0.10	0.90
	Children	US children under age 15	0.32	0.68
	Adults	US adults 15-90 years	0.08	0.92
	Ultrasonography			
	All countries, all studies	Under 15 years	0.58	0.42
		15-20 years	0.52	0.48
		20-90 years	0.31	0.69

Source: Malboosbaf et al. 2013[49]

number of thyroid surgeries performed in the US due to thyroid nodules between 2006 and 2011. For all operations during this period, 51% were thyroidectomies and 49% were lobectomies, with 40% being inpatient and 60% outpatient. Trend analysis showed that thyroidectomies increased over this 5-year time period, exceeding lobectomies as a percentage of all thyroid nodule related operations in 2009.[28]

The aforementioned study also analyzed the yield of malignancy per operation, comparing results using claims data and American Cancer Society (ACS) incidence estimates. From the study calculations, the yield malignancy per operation increased from 30.3% in 2006 to 36.9% in 2011 according to ACS data, whereas claims data suggested no increase in the incidence of malignancy per operation.[28]

Table 9

Thyroid nodule physician office visit demographics in the US.	
GENDER	
Male	14.1%
Female	85.9%
ETHNICITY	
White	77.1%
Not answered	22.9%
HISPANIC/NON-HISPANIC ETHNICITY	
Hispanic	27.4%
Non-Hispanic	71.3%
Not answered	1.3%
PRINCIPAL EXPECTED SOURCE OF PAYMENT	
Private Insurance	73.7%
Medicare	11.4%
Other	5.4%
Not answered	9.5%
AGE	
0-9 years	0.0%
10-19 years	14.9%
20-29 years	11.5%
30-39 years	0.0%
40-49 years	9.9%
50-59 years	19.0%
60-69 years	31.8%
70-79 years	2.1%
80+ years	10.9%
NUMBER OF VISITS IN PAST YEAR	
None	0.0%
1-2	40.0%
3-5	8.0%
6+	26.0%
Not applicable	26.0%
Source: National Ambulatory Medical Care Survey 2010[50]	

2.5

HEALTH OUTCOMES MEASURES

Table 12 presents data on treatment-based health outcomes for benign thyroid nodules, based on 31 completed randomized controlled trials selected for review through a rigorous evaluation of methodology. In some cases, the number of trial participants was lower

Table 10

Number of thyroidectomies in the US, 1996-2006.

SURGERY TYPE	1996	2006	% INCREASE, 1996-2006
Thyroidectomies	66,864	92,931	39%
Outpatient procedures	19,099	30,731	61%
Inpatient procedures	52,062	62,200	30%
Source: Sun et al. 2013[22]			

Note: Outpatient denotes a hospital stay of less than 24 hours

Table 11

Thyroid nodule surgeries in the US, 2006-2011.

NODULE SURGERY TYPE	2006	2011	% INCREASE, 2006-2011
All nodule surgeries	99,613	130,216	31%
Combined thyroidectomy	45,558	72,344	59%
Inpatient thyroidectomy	22,916	33,611	47%
Outpatient thyroidectomy	22,641	38,733	71%
Combined lobectomy	54,055	57,872	7%
Inpatient lobectomy	21,455	15,625	-27%
Outpatient lobectomy	32,600	42,246	30%
Source: Sosa et al. 2013[28]			

Note: Outpatient denotes a hospital stay of less than 24 hours than ideal. Importantly, many of these treatment strategies are not routinely available in the US.

Studies have attempted to demonstrate the difference in cancer prevalence between single thyroid nodules and MNGs. A systematic analysis of 14 trials found lower prevalence of differentiated thyroid cancer in MNGs of 16.4%, compared with 23.1% among single nodules.[58] In a mildly iodine-deficient area (mid/southern Italy) the prevalence of cancer was 20.1% overall, and higher in single nodules (23.1%) than in MNGs (14.4%). By phenotype, single nodules harbored the follicular thyroid cancer phenotype more than twice as frequently as MNGs did (33% vs. 13%).[59] For further information about thyroid cancer please refer to the Cancers and Neoplasias Chapter.

In the past two decades, the frequency of thyroid surgery has increased, leading to a debate about how the increase in volume has affected outcomes. For example, Misiakos and colleagues conducted a retrospective analysis of patients age 18-89 years, who underwent thyroid surgery during 1995-1999 (phase 1) and 2000-2005 (phase 2) and found a trend toward increased morbidity during the second phase of the study. In the first phase, 5% had hypocalcemia and 4% had some degree of vocal cord paralysis vs. 8% and 5% in the second phase.[60]

Table 13 presents data based on the 2003-2009 Nationwide Inpatient Sample showing the effect of factors that have been found to affect the rate of postoperative complications.[61] First, surgeon volume defined as number of thyroidectomies performed per year (i.e. low (fewer than 100 per year) or high (100 or more per year). Second, hospital volume or number of thyroidectomies taking place in a given hospital per year (i.e. low (fewer than 42) or high (42 or more)). In addition, the study analyzed the relationship between hospital region and patient demographics.

Table 12

Effects of levothyroxine and minimally invasive therapies on benign thyroid nodules.

DATA SOURCE	THERAPY	OUTCOME
Systematic review of 31 studies based on randomized controlled trials up to April 2014	Levothyroxine (16 trials, n=7083; 780 intervention, 1294 comparator)	Nodule volume reduction of 50% or more in 16% of patients vs 10% of patients receiving no treatment or placebo after 6-24 months of follow-up Symptoms of hyperthyroidism were apparent in 25% of treated patients vs. 7% of placebo-treated at 12-18 months of follow-up
	Percutaneous ethanol injection (8 trials, 7 using ethanol, 1 using tetracycline)], n=607, 337 intervention, 270 comparator)	Nodule volume reduction of 50% or more in 83% of patients vs 44% of patients receiving cyst aspiration after 1-24 months of follow-up 78% of patients reported improvement in neck compression symptoms after 6-12 months vs. 38% of those in comparator groups 26% of patients reported slight to moderate pain vs 12% of those receiving cyst aspiration only
	Laser photocoagulation)/T_4 (2 trials, 50)	After 12 months of follow-up, one study showed a nodule volume reduction of 50% or more in 33% of laser photocoagulation patients vs 0% of T_4 patients
	Laser photocoagulation (5 trials, n=192, 101 intervention, 91 comparator)	82% of laser photocoagulation patients showed improvements in pressure symptoms after 6-12 months vs. 0% of untreated patients About 20% of laser photocoagulation-treated patients reported light-to-moderate cervical pain for 48+ hours following treatment
	Radiofrequency ablation (2 trials; n=70, 50 intervention, 20 comparator	Among radiofrequency patients at 6-month follow-up, mean nodule volume reduction was 76% vs 0% for those untreated; the radiofrequency patients also had fewer pressure symptoms and cosmetic complaints after 12 months of follow-up

Source: Bandeira-Echtler et al. 2014[57]

Table 14 provides data specific to the effect of surgeon volume on in-hospital mortality, postoperative complication, length of stay, and hospital charges derived through a retrospective, cross-sectional analysis of all 2003-2009 discharge information according to the Nationwide Inpatient Sample. This study further characterized surgeon volume as low (fewer than 10 surgeries per year), intermediate (10-99 surgeries per year), and high (100 or more surgeries per year). Interestingly, 57.9% of the procedures were total thyroidectomies for benign conditions, which comprised 60.8% of the total number of thyroidectomies.

Table 15 presents the effects of ethnicity on a series of variables based on 106,314 procedures, including both thyroidectomies and parathyroidectomies.[63]

Table 13

Effect of surgeon volume, hospital volume, race, and household income on the rate of postoperative complications after thyroid procedures, 2003-2009.

	WEIGHTED % OF DISCHARGE RECORDS (N=62,722)	POSTOPERATIVE COMPLICATION AMONG PATIENTS PRESENTING COMPLICATIONS (N=10,257)	POSTOPERATIVE COMPLICATION AMONG ALL PATIENTS (N=62,722)
SURGEON VOLUME			
Low	90.8%	55.4%	17.2%
High	9.2%	3.5%	12.1%
HOSPITAL VOLUME			
Low		77.4%	17.7%
High		22.6%	15.1%
RACE			
White	71.7%	71.4%	
Black	11.5%	12.0%	
Hispanic	8.5%	9.2%	
Other	8.4%	7.4%	
HOUSEHOLD INCOME			
<$39,000	20.0%	22.0%	
$39,000-$47,999	23.2%	23.5%	
$48,000-$62,999	25.1%	25.4%	
>$62,999	31.8%	29.1%	

Source: Hauch et al. 2014[62]

Table 14

Effect of surgeon volume on mortality, postoperative complications length of stay, and hospital charges, for 8 primary thyroid surgical procedures, 2003-2009.

SURGEON VOLUME	IN-HOSPITAL MORTALITY	POSTOPERATIVE COMPLICATIONS	LENGTH OF STAY > 75^{TH} PERCENTILE	HOSPITAL CHARGES > 75^{TH} PERCENTILE
Low	1.0%	17.7%	29.1%	32.3%
Intermediate	0.1%	14.2%	14.2%	19.3%
High	0.1%	6.4%	7.4%	14.1%

Source: Noureldine et al. 2014[63]

Table 16 presents data from a retrospective review of over 1000 thyroidectomies in which the length of hospital stay was less than 24 hours (i.e., "outpatient" by Medicare terminology); this analysis shows that, in the hands of an experienced surgeon, outpatient thyroidectomy is safe and reasonable. In addition, a comparative cross-sectional analysis of all cases of thyroid surgery reported in the 2006 National Survey of Ambulatory Surgery and 1996-2006 Nationwide Inpatient Sample not only shows an increase in the total number of thyroidectomies (66,684 in 1996 vs. 92,931 in 2006), but a significant increase of outpatient vs. inpatient procedures. Similarly, this study shows lower per capita charges associated with outpatient procedures as opposed to the inpatient counterpart (Table 17).[22]

Using the 2011-2012 National Surgical Quality Improvement Program database, 8,185 patients who underwent thyroidectomy were identified in each treatment arm. Overall, inpatient thyroidectomy was associated with increased risks of readmission, reoperation, and any complication. The authors cautioned,

Table 15

Ethnicity-based differences in number of procedures, surgeon volume, overall complications, length of stay and in-hospital mortality, 2003-2009.

	PROPORTION OF TOTAL PROCEDURES	SURGEON VOLUME			OVERALL COMPLICATIONS	LENGTH OF STAY (MEAN)	IN-HOSPITAL MORTALITY
		LOW	INTERMEDIATE	HIGH			
Caucasian	54%	32%	49%	19%	11%	2 days	0.3%
African American	11%	39%	45%	16%	16.8%	4 days	0.8%
Hispanic	7%	38%	50%	13%	13.5%	3 days	0.4%
Asian	3%	24%	51%	24%	12%	2 days	0.5%
Other or Unknown	25%	33%	49%	18%	11.5%	2 days	0.3%

Source: Noureldine et al. 2014[63]

Note: Data is based on the overall number of thyroidectomies and parathyroidectomies.

Table 16

Outpatient thyroidectomy (stay in hospital <24 hours) — related complications.

	PERCENTAGE OF COMPLICATION AMONG DISCHARGED PATIENTS (N=122)
Symptomatic hypocalcemias	5.2%
Transient recurrent laryngeal nerve injuries	3.7%
Permanent recurrent laryngeal nerve injuries	0.4%
Hematomas	0.19%
Readmissions within 30 days	2.3%

Source: Snyder et al. 2010[64]

Table 17

Increase in outpatient (stay in hospital <24 hours) vs. inpatient procedures and associated per capita charges.

	OVERALL NUMBER OF PROCEDURES	OUTPATIENT PROCEDURES	INPATIENT PROCEDURES
PERCENTAGE INCREASE IN PROCEDURES (1996 VS. 2006)	39%	61%	30%
PER CAPITA CHARGES, 2006		$7,222	$22,537

Source: Sun et al. 2013[22]

however, that there are as-of-yet unknown risk factors that may resolve the discrepancy.[65]

In any thyroid surgery, common comorbidities can have a significant affect. A retrospective cohort study using data from the American College of Surgeons National Surgical Quality Improvement Program from 38,577 thyroidectomy patients between 2005-2010, showed 30-day mortality of 0.06% and 1.49% postoperative morbidity. The risk factors associated with morbidity included hypertension, diabetes, age older than 70 years, malignant thyroid disease, and total as opposed to partial thyroidectomy. Significant predictors of mortality were substernal thyroidectomy, hypertension, diabetes, and age older than 70 years.[66]

A 20-year review of case histories of patients who had thyroid surgery reported that 20% of patients developed hyperthyroidism caused by the appearance of hyper-functioning nodules 6-18 years after the initial diagnosis.[67] Health outcomes data related to toxicity caused by the presence of nodules will be discussed in the hyperthyroidism section of this chapter.

III HYPOTHYROIDISM

Hypothyroidism results from an underactive thyroid gland. Overt hypothyroidism is defined as elevated serum TSH levels with low-serum free T_4, while subclinical hypothyroidism, or mild thyroid failure, is defined as elevated serum TSH with a serum free T_4 level in the normal range. In rare cases, hypothyroidism may be due to pituitary disease causing a deficient secretion of TSH, in such cases both TSH and free T_4 are expected to be low.[68]

3.1 PREVALENCE AND INCIDENCE

3.1.1 Overt Hypothyroidism

A study conducted in Whickham, UK in 1972 became the model for later epidemiological studies; it reported a prevalence of overt hypothyroidism in 1.4% (14/1000) of females and less than <0.1% (<1/1000) of males, and overall, 0.8% in a population of 2779 persons (1494 women, 1285 men).[48] The 20-year follow-up study of 1877 survivors (1051 women, 826 men) of the original Whickham cohort found a prevalence of 7.7% among women and 1.3% among men, and 9.3% overall. The incidence among survivors per year was 3.5/1000 among women and 0.6/1000 among men.[7]

A study in Tayside, Scotland with a much larger population (390,000) between 1994 and 2001 found that the overall prevalence of thyroid dysfunction increased from 2.3% to 3.8% over that period. The prevalence of hypothyroidism among females increased from 3.18% to 5.46%, and among males from 0.51% to 0.95%. The incidence of hypothyroidism also showed significant increases: from 4.23/1000 to 4.57/1000, and among males from 0.65/1000 to 1.01/1000.[69]

There are few US-based data regarding incidence of hypothyroidism. In a study of children age 11-18 years in southwestern Nevada and Utah, the prevalence of overt hypothyroidism was 0.19% (1965-1968); in follow-up examinations of two-thirds of the original cohort (1985-1986), it was 1.59%.[70] Although the impetus for the study was in part to discern whether fallout from nuclear testing in the region might have increased thyroid disorders, the authors could only conclude that these disorders are dynamic and changeable in form, function, appearance, and disappearance.

Analysis of NHANES III (1988-1994) data for patients age 12 years and older found a prevalence of 0.3% for overt hypothyroidism.[9] A cross-sectional study of 70- to 79-year-olds in Memphis, Tennessee and Pittsburgh, Pennsylvania reported the incidence of overt hypothyroidism to be 0.54% in males and 1.3% in females.[71] Interestingly, the Cardiovascular Health Study (CHS), a population-based longitudinal study of adults age 65 years and older throughout the US, found that in 1992 the prevalence of untreated overt hypothyroidism was 0.61%.[72]

Table 18 summarizes US inpatient, outpatient and physician office visits for ICD-9 code 244.9 (unspecified acquired hypothyroidism) between 2008 and 2010.

3.1.2 Subclinical Hypothyroidism

Subclinical hypothyroidism is more prevalent than overt hypothyroidism. NHANES III data for patients age 12 years and older indicated a prevalence of 4.3% for subclinical hypothyroidism.[9]

Observational data indicate that pregnant women with subclinical hypothyroidism have demonstrated an increased risk of adverse pregnancy outcomes. Subclinical hypothyroidism may increase the odds of pregnancy complications, including preeclampsia, placental abruption, preterm birth and neonatal mortality.[74]

Shields and colleagues reported the presence of subclinical hypothyroidism in 12.4% of pregnant healthy women (n=523) with no known thyroid disorders. Of these, 75.4% had normal thyroid function after pregnancy and 24.6% showed persistent high TSH.[75]

Among US adults age 70-79 years, in Memphis and Pittsburgh, the prevalence of subclinical hypothyroidism was 3.1%.[71] Interestingly, the 1992 Cardiovascular Health Study (CHS) reported the prevalence of subclinical hypothyroidism to be 12.8% among adults age 65 years and older.[72] In addition, data collected from adults aged 18 years and older at the Colorado Heath Fair in 1995 revealed a prevalence of 9.0% for subclinical hypothyroidism.[76]

3.1.3 Congenital Hypothyroidism

Congenital hypothyroidism occurs in approximately 1:2000 to 1:4000 newborns. Universal neonatal screening for this condition is carried out in the US and most developed countries. The symptomatology includes decreased activity, increased sleep, feeding difficulty, constipation, and prolonged jaundice.[77]

Table 18

Patient discharge summary ICD-9 code 244.9 (unspecified acquired hypothryoidism), 2008-2010

	2008	2009	2010
HOSPITAL INPATIENT[73]			
First-listed diagnoses	25,983	28,477	30,245
All-listed diagnoses	1,733,161	1,721,205	2,705,909
HOSPITAL OUTPATIENT[50]			
Primary diagnoses	359,727	479,803	513,734
All-listed diagnoses	889,213	1,009,289	1,370,797
PHYSICIAN OFFICE VISITS[50]			
Primary diagnoses	4,449,684	5,505,668	4,303,425
All-listed diagnoses	11,851,593	12,907,577	14,029,158

Sources: National Ambulatory Medical Care Survey 2010[50]; National Hospital Discharge Survey 2010[73]

The incidence of congenital hypothyroidism has increased since the early 1990s, resulting in part from changes in testing protocols that enhanced detection of mild disease.[78]

In 2010, a study examining data from 11 states' newborn screening databases reported congenital hypothyroidism incidence to be 0.04%.[12] Moreover, this study indicated an increase in incidence from 0.029% to 0.04% between 1991 and 2000, as well as an overall increase of 30.4% across the decade.[12] Importantly, congenital hypothyroidism is more frequent in iodine-deficient regions. Indeed, the prevalence of neonatal TSH levels above 5 mIU/L may be greater than 40% in severely iodine-deficient regions, but should be below 3% in iodine-sufficient populations.[79]

According to data collected on all newborn infants in Rhode Island, US from 2000-2006, the incidence of congenital hypothyroidism with a delayed TSH elevation was higher among lower birth weight infants (Table 19).[80]

3.1.4 Gestational Hypothyroidism

For information related to gestational hypothyroidism, refer to section 3.2.3 of this chapter.

3.2 DEMOGRAPHIC DIFFERENCES

NHANES III data for patients aged 12 and older indicated that mean TSH levels and antithyroid antibody (TPOAb and TgAb) prevalence were greater in whites and Mexican Americans than in blacks. Prevalence of overt and subclinical hypothyroidism was highest among whites and lowest among blacks (Table 20).[9]

Table 19

Incidence of hypothyroidism in Rhode Island, by birth weight, 2000-2006.

BIRTH WEIGHT	INCIDENCE OF HYPOTHYROIDISM
<1,000 g	1.72%
1,000–1,499 g	0.34%
1,500+ g	0.0033%

Source: Woo et al. 2011[80]

3.2.1

Subclinical Hypothyroidism

Among adults age 70-79 years in Memphis and Pittsburgh, older black adults had a lower prevalence of subclinical hypothyroidism than older white adults. In blacks, the prevalence was 2% in males and 3% in females compared to 4% and 6% in whites.[71] The prevalence of subclinical hypothyroidism by race and ethnicity is summarized in Table 20.

3.2.2

Congenital Hypothyroidism

In 2010, a study reported that the incidence of congenital hypothyroidism was 100% higher in Hispanic newborns compared with whites, and 44% higher in Asian and Native Hawaiian/Other Pacific Islanders. However, the incidence was 30% lower in black newborns than in whites.[12]

3.2.3

Gestational Hypothyroidism

There is currently insufficient evidence to recommend universal thyroid function testing for all women considering pregnancy or who are newly pregnant. However, there is general agreement in favor of screening in women who are at high risk for thyroid dysfunction or in those with a history of thyroid dysfunction and/or thyroid hormone use. Guidelines for the assessment and management of thyroid dysfunction in pregnancy have been issued by a variety of professional associations, including the Endocrine Society;[81-84] notable differences between these guidelines have been discussed elsewhere.[85-87]

Table 20

Prevalence of overt and subclinical hypothyroidism by race/ethnicity in patients age 12 years and older.

RACE/ETHNICITY	HYPOTHYROIDISM		
	OVERALL	OVERT	SUBCLINICAL
All	4.6%	0.3%	4.3%
White, non-Hispanic	5.1%	0.4%	4.8%
Black, non-Hispanic	1.7%	0.1%	1.6%
Mexican American	4.1%	0.2%	3.9%
Other races/ ethnicities	4.2%	0.2%	4.0%

Source: Hollowell et al. 2002[9]

In unselected iodine-sufficient populations, the prevalence of subclinical hypothyroidism in pregnant women is about 2.5%, and the prevalence of overt hypothyroidism is 0.5%.[88,89] As mentioned earlier, a study of 523 pregnant healthy women with no known thyroid disorders found subclinical hypothyroidism in 12.4% of the population, with 75.4% presenting normal thyroid function after pregnancy, and 24.6% exhibiting persistently high TSH.[75]

An evaluation of data collected between 2005 and 2008 from the Quest Diagnostic Informatics Data Warehouse, including results from TSH tests for pregnant women aged 18 to 40 years, reported a 15.5% prevalence of gestational hypothyroidism (overt and subclinical).[11] The Quest data indicated that Asian women were 1.8 times more likely than African-American women to be tested for gestational hypothyroidism and almost 5 times as likely to develop this condition.

According to the aforementioned Quest data, only 23% of pregnant women (18-40 years) were tested for gestational hypothyroidism between 2005 and 2008. However, the study estimated that an additional 483,000 pregnant women in the US may have gestational hypothyroidism.[11] While this study offers important insights on the prevalence of gestational hypothyroidism, it is critical to note that the study did not report the indicators used for thyroid function testing during gestation nor whether women taking thyroid hormone preparations or antithyroid drugs were excluded.

3.3

LIFE EXPECTANCY AND MORTALITY

Hypothyroidism has been linked to many conditions limiting life expectancy, including cardiac dysfunction, atherosclerosis, hypertension, and coagulopathy.[90] A review of available studies on hypothyroidism-related morbidity found varying and inconsistent data supporting the increased mortality related to either subclinical or overt hypothyroidism.[90] Conversely, data from NHANES III indicate that hypothyroidism is associated with greater mortality than euthyroidism in blacks, but not in non-blacks.[91]

Whereas US-based data is limited, a British study analyzing death registration data between 1979-2010 found that mortality rates for acquired hypothyroidism decreased significantly during this period as a result of improved care.[92] Average annual percentage change was 2.6%, with the highest decrease observed during the 1980's. Both overt and subclinical hypothyroidism have been associated with increased risk of coronary heart disease, congestive heart failure, and cardiovascular mortality.[93,94,95]

Data from NHANES III indicated that mortality rates were higher in congestive heart failure patients with subclinical hypothyroidism compared with euthyroid heart failure patients.[91] In fact, studies have linked the risk for coronary heart disease (CHD) events and a rise in CHD mortality with both elevated and reduced TSH levels.[95] A meta-analysis of studies from 11 prospective cohorts in the US, Europe, Australia, Brazil, and Japan found subclinical hypothyroidism in 6.2% among a cohort of 55,287 adults. The risk of CHD events rose with TSH level, from a hazard ratio of 1.00 for TSH level of 4.5 to 6.9 mIU/L, to 1.17 for a TSH level of 7.0 to 9.9 mIU/L, and to 1.89 for a TSH level of 10.0 to 19.9 mIU/L. The corresponding hazard ratios for CHD mortality were 1.09 for euthyroid participants, 1.42, and 1.58.[95]

Importantly, total mortality was not elevated among patients with subclinical hypothyroidism.[95] Similarly, a more recent study also failed to demonstrate a link between subclinical thyroid dysfunction and increased mortality risk in heart failure patients.[96]

The Cardiovascular Health All Stars Study, an ancillary study to the CHS, was designed to evaluate the relationship between healthy aging and longevity. It examined the relationship between thyroid function and mortality in the elderly (mean age 85 years) in four participating centers in different areas of the US between 2005-2006. It found a link between free T_4 and mortality. The study did not, however, show a link between observed TSH elevation and increased or decreased mortality, raising a concern about treatment of mild elevations of TSH in advanced age.[97]

In 5816 randomly selected Dutch participants, age 80 years or older, free T_4 levels even within the high-normal range (18.5–22 pmol/L) were associated with 70% higher mortality as compared with those whose T_4 levels were within the middle range. In those elderly persons, TSH levels within the high-normal range (3.0–4.0 mIU/L) were also associated with an 80% higher mortality in comparison with those persons having TSH levels within the middle range (1.0–2.0 mIU/L).[98]

In a study based on the NHANES III, the authors affirmed that TSH distribution progressively shifts toward higher concentrations with age. Without thyroid disease, 10.6% of patients age 20-29 years had TSH greater than 2.5 mIU/liter, increasing to 40% in the >80 group, 14.5% of whom had TSH greater than 4.5 mIU/liter. When TSH was greater than 4.5 mIU/liter, the percentage with antibodies was 67.4% (age 40-49 years) and progressively decreased to 40.5% in the >80 group. The prevalence of subclinical hypothyroidism may be significantly overestimated unless an age-specific range for TSH is used.[99]

3.4

DIAGNOSIS, TREATMENT, AND PRESCRIPTION TRENDS

Following an extensive evidence review, the American Thyroid Association recently concluded that levothyroxine (LT_4) monotherapy is the standard of care for hypothyroidism, and found insufficient evidence to recommend alternative preparations such as T_4/T_3 combination therapy or thyroid extract therapy.[100] Others have concluded that while there may be a role for T_4/T_3 combination therapy in selected patients, there remains a lack of well-conducted trials examining the effectiveness and health outcomes associated with such therapies.[101]

There remains some controversy regarding the treatment of subclinical hypothyroidism,[82,83,102] though patients with this condition have an increased risk of progression to overt hypothyroidism and may also be at risk of cardiovascular disease.[103] It has been suggested that treatment of subclinical hypothyroidism (TSH values 10 mIU/L or lower) should be avoided in patients over age 85 years. There is insufficient evidence regarding an association between subclinical hypothyroidism and adverse cardiac events and other systemic symptoms of hypothyroidism in patients with TSH values <10 mIU/L, suggesting treatment of this patient group may be unnecessary. In addition, there is evidence that suggests that subclinical hypothyroidism in persons over 85 years of age is associated with longevity.[104]

3.5

HEALTH OUTCOMES MEASURES

Among hypothyroid patients treated with T_4 for at least 12 months between 2006 and 2011, normal TSH was found in 75% of those with spontaneous hypothyroidism and

68% of those with hypothyroidism following surgery or RAI therapy. T_4 overtreatment was observed in 4% and 6% of patients respectively.[105]

There are few studies that have evaluated the incidence and progression of thyroid dysfunction in a single older population-based cohort. The Blue Mountains Eye Study (New South Wales, Australia) offered this opportunity by evaluating the 5-year incidence, progression, and risk factors for thyroid dysfunction. During this 5-year period progression from subclinical to overt hypothyroidism, associated with obesity, was observed in 17.9% of 1768 subjects with subclinical hypothyroidism.[106]

Subclinical hypothyroidism during pregnancy can persist postpartum. Among 523 pregnant healthy women with no known thyroid disorders, blood samples were taken at 28 weeks of pregnancy and at a mean of 4.9 years postpregnancy. Subclinical hypothyroidism (TSH 3 mIU/L) was present in 12.4%. Postpregnancy, 24.6% had persistent high TSH (>4.5 mIU/L). Of the women with subclinical hypothyroidism in pregnancy for whom antibody measurements were available, those with thyroid peroxidase antibodies in pregnancy were more likely to have persistently elevated TSH or to be receiving T_4 replacement after pregnancy) 86% vs 18%).[75]

In addition, thyroid dysfunction during pregnancy has been associated with pregnancy complications and negative effects on pregnancy outcomes. Among 17,298 pregnant women screened for TSH and free T_4 levels at a US hospital during 2000-2003, 404 (2.3%) were considered to have subclinical hypothyroidism. These women had a 3-times higher risk of placental abruption and a 1.8-fold risk of preterm birth.[88] In a later evaluation of 6,985 women identified among those previously screened at the same hospital, 230 (3.3%) were found to have subclinical hypothyroidism after a subsequent delivery. In subsequent pregnancies, subclinical hypothyroidism was associated with diabetes (adjusted odds ratio, aOR 1.58) and stillbirth (aOR 3.41).[107]

IV HYPERTHYROIDISM

Hyperthyroidism, also called overactive thyroid, is a condition in which the thyroid produces too much of the thyroid hormones T_4 and/or T_3.[2]

4.1 PREVALENCE AND INCIDENCE

4.1.1 Overt Hyperthyroidism

The estimated prevalence of overt hyperthyroidism ranges from 0.1% to 0.5%, and is higher among females than males.[9] Based on data from the NHANES III, the prevalence of overt hyperthyroidism among persons age 12 years and older was 0.5%.[9] Examinations of 3,121 adults ages 31-38 years between 1985-1986, in a 3-state area of the southwestern US where nuclear testing had been carried out, indicated a hyperthyroidism prevalence of 0.39%.[70]

In 1992, the Cardiovascular Health Study found that the prevalence of overt hyperthyroidism in persons 65 years and older was 0.33%.[72] In a review article examining studies published from 1990-2013, the relative incidence of overt hyperthyroidism in pregnancy was estimated to range from 0.1% to 0.4%.[108]

In the UK the 20-year follow-up of the Whickham Survey found that the annual incidence of hyperthyroidism was 0.008% among females and undetectable among males.[7] The prevalence of previously unsuspected hyperthyroidism was 0.5% in females, and undetectable in males.[7]

An increase in primary hyperthyroidism between 1994 and 2001 was documented in a population-based study of patients in Tayside, Scotland. Among participants in this study, the overall prevalence of hyperthyroidism increased from 0.86% to 1.26% in females and 0.17% to 0.24% in males. The standardized incidence of hyperthyroidism increased from 0.68 to 0.87 per 1000 females per year, representing a 6.3% annual increase.[69]

A recent study found 1682 new cases of overt hyperthyroidism in a large cohort from two cities in Denmark, one with moderate iodine deficiency (Aalborg, population 311,102) and another with only mild iodine deficiency (Copenhagen, population 227,632). The overall standardized incidence rate (SIR) per 100,000 person-years was 81.6, and was higher in Aalborg compared with Copenhagen (96.7 vs. 60.0). The SIR ratio between moderate versus mild iodine-deficient areas was 1.6.[109]

Whereas there are limited incidence data for hyperthyroidism in the US, based on the number of new prescriptions of thionamide antithyroid drugs, incidence per 1000 subjects by age group and data from the 2008 US census is presented in Table 21.

The prevalence of hyperthyroidism during pregnancy, according to one study, has been found in 0.1%-0.4% of pregnancies.[108] Another study quotes a higher range: 0.4%-1.7%.[111] The latter study notes that thyroid disorders during pregnancy can be missed because of nonspecific symptoms and normal changes in thyroid gland that accompany pregnancy. As mentioned earlier, thyroid function tests need to be interpreted properly with trimester specific TSH reference ranges.

4.1.2

Subclinical Hyperthyroidism

The clinical consequences of subclinical hyperthyroidism, such as atrial dysrhythmia, accelerated bone loss, increased fracture rate, and higher rates of cardiovascular mortality, are dependent on age and severity.[112] NHANES III reports the prevalence of subclinical hyperthyroidism among people age 12 years and older as 0.7%.[9] According to the CHS, in 1992 the prevalence of subclinical hyperthyroidism was 1.2% among adults age 65 years and older.[72]

4.1.3

Graves' Disease

The Defense Medical Surveillance System reported that in US active-duty military personnel age 20-54 years (1997-2011), compared with whites, the incidence rate ratio (IRR) for Graves' disease was significantly elevated in black women (IRR, 1.92) and men (IRR, 2.53), as well as Asian/Pacific Islander women (IRR, 1.78) and men (IRR, 3.36).[19] Table 22 summarizes data on the epidemiology of Graves' disease.

Table 21

Incidence per 1000 of overt hyperthyroidism by age.	
AGE	INCIDENCE PER 1000 SUBJECTS
4-11 years	0.44
12-17 years	0.26
18-44 years	0.59
56-64 years	0.78
65 years and older	1.01
Source: Emiliano et al. 2010[110]	

4.2

DEMOGRAPHIC DIFFERENCES

4.2.1

Overt Hyperthyroidism

NHANES III data for patients age 12 years and older indicate that prevalence of hyperthyroidism differs only slightly by ethnicity (Table 23).[9]

4.3

LIFE EXPECTANCY AND MORTALITY

A prospective, observational study of British patients presenting with a first episode of hyperthyroidism between 1989-2003, and followed until 2012, found that over time, 32% of the initial cohort of 1036 patients (age 40 years and older) died. This was 15% higher for all-cause mortality than the expected deaths for this population. However, comorbidity was high in the population. Cardiovascular and cerebrovascular causes were 20% higher than expected, and in study subjects presenting with atrial fibrillation the risk of death was 59% higher. Excess mortality was not observed in the subgroup having no preceding comorbidities. Among subjects with Graves' disease, all-cause mortality increased by 16%. However, excess mortality was not observed in subjects rendered hypothyroid by RAI.[116]

A recent meta-analysis selected 8 (seven cohort, one case–control) studies for analysis by stringent criteria. Most of the studies were performed in Europe, with only 2 from the US. Six of the 8 studies found a higher mortality in hyperthyroid patients compared with controls. As in the British study mentioned above, cardiovascular disease imposed an increased risk: 19% higher than in the general population. As a whole, the studies found an overall relative mortality risk of 1.21 among patients with overt hyperthyroidism, indicating an increased mortality risk of about 21%.[117] Subsequent analysis of data from the Thyroid Studies Collaboration reached similar conclusions for subclinical hypothyroidism, including an association with increased risk of total mortality, coronary heart disease mortality, and incident atrial fibrillation.[118]

Data from the OPENTHYRO database regarding thyroid-stimulating hormone (TSH) levels show that thyroid dysfunction, including both hypo- and hyperthyroidism, is associated with an increased risk of comorbidities. Hyperthyroidism was linked to a higher burden of comorbidity and increased mortality; subclinical hyperthyroidism was associated with a 9% excess mortality per year of age, and 12% with overt hyperthyroidism.[119] The Nijmegen Biomedical Study found an association between increased mortality for subjects under 65 years of age, but not those older than 65 years. In a cohort of community-dwelling men age 70-89 years, free T_4 levels in euthyroid men were associated with all-cause mortality independently of conventional risk factors and medical comorbidities.[120]

A 2013 review cited long-term adverse effects resulting from subclinical hyperthyroidism, including an increased 24 hour heart rate and increased frequency of atrial and ventricular ectopic beats. Large studies of older adults showed a 13% increase in the frequency of atrial fibrillation. Some studies show an increase in all-cause mortality; the highest risk of coronary heart disease mortality and atrial fibrillation is found in patients with serum TSH is under 0.10 mIU/L.[74]

4.4

DIAGNOSIS, TREATMENT, AND PRESCRIPTION TRENDS

In 2011, a survey of members of the Endocrine Society (ES), American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) found that most members' initial treatment of choice for uncomplicated Graves' disease was antithyroid drugs. Initial treatment preferences are outlined in Table 24.[121]

Moreover, the majority of respondents cited methimazole as the preferred antithyroid drug (Table 25).

Table 22

Epidemiology of Graves' disease.

POPULATION	METHOD	INCIDENCE PER 100,000/YEAR	PREVALENCE	REFERENCE
Rochester, Minnesota, US (1935-1967)	Hospital records	36.8 (F)		Furszyfer et al. 1972[113]
Nurses' Health Study, US (1989-2001)	724 supplemental questionnaires	40.9 (F)		Holm et al. 2005[114]
Specialized clinic, UK	Estimate from population studies in literature		0.65% (F, 2.3%; M, 0.145%)	Boelaert et al. 2010[115]
US active-duty military personnel, age 20-54 years, (1997-2011)	Data analysis of records of patients with ICD-9 code 242.0	47.9 (F); 8.0 (M)		McLeod et al. 2014[19]

Abbreviations: F, females; M, males

Table 23

Prevalence of overt and subclinical hyperthyroidism by race/ethnicity in the US.

RACE/ETHNICITY	HYPERTHYROIDISM		
	OVERALL	OVERT	SUBCLINICAL
All	1.3%	0.5%	0.7%
White, non-Hispanic	1.4%	0.6%	0.8%
Black, non-Hispanic	1.1%	0.5%	0.6%
Mexican American	0.7%	0.2%	0.5%
Other races/ethnicities	0.7%	0.4%	0.3%

Source: Hollowell et al. 2002[9]

Compared to findings from a similar survey conducted in 1991, fewer respondents opted for RAI during treatment (59.7% in 2011 vs. 69% in 1991).[121]

A retrospective evaluation of data from patients with Graves' disease treated with RAI, found that the 1- and 5-year recurrence rate was 5%. In addition, after 5 years, 78% of patients developed hypothyroidism and 17% showed euthyroid state.[122]

The aforementioned survey of endocrinologists found that patients with Graves' ophthalmology were treated with antithyroid drugs or surgery most frequently (Table 26).[121]

4.5 HEALTH OUTCOMES MEASURES

4.5.1 Graves' Disease

Three treatment modalities for Graves' disease — RAI, anti-thyroid drug therapy, and surgery — are largely focused on controlling hyperthyroidism.[123]

In the case of RAI, a critical step is determining the appropriate dosage to achieve optimal efficacy. Interestingly, Bakos and colleagues presented data of 326 patients with a mean follow-up of 5.7 years, in which Graves' disease patients had a hyperthyroidism recurrence rate of 5% after 5 years. In those with toxic goiter, the 5-year recurrence rate was 7%. In the Graves' disease population, subsequent recurrence of hyperthyroidism and hypothyroidism is not unusual.[122]

A systematic review of trials related to radioactive iodine administration due to hyperthyroidism caused by toxic nodular goiter found that patients who received calculated dosimetry treatment had a 9.6% higher cure rate and 0.3% more permanent hypothyroidism than those treated with the fixed dose method.[124]

A retrospective analysis of 384 patients in northern Italy presented varying results in the 249 patients who were treated with the anti-thyroid drug methimazole (MMI). After excluding those with inadequate response to MMI at low doses, 138 patients maintained euthyroidism beyond 20 to 24 months.[125]

The European Multicentre Trial Group randomized two patient groups to treatment with 10 or 40 mg of MMI. The overall relapse rate a mean observation period of 4.3 years was 58%, and did not differ between patients treated with the higher or lower dose. The conclusion was that the dose of MMI in Graves' disease therapy can be kept to the minimal required dose to provide the best balance of risk and benefit.[126]

In a trial designed to investigate the 6-year outcome of MMI treatment with or without exogenous T_4 in Chinese patients with Graves' disease, the conclusion was that the addition of T_4 to methimazole treatment neither improved or prevented the remission or recurrence of Graves' disease.[126]

Table 24

Initial treatment preferences for patients with Graves' disease.

INITIAL TREATMENT	PREFERENCE
Antithyroid drugs	53.9%
Radioactive iodine therapy (RAI)	45.0%
Thyroid surgery	0.7%
56-64 years	0.78
65 years and older	1.01

Source: Burch et al. 2012[121]

Table 25

Preferred antithyroid medication for patients with Graves' disease.

ANTITHYROID DRUG	PREFERENCE
Methimazole	83.5%
Carbimazole (not available in US)	13.8%
Propylthiouracil	2.7%

Source: Burch et al. 2012[121]

Table 26

Treatment preferences for patients with Graves' ophthalmology.

TREATMENT	PREFERENCE
Antithyroid drugs	62.9%
Thyroid surgery	18.5%
RAI + corticosteroids	16.9%
RAI alone	1.9%

Source: Burch et al. 2012[121]

Abbreviation: RAI, radioactive iodine

A review of 31 cohort studies found adverse effects reported in 13% of patients. These were more common with MMI and were typically dermatological, whereas hepatic effects were more common with propylthiouracil. Drug therapy yielded higher relapse rates than surgery or RAI.[127]

Additional therapeutic approaches are in the development pipeline. Among biological agents, rituximab is a humanized chimeric monoclonal antibody targeting CD20, an antigen expressed on lymphocytes. A high affinity antibody, termed 5C9, blocks the effects not only of the monoclonal stimulatory TRAb and thyroid stimulating hormone, but also the polyclonal TRAb found in the sera of Graves' disease patients.[128] Also, newly developed drug-like small molecule ligands antagonize TSHR signaling.[129]

A recent meta-analysis reached similar conclusions, but indicated that total thyroidectomy was associated with an increase in both temporary and permanent hypoparathyroidism.[130]

The potential risk of damage to the recurrent laryngeal nerve (RLN) is a consideration to be kept when opting for surgery as treatment. In 844 thyroidectomies for benign thyroid diseases in Japan between 2008 and 2010, 1,372 nerves were at risk during the surgery. The RLN was involuntarily transected in 5 patients during the operation and the incidence of RLN palsy was 5.3% per patient and 3.3% per nerve.[131] Conversely, a cohort study of 780 patients, of whom 203 had Graves' disease, found no permanent laryngeal damage among the Graves' disease patients. In addition, 80% of the reported thyroidectomies were performed as outpatient procedures.[132]

V THYROIDITIS

Thyroiditis is a broad term encompassing a group of conditions whose primary symptom is inflammation of the thyroid gland. These conditions include Hashimoto's thyroiditis, postpartum thyroiditis, painless thyroiditis, subacute thyroiditis, drug-induced and radiation-induced thyroiditis, and acute or infectious thyroiditis. Hashimoto's thyroiditis is considered the most common autoimmune disease, at 46 cases per 1000 when measured by levels of circulating thyroid antibodies.[133]

5.1 PREVALENCE AND INCIDENCE

5.1.1 Hashimoto's Thyroiditis

Tables 27, 28, and 29 present data related to epidemiology of Hashimoto's thyroiditis. Please note that in these tables, disease-free population is defined as those not reporting thyroid disease, goiter, or taking thyroid medication at the time of the study.

5.1.2 Subacute Thyroiditis

Subacute thyroiditis is an acute painful inflammatory disorder of the thyroid gland, most likely due to viral infection.[2] According to data collected between 1960 and 1997 from the residents of Olmsted County, Minnesota, the total incidence of subacute thyroiditis in the 1990's was 3.6 per 100,000. Incidence was 2.8 per 100,000 among males and 4.6 among females.[136] The data indicated a decrease in incidence from 8.7 per 100,000 in the 1960s to 5.6 during the 1970s and 3.2 in the 1980s, followed by a period of stability during the 1990s.[136]

A recent study examined a large cohort from two cities in Denmark, one with moderate iodine deficiency (Aalborg) and another with only mild iodine deficiency (Copenhagen). 2.3% of the cases of subacute thyroiditis presented in subjects from the moderate iodine deficiency area and 0.9% from the area with only mild iodine deficiency.[109]

5.1.3 Postpartum Thyroiditis

Postpartum thyroiditis is an inflammatory autoimmune disorder of the thyroid gland that occurs in the first year following delivery. A review of 21 studies prospectively performed in women without another autoimmune disease estimated that the average incidence of postpartum thyroiditis was 5.4%; and it is increased in individuals with autoimmune diseases such as type 1 diabetes. Long-term follow-up of women after an episode of postpartum thyroiditis showed a 20% to 40% incidence of permanent hypothyroidism.[137] A study of Japanese women stated that postpartum thyroid dysfunction occurs in in 5% to 10% of women, mostly thyrotoxicosis that appears early in the postpartum period and is usually followed by transient hypothyroidism.[138]

In a study of Iranian women with subclinical and overt postpartum thyroid dysfunction, after treatment with T_4 for 23 months and subsequent withdrawal of treatment, 59% of women with subclinical thyroid dysfunction and 64% of women with overt hypothyroidism became hypothyroid. The author concluded that a high percentage of patients with subclinical postpartum thyroid dysfunction will proceed to permanent hypothyroidism.[139] In a review of studies on postpartum thyroiditis, the authors found a wide range of permanent hypothyroidism, from 12% to 61%. They also stated that postpartum thyroiditis is an acute stage of autoimmune thyroid destruction, frequently leading to permanent thyroid failure.[140]

Table 27

Incidence and prevalence of Hashimoto's thyroiditis.

POPULATION	METHOD	INCIDENCE PER 100,000/YEAR	PREVALENCE	REFERENCE
Rochester, Olmsted County, Minnesota, US (1935-1967)*	Tissue sample; clinical manifestations	1935-1944, 6.5 (F); 1945-1954, 21.4 (F) 1955-1964, 67.0 (F) 1965-1967, 69.0 (F)	Overall, 246/2336 (10.53%); F, 240 (10.27%); M, 6 (0.26%)	Furszyfer et al. 1972[113]
Whickham, UK (1972), adults age ≥20 years (n=2779)	Hemagglutination, TgAb immunoreactivity		F, 16.2% ; M, 4.3%	Tunbridge et al. 1977[48]; McLeod et al. 2012[134]
Whickham, UK (1972-1992) (n=1877)	Serum TSH, free T_4	350 (F), 60 (M)	F, 10.3%; M, 2.7%	Vanderpump et al. 1995[7]; McLeod et al. 2012[134]
7 towns (n=719) England and Wales previously characterized in terms of past and present iodine intake	TPOAb immunoreactivity	15 (F)	F, 20.2%	McLeod et al. 2012[134]; Prentice et al. 1990[135]
Tayside, Scotland (1994-2001) TEARS database (n=390,000)	Serum TSH	448 (F), 92 (M)	Increased from 1.83% to 3.01% over 1994-2001	Leese et al. 2008[69]
US active-duty military personnel, age 20-54 years, (1997-2011)	Diagnosis per ICD-9-CM code 245.2	26.3 (F), 3.2 (M)		McLeod et al. 2014[19]
761 patients, U. Wisconsin Thyroid Clinic, 2006-2008	FNA, cytological diagnosis		13.4%	Staii et al. 2010[13]
NHANES III (1988-1004) (n=17,353; 8,043 (M) and 9,310 (F)), age ≥12 years **	Serum TSH, T_4, thyroid antibodies (TPOAb and TgAb)			Hollowell et al. 2002[9]
Total population (n=17,353)	TPOAb		13.0%	
	TgAb		11.5%	
Disease-free population (n=16,533)	TPOAb		11.3%	
	TgAb		10.4%	

Note: *The detailed analysis for the incidence of Hashimoto's was done only for the female population;
Abbreviations: F, females; M, males; TPOAb, antithyroid peroxidase; TgAb, antithyroglobulin; TSH, thyroid stimulating hormone.
**Positive TPOAb ≥0.5 IU/mL; positive TgAb ≥1.0 IU/mL

5.2

DEMOGRAPHIC DIFFERENCES

The Defense Medical Surveillance System reported the number of Hashimoto's thyroiditis cases among all US active duty military personnel aged 20 to 54 years from January 1, 1997 to December 31, 2011. Hashimoto's thyroiditis incidence was highest in whites and lowest in black women (IRR, 0.33) and men (IRR, 0.22) and Asian/Pacific Islander women (IRR, 0.31) and men (IRR, 0.23).[19]

5.3

LIFE EXPECTANCY AND MORTALITY

Among pregnant women, thyroid autoimmunity in euthyroid women is associated with preterm delivery and miscarriage.[141] Evidence is emerging that as women age subclinical hypothyroidism-as a sequel of postpartum thyroiditis-predisposes them to cardiovascular disease. Hence, postpartum thyroiditis is no longer considered a mild and transient disorder.[140]

Table 28

Antibody prevalence by thyroid status, antibody prevalence, all ethnic groups by age (%) in the US, NHANES III (1988-1994).				
	TPOAb		TgAb	
	TOTAL POPULATION	DISEASE-FREE POPULATION	TOTAL POPULATION	DISEASE-FREE POPULATION
All ages	13.0	11.3	11.5	10.4%
12-19	4.8	4.8	6.3	6.3
20-29	8.5	7.9	7.2	6.7
30-39	11.9	10.5	11.2	10.1
40-49	14.7	13.1	12.0	11.3
50-59	16.0	13.5	13.9	12.0
60-69	20.2	16.7	16.9	14.7
70-79	22.3	19.6	18.8%	17.0
80-89	23.9	20.4	21.6%	19.4
Source: Hollowell et al. 2002[9]				

Abbreviations: F, females; M, males. TPOAb, antithyroid peroxidase; TgAb, antithyroglobulin.
Definition: positive TPOAb; ≥0.5 IU/mL; positive TgAb; ≥1.0 IU/mL

Table 29

Antibody prevalence by thyroid status, gender, and ethnicity in the US, NHANES III (1988-1994)												
	TPOAB						TGAB					
	TOTAL POPULATION			DISEASE-FREE POPULATION			TOTAL POPULATION			DISEASE-FREE POPULATION		
	Total	M	F	Total	M	F	Total	M	F	Total	M	F
All ethnic groups	13.0	8.7	17.0	11.3	8.0	14.6	11.5	7.6	15.1	10.4	6.9	13.8
White non-Hispanic	14.3	10.0	18.4	12.3	9.1	15.6	12.9	8.9	16.6	11.5	8.1	15.0
Black non-Hispanic	5.3	2.5	7.6	4.5	6.2	6.4	3.0	2.2	4.4	2.7	1.1	4.1
Mexican American	10.9	16.2	15.9	10.1	5.9	14.7	8.8	4.7	13.1	8.2	4.6	12.3
Source: Hollowell et al. 2002[9]												

Abbreviations: F, females; M, males. TPOAb, antithyroid peroxidase; TgAb. antithyroglobulin.
Definition: positive TPOAb ≥0.5 IU/mL); positive TgAb ≥1.0 IU/mL

5.4 DIAGNOSIS, TREATMENT, AND PRESCRIPTION TRENDS

Postpartum thyroiditis is typically self-limited and does not always require treatment. However, postpartum thyroiditis may persist for up to 4 or more years in 25% of cases.[142] Women who are symptomatic in the thyrotoxic phase may be treated with beta blockers. In the hypothyroid phase, T_4 may be required if women are symptomatic or if the serum TSH is higher than 10 mIU/L.

Selenium supplementation for Hashimoto's thyroiditis has yielded non-definitive results, due to significant bias in four clinical trials reviewed in 2013.[27]

A retrospective review of the records of 72 patients with subacute thyroiditis found that 92% of the patients presented with local symptoms such as tenderness, pain, and dysphagia. 57% of patients showed symptoms of hyperthyroidism. Within 6 months after onset, subclinical hyperthyroidism was found in 15% and overt hyperthyroidism in 1.3% of patients. Long-term hormone replacement was deemed necessary if the TSH was higher than 3.5 mU/L. After a 12 month follow-up, 95.5% of patients were free of symptoms. At the endpoint of the study the thyroid gland volume was lower in the long term hormone replacement group compared with patients without need of T_4 (41.7% vs 57.2% of sex-adjusted upper norm, respectively).[143]

VI IODINE DEFICIENCY

6.1 PREVALENCE AND INCIDENCE

In 2013, the US was included among the 111 countries identified as having sufficient iodine intake defined by a national or subnational median urinary iodine (UI) concentration of 100–299 mcg/L in school-aged children.[144] The proportion of the US population with UI lower than 100 mcg/L was 17% according to the 2013 International Council for Control of Iodine Deficiency Disorders (ICCIDD) scorecard.[145] Overall, the US is currently considered iodine sufficient. However, mild iodine deficiency may be present in pregnant US women and women of childbearing age.[146]

Sufficient population iodine intake as assessed by median urinary iodine was set in 1992 as 100 to 199 micrograms per liter for school-age children adults, with the exception of pregnant and lactating women. For that population, a median value of 150 to 249 micrograms per liter (mcg/L) signals adequate intake. Excessive intake for school-age children and adults was signaled by urinary concentration 300 mcg/L and higher, and for pregnant and lactating women, 500 mcg/L and higher.[79]

According to data in a one-third subsample of the NHANES 2005-2010 participants, the overall prevalence of low UI concentrations among 6- to 75-year-olds was 31.1% between 1988 and 1994. In 2001 and 2002, 38.0% of women aged 15 to 45 had urinary iodine concentrations of 100 mcg/L or lower.[147]

6.2 DEMOGRAPHIC DIFFERENCES

According to data in a one-third subsample of the NHANES 2005-2006 and 2009-2010 participants and in all 2007-2009 participants age 6 years and older, median UI concentration in 2009-2010 (144 mcg/L) was lower than in 2007-2008 (164 mcg/L). Non-Hispanic blacks had the lowest UI concentrations (131 mcg/L) compared with non-Hispanic whites or Hispanics (147 and 148 mcg/L, respectively). The median for all pregnant women in NHANES 2005-2006 was less than adequate (129 mcg/L; optimal is 150-249 mcg/L), whereas third trimester women had UI concentrations that were adequate (median UI 172 mcg/L).[148] The demography of UI according to the NHANES 2009-2010 is reported in Tables 30 and 31.

Whereas fewer than 10% of households in the world in 1990 had access to iodized salt, by the year 2000, that percentage had increased to 68%. As a strategy for reducing mental retardation resulting from iodine deficiency, salt iodization also introduces the possibility of excessive intake of iodine if appropriate monitoring is not carried out. An evaluation of iodine levels in 35,233 schoolchildren at 378 sites of 28 countries has shown that many previously iodine deficient parts of the world now have median urinary iodine concentrations well above 300 mcg/L, which is excessive and carries the risk of adverse health consequences.[149]

6.3 LIFE EXPECTANCY AND MORTALITY

Elderly people, especially those living in iodine-deficient areas, are more prone to abnormal thyroid function. A 6-year study in a mildly iodine-deficient area of Italy showed all-cause mortality among persons with hyperthyroidism was 65% higher than in those with normal thyroid function.[150]

In severely iodine deficient areas, iodine deficiency has been documented to be an important etiological factor leading to poor fetal growth and development. Iodine is essential for physical growth and development of the central nervous system of the fetus. Some studies have shown that severe iodine deficiency in pregnant mothers leads to increased incidence of perinatal and infant child mortality.[151]

6.4

DIAGNOSIS, TREATMENT, AND PRESCRIPTION TRENDS

Among 51 newborns, 26 who were diagnosed with congenital hypothyroidism due to severe iodine deficiency were treated with T_4. The remaining 25 cases were given T_4 plus 100 mcg/day of oral iodine. Free T_3, free T_4, TSH, thyroglobulin, thyroid volume, urine iodine, and breast milk iodine levels were measured in the first and third months of treatment, and the data were compared between the two groups. It was found that the addition of oral iodine to T_4 treatment provided no benefit compared to treatment with T_4 alone.[152]

The effect of the mandatory nationwide iodine fortification program in two areas of Denmark was measured in 2465 adults. Age-dependent differences in thyroid volume

Table 30

Urinary iodine by age and sex in the US.

	IODINE LEVEL, 1 MCG/L	IODINE LEVEL CORRECTED FOR CREATININE LEVEL, 1 MCG/G
AGE		
>6 years	144	143
6-11years	213	250
12-19 years	131	117
20-29 years	132	112
30-39 years	132	114
40-49 years	128	114
50-59 years	136	147
60-69 years	148	181
>70 years	182	239
SEX		
Male	147	149
Female	134	150
Females of childbearing age	124	117

Source: Caldwell et al. 2013[146]

Table 31

Urinary iodine by race/ethnicity in the US.

RACE/ETHNICITY	IODINE LEVEL, 1 MCG/L	IODINE LEVEL CORRECTED FOR CREATININE LEVEL, 1 MCG/G
Non-Hispanic white	147	149
Non-Hispanic black	131	98
All Hispanic	148	142

Source: Caldwell et al. 2013[146]

and enlargement had leveled out, suggesting that the previously observed increase in thyroid volume with age may have been caused by iodine deficiency.[153]

6.5 HEALTH OUTCOMES MEASURES

In a double blind, randomized, placebo-controlled trial that recruited 241 breast-feeding mother-infant pairs between 2010 and 2011, median urinary iodine concentrations suggested iodine deficiency. The indirect supplementation group received one dose of 400 mg to the mother and placebo to the infant, and the direct supplementation group received one dose of about 100 mg iodine to the infant and placebo to the mother. Urinary iodine levels, breast milk iodine, mother and infant TSH, maternal and infant T_4 and infant growth were measured at baseline (it was 35 mcg/L in mothers and 73 mcg/L in infants), and when the infants were 3, 6, and 9 months. The number of infants with thyroid hypofunction was lower in the indirect supplementation group than in the direct supplementation group. The infant groups did not differ in anthropomorphic measures, except that length-for-age Z score was slightly greater in the direct infant supplementation group. At 3 months and 6 months of age, median infant urinary iodine concentration in the indirect infant supplementation group was sufficient (>100 mcg/L), whereas infant urinary iodine concentration was sufficient only at 6 months in the direct supplementation group.[154]

Iodine supplementation during pregnancy or the peri-conceptional period in regions of severe iodine deficiency reduces risk of cretinism.[155] A systematic review of studies on the impact of iodine supplementation on maternal and newborn thyroid function in regions of mild to moderate iodine deficiency noted the lack of controlled trials on infant neurodevelopment. However, gestational iodine supplementation reduced maternal thyroid volume and serum thyroglobulin. In some studies, it prevented a rise in serum TSH.[156]

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