The epidemiology of thyroid disease

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Introduction: Thyroid disorders are prevalent and their manifestations are determined by the dietary iodine availability.

Sources of data: Data from screening large population samples from USA and Europe.

Areas of agreement: The most common cause of thyroid disorders worldwide is iodine deficiency, leading to goitre formation and hypothyroidism. In iodine-replete areas, most persons with thyroid disorders have autoimmune disease.

Areas of controversy: Definition of thyroid disorders, selection criteria used, influence of age and sex, environmental factors and the different techniques used for assessment of thyroid function.

Growing points: Increasing incidence of well-differentiated thyroid cancer. Environmental iodine influences the epidemiology of non-malignant thyroid disease.

Areas timely for developing research: Iodine supplementation of populations with mild-to-moderate iodine deficiency. An evidence-based strategy for the risk stratification, treatment and follow-up of benign nodular thyroid disease. Is there any benefit in screening adults for thyroid dysfunction?

Keywords: thyroid disease/epidemiology/thyroid nodules/iodine/hypothyroidism/hyperthyroidism

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Introduction

Almost one-third of the world's population lives in areas of iodine deficiency.[1] In areas where the daily iodine intake is <50 μg, goitre is usually endemic, and when the daily intake falls <25 μg, congenital hypothyroidism is seen. The prevalence of goitre in areas of severe iodine deficiency can be as high as 80%. Populations at particular risk tend to be remote and live in mountainous areas in South-East Asia, Latin America and Central Africa. Iodization programmes are of proven value in reducing goitre size and in preventing goitre development and cretinism in children. Autonomy can develop in nodular goitres leading occasionally to thyrotoxicosis and iodization programmes can also induce thyrotoxicosis, especially in those aged >40 years with nodular goitres.[2]

In iodine-replete areas, most persons with thyroid disorders have autoimmune disease, ranging from primary atrophic hypothyroidism, Hashimoto's thyroiditis to thyrotoxicosis caused by Graves' disease. Cross-sectional studies in Europe, the USA and Japan have determined the prevalence of hyperthyroidism and hypothyroidism and the frequency and distribution of thyroid autoantibodies in different, mainly Caucasian, communities.[2] Data from screening large US population samples[3,4] have revealed differences in the frequency of thyroid dysfunction and serum thyroid antibody concentrations in different ethnic groups, whereas studies from Europe have revealed the influence of dietary iodine intake on the epidemiology of thyroid dysfunction.[5] Studies of incidence of autoimmune thyroid disease have only been conducted in a small number of developed countries.[6]

Goitre and thyroid nodules

The most common thyroid disease in the community is simple (diffuse) physiological goitre. Ultrasonography has been used in epidemiological studies to assess thyroid size, leading to much higher estimates of goitre prevalence than in studies in which goitre size was assessed by physical examination.[2] In cross-sectional surveys, the prevalence of diffuse goitre declines with age, the greatest prevalence is in pre-menopausal women, and the ratio of women to men is at least 4:1.[7] This is in contrast to the increase in frequency of thyroid nodules and thyroid antibodies with age. In a study of 5234 subjects aged >60 years in Framingham, clinically apparent thyroid nodules were present in 6.4% of women and 1.5% of men.[8] The prevalence of single thyroid nodules was 3% and multinodular goitre was 1%.

In several early autopsy surveys, up to 50% of patients had thyroid nodules and using ultrasonography between 20 and 76% of women have at least one thyroid nodule.[2] In Germany, an area of relative iodine deficiency, thyroid nodules or goitre were found in 33% of 96 278 working adults aged 18–65 years screened by an ultrasound scan.[9] Thyroid nodules >1 cm were found in 12% of this population and increased with age. In patients with a single palpable nodule, 20–48% have additional nodules as detected by ultrasonography.

Thyroid cancer

The clinical presentation of thyroid cancer is usually as a solitary thyroid nodule or increasing goitre size. Although thyroid nodules are common, thyroid cancers are rare. Thyroid cancer is the most common malignant endocrine tumour and accounts for >90% of the cancers of the endocrine glands but constitute <1% of all malignancies registered in the UK.[10] The incidence of thyroid cancer is increasing. In 2001, data from Cancer Research UK showed 1200 new cases in England and Wales, with a reported annual incidence for the UK of 3.5 per 100 000 women and 1.3 per 100 000 men. The majority of the increase can be attributable to an increase in incidence of papillary thyroid cancer measuring ≤2 cm.[11] Papillary thyroid microcarcinomas (diameter <1 cm) are found in up to one-third of adults at post-mortem in population-based studies.

Congenital hypothyroidism

Congenital hypothyroidism affects about one newborn in 3500–4000 births and is the most treatable cause of mental retardation.[12] There is an inverse relationship between age at diagnosis and intelligence quotient in later life. In iodine-replete areas, 85% of the cases are due to sporadic developmental defects of the thyroid gland (thyroid dysgenesis), such as the arrested migration of the embryonic thyroid (ectopic thyroid) or a complete absence of thyroid tissue (athyreosis). The remaining 15% have thyroid dyshormonogenesis defects transmitted by an autosomal recessive mode of inheritance. A daily iodine intake <25 μg, particularly in preterm infants, accounts for many cases in Europe, Asia and Africa. Clinical diagnosis occurs in <5% of newborns with hypothyroidism because symptoms and signs are often minimal. As a result, it is not possible to predict which infants are likely to be affected. Without prompt diagnosis and treatment most

affected children gradually develop growth failure, irreversible mental retardation and a variety of neuropsychological deficits.

Asymptomatic autoimmune thyroiditis

Raised serum concentrations of thyroid antibodies [anti-thyroid peroxidase (microsomal) (TPOAb) and anti-thyroglobulin (TGAb)] correlate with the presence of focal thyroiditis in thyroid tissue obtained by biopsy and at autopsy from patients with no evidence of hypothyroidism during life. Early post-mortem studies confirmed histological evidence of chronic autoimmune thyroiditis in 27% of adult women, with a rise in frequency over 50 years, and 7% of adult men, and diffuse changes in 5% of women and 1% of men.[2] Patients with hypothyroidism caused by either atrophic or goitrous autoimmune thyroiditis usually have high-serum concentrations of these same antibodies. These antibodies also are often detected in serum of patients with Graves' disease and other thyroid diseases, but the concentrations are usually lower.

The percentage of subjects with high-serum TPOAb and TGAb concentrations increases with age in both men and women, and high concentrations are more prevalent in women than in men and less prevalent in blacks than in other ethnic groups.[4] Using a competitive immunoassay procedure, the reported prevalence of detectable TGAb and TPOAb levels were 10 and 12% of the healthy population. A hypoechoic ultrasound pattern or an irregular echo pattern may precede TPOAb positivity in autoimmune thyroid disease and TPOAb may not be detected in $>20\%$ of individuals with ultrasound evidence of thyroid autoimmunity.[13]

Hypothyroidism

In iodine-replete communities, the prevalence of spontaneous hypothyroidism is between 1 and 2%, and it is more common in older women and 10 times more common in women than in men.[2] Studies in Northern Europe, Japan and the USA have found the prevalence to range between 0.6 and 12 per 1000 women and between 1.3 and 4.0 per 1000 in men investigated (Table 1). The prevalence is higher in surveys of the elderly in the community.[14] Overt hypothyroidism was found in 7% of 558 subjects aged between 85 and 89 years in Leiden, Netherlands.[15] A lower prevalence is seen in areas of iodine deficiency.[16,17]

Table 1 Prevalence of previously undiagnosed overt hypothyroidism and incidence of overt hypothyroidism in selected epidemiological surveys of thyroid dysfunction.

Study name	*n*	Age (years)	Test	Prevalence (*n*/1000)		Incidence (*n*/1000/year)		
				Men	Women	Follow-up	Men	Women
Whickham, UK[7,22]	2779	18+	TSH, T_4	0	3.3	20 years	0.6 (0.3–1.2)	3.5 (2.8–4.5)
Colorado, USA[3]	25 862	18+	TSH	4.0				
NHANES III, USA[4]	16 533	12+	TSH	2.0				
Pescopagano, Italy[16]	992	15+	TSH, FT_4	0	3.0			
Sapporo, Japan	4110	25+	TSH	2.4	8.5	–	–	–
Copenhagen, Denmark[17]	2656	41–71	TSH, FT_4	2.0	5.0			
Memphis/Pitttsburgh, USA[20]	2797	70–79	TSH, FT_4	5.4	13.0			
Leiden, Netherlands[15]	558	85–89	TSH, FT_4	70				
Tayside, UK (1993–1997)[23]	390 000	0+	Treatment for hypothyroidism	–	–	4 years	0.88 (0.80–0.95)	4.98 (4.81–5.17)
Tayside, UK (1997–2001)[24]	390 000	0+	As above			4 years	1.09 (0.95–1.25)	4.75 (4.46–5.07)
Göteborg, Sweden	1283	44–66	TSH	–	6.4	4 years	–	1–2
Birmingham, UK[14]	1210	60+	TSH	7.8	20.5	1 year	11.1	
Gothenburg, Sweden	1148	70+	TSH	–	–	10 years	–	2

TMA, antithyroid microsomal antibodies; TGA, anti-thyroglobulin antibodies (see reference 1 unless stated).

Subclinical hypothyroidism

The term subclinical hypothyroidism is used to describe the finding of a raised serum thyrotropin (TSH) but a normal free thyroxine (T_4). In the community, the most common aetiology is chronic autoimmune thyroiditis.[13] In the original Whickham survey in Northeast England, 8% of women (10% of women over 55 years of age) and 3% of men had subclinical hypothyroidism.[7] In the Colorado study, 9.4% of the subjects had a high-serum TSH concentration, of whom 9.0% had subclinical hypothyroidism.[3] Among those with a high-serum TSH concentration, 74% had a value between 5.1 and 10 mIU/l and 26% had a value >10 mIU/l. The percentage of subjects with a high-serum TSH concentration was higher for women than for men in each decade of age, and ranged from 4 to 21% in women and 3 to 16% in men. In the National Health and Nutrition Examination Survey (NHANES III) serum TSH concentrations increased with age in both men and women and were higher in whites than in blacks, independent of serum anti-thyroid antibody concentrations.[4] Approximately 2% of adolescents aged 12–19 years had a serum TSH >4.5 mIU/l.

Studies of elderly persons have confirmed the high prevalence of a raised serum TSH in this age group, with ~10% of subjects >60 years in a single general practice in Birmingham, UK having serum TSH values above the reference range.[14] More recent data from Birmingham suggest that there is now an increased awareness of thyroid disease and testing of thyroid function and perhaps earlier use of levothyroxine in mild thyroid failure. A community-based sample of 5960 participants aged ≥65 years demonstrated a lower prevalence of subclinical hypothyroidism of 2.9% (95% confidence interval (CI): 2.6–3.1%).[18] A further analysis of the NHANES III data suggests that the reference range for serum TSH rises with age as the 97.5 centile for those subjects aged >80 was 7.49 mIU/l and 70% had a serum TSH greater than the population defined upper limit of the reference range of 4.5 mIU/l of whom only 40% were anti-thyroid antibody positive.[19] Data from a US cohort aged 70–79 years found that black subjects had a significantly lower prevalence of subclinical hypothyroidism (2% in men and 3% in women), as compared with white subjects (4% in men and 6% in women).[20] Subclinical hypothyroidism is found at higher frequency (18% in Iceland and 24% in Hungary) in areas where iodine intake is high, but most cases are not of autoimmune origin. In surveys of hospital in-patients, the point prevalence rates were similar being between 3 and 6% with most subjects reverting to normal thyroid function 3 months following the acute illness.[2]

Spontaneous recovery has also been described in subjects with subclinical hypothyroidism, although the frequency of this phenomenon is

unclear. In one study, 37% of patients normalized their serum TSH levels over a mean follow-up time of 32 months.[21] Normalization of serum TSH concentrations is more likely to occur in patients with negative antithyroid antibodies and serum TSH levels <10 mIU/l, and within the first 2 years after diagnosis.[13]

Incidence of hypothyroidism

The 20-year follow-up of the Whickham cohort provided incidence data and allowed the determination of risk factors for spontaneous hypothyroidism in this period.[22] The mean annual incidence of spontaneous hypothyroidism during the 20-year follow-up period was 3.5 per 1000 and 0.6 per 1000 in surviving women and men, respectively. Either raised serum TSH or positive thyroid antibodies alone or in combination were associated with a significantly increased risk of developing hypothyroidism. In the surviving women, the annual risk of spontaneous overt hypothyroidism was 4% in those who had both high-serum TSH and antithyroid antibody concentrations, 3% if only their serum TSH concentrations was high, and 2% if only their serum thyroid antibody concentration was high; at the time of follow-up, the respective rates of hypothyroidism were 55, 33 and 27%. The probability of developing hypothyroidism was higher in those women who had serum TSH concentrations >2.0 mU/l and high-serum titres of antithyroid microsomal antibodies during the first survey. All studies indicate that the higher the serum TSH value, the greater the likelihood of development of overt hypothyroidism in subjects with chronic autoimmune thyroiditis.

The other incidence data for hypothyroidism are from short (and often small) follow-up studies.[6] In elderly subjects, the annual incidence rate of hypothyroidism varies widely between 0.2 and 7% in the available studies (see Table 1). Data from the large population study in Tayside, UK has demonstrated that the standardized incidence of primary hypothyroidism varied between 3.90 and 4.89 per 1000 women per year between 1993 and 2001. The incidence of hypothyroidism in men significantly increased from 0.65 to 1.01 per 1000 per year ($P = 0.0017$). The mean age at diagnosis of primary hypothyroidism decreased in women from 1994 to 2001.[23,24]

Hyperthyroidism

The most common causes of hyperthyroidism are Graves' disease, followed by toxic multinodular goitre, whilst rarer causes include an

autonomously functioning thyroid adenoma or thyroiditis. In epidemiological studies, however, the aetiology is rarely ascertained. The prevalence of hyperthyroidism in women is between 0.5 and 2%, and is 10 times more common in women than in men in iodine-replete communities (Table 2). In NHANES III, in those subjects who were neither taking thyroid medication nor reported histories of thyroid disease, 2 per 1000 had 'clinically significant' hyperthyroidism, defined as a serum TSH concentration <0.1 mIU/l and a serum total T_4 concentration >170 nmol/l.[4] The prevalence data in elderly persons show a wide range between 0.4 and 2.0% [14,15,20] and a higher prevalence is seen in iodine-deficient areas.[16,17]

Subclinical hyperthyroidism

The introduction of assays for serum TSH sensitive enough to distinguish between normal and low concentrations allowed subjects with subclinical hyperthyroidism to be identified. Subclinical hyperthyroidism is defined as a low-serum TSH concentration and normal serum T_4 and T_3 concentrations, in the absence of hypothalamic or pituitary disease, non-thyroidal illness or ingestion of drugs that inhibit TSH secretion such as glucocorticoids or dopamine.[2] Epidemiological studies differ in the definition of a low serum TSH concentration and whether the subjects included were receiving levothyroxine therapy. The reported overall prevalence is $\sim$3%, with men and women over 65 years having the highest prevalence with $\sim$50% taking levothyroxine. In the NHANES III study the prevalence was highest in those subjects aged 20–39 years and those aged >79 years.[4] In this study, the percentage of subjects with serum TSH concentrations <0.4 mIU/l was significantly higher in women than in men, and black subjects had significantly lower mean serum TSH concentrations, and therefore a higher prevalence of subclinical hyperthyroidism (0.4%) than whites (0.1%) or Mexican Americans (0.3%). The prevalence of subnormal serum TSH concentrations is higher in iodine-deficient populations (6–10%), due to functional autonomy from nodular goitres.[2]

Among subjects with subclinical hyperthyroidism, those with low but detectable serum TSH values may recover spontaneously when re-tested. Non-thyroidal illness is an important cause of false-positive TSH test results. In a systematic review of screening patients admitted to acute care and geriatric hospitals $\sim$25% of patients with a low serum TSH (<0.1 mIU/l) proved to have hyperthyroidism.[25] The predictive value of a low serum TSH may also be low in frail or very elderly subjects.[26] Data on the risk of progression of subclinical hyperthyroidism to overt hyperthyroidism are limited. In

Table 2 Prevalence of previously undiagnosed overt hyperthyroidism and incidence of overt hyperthyroidism in selected epidemiological surveys of thyroid dysfunction.

Study name	*n*	Age (years)	Test	Prevalence (*n*/1000)		Incidence (*n*/1000/year)		
				Men	Women	Follow-up	Men	Women
Whickham, UK[7,22]	2779	18+	T_4, FT_4I	0	4.7	20 years	<0.1	0.8 (0.6–1.4)
Colorado, USA[3]	25 862	18+	TSH	1.0				
NHANES III, USA[4]	16 533	12+	TSH, TT_4	2.0				
Pescopagano, Italy[16]	922	15+	TSH, FT_4	20.0				
Sapporo, Japan	4110	25+	TSH, TRAB	2.7	5.1	–	–	–
Copenhagen, Denmark[17]	2656	41–71	TSH, FT_4	0	12.0			
Memphis/Pittsburgh, USA[20]	2797	70–79	TSH, FT_4	0.7	2.8			
Leiden, Netherlands[15]	599	85–89	TSH, FT_4	4.0				
Tayside, UK (1993–1997)[23]	390 000	0+	Treatment for hyperthyroidism	–	–	4 years	0.14 (0.11–0.17)	0.77 (0.70–0.84)
Tayside, UK (1997–2001)[24]	390 000	0+	As above	–	–	4 years	0.15 (0.10–0.22)	0.91 (0.78–1.05)
Johannesburg, South Africa	?	0+	T_4			1 year	0.007	0.09
Birmingham, UK[14]	1210	60+	TSH	0.9	1 year	0	1.5	
Gothenburg, Sweden	1148	70+	TSH	–	–	10 years	–	1.0
Funen, Denmark	450 000	0+	PBI, T_4, T_3	–	–	3 years	0.1	0.5
Iceland	230 000	0+	T_4, T_3	–	–	3 years	0.1	0.4
Malmö, Sweden	257 764	0+	PBI	–	–	5 years	0.1	0.4

TRAB, TSH receptor antibody; PBI, protein-bound iodine; FT_4I, free thyroxine index (see reference 1 unless stated).

the majority of subjects, a detectable below normal serum TSH will eventually rise towards normal. In those subjects with an undetectable serum TSH and a confirmed aetiology as determined by thyroid scintigraphy due to Graves' disease or nodular disease, it has been calculated that the annual incidence is ~5–8%.[27] A recently published large population study in Tayside, Scotland followed 2024 subjects with at least two serum TSH measurements below the reference range for at least 4 months for up to 7 years.[28] Few subjects developed hyperthyroidism (0.5–0.7%) and the percentage of those reverting to normal increased with time and this was more common in those with a baseline serum TSH between 0.1 and 0.4 mIU/l. Thus, in the vast majority of subjects a below normal serum TSH will eventually rise towards normal.

Incidence of hyperthyroidism

The incidence data available for overt hyperthyroidism in men and women from large population studies are comparable, at 0.4 per 1000 women and 0.1 per 1000 men, but the age-specific incidence varies considerably (Table 2). The peak age-specific incidence of Graves' disease was between 20 and 49 years in two studies, but increased with age in Iceland and peaked at 60–69 years in Malmö, Sweden.[1] The peak age-specific incidence of hyperthyroidism caused by toxic nodular goiter and autonomously functioning thyroid adenomas in the Malmö study was >80 years. The only available data in a black population, from Johannesburg, South Africa, also suggest a 10-fold lower annual incidence of hyperthyroidism (0.09 per 1000 women and 0.007 per 1000 men) than in whites.

In the Whickham survey cohort, the mean annual incidence of hyperthyroidism in women was 0.8 per 1000 with no new cases detected in men.[22] Other cohort studies provide comparable incidence data, which suggests that many cases of hyperthyroidism remain undiagnosed in the community unless routine testing is undertaken.[2] In the large population study in Tayside, Scotland, 620 incident cases of hyperthyroidism were identified with an incidence rate of 0.77/1000 per year (95% CI): 0.70–0.84) in women and 0.14/1000 per year (95% CI: 0.12–0.18) in men.[23] The incidence increased with age, and women were affected two to eight times more than men across the age range. Recent further analysis suggested that the incidence of thyrotoxicosis was increasing in women but not in men between 1997 and 2001.[24]

Screening for thyroid disorders

Thyroid nodules may be detected because of their size or anterior position in the neck, or the skill of the physician performing the examination. However, most thyroid nodules are not clinically recognized. Ultrasonography as a screening tool is too sensitive and will result in unnecessary pursuit of findings, which are so common that they rarely have pathological significance. However, it may have a place in investigating patients presenting with thyroid nodules to determine whether they are single or multiple. As diagnostic techniques for thyroid cancer have become more sensitive, particularly with the advent of ultrasound and fine-needle aspiration, there has been an increased detection of subclinical papillary cancers.

Epidemiological data suggest that the children of women with hypothyroxinaemia may have psycho-neurological deficits.[29] In classic areas of iodine deficiency, a similar range of deficits in children has been described where maternal hypothyroxinaemia rather than high-serum TSH is the main biochemical abnormality. In these areas, maternal iodine intake is often substantially <200 μg per day currently recommended. Even in areas previously thought to be iodine sufficient, there is now evidence of substantial gestational iodine deficiency, which may lead to low maternal circulating T_4 concentrations. In addition to the childhood neuropsychological problems relating to low T_4 values, there is evidence that maternal TPOAb may result in intellectual impairment even when there is normal thyroid function.[29] The value of screening for congenital hypothyroidism in heel-prick blood specimens is unquestioned, and it is now done routinely in many countries.

Controversy exists as to whether healthy adults living in an area of iodine sufficiency benefit from screening for thyroid disease. The benefit from a screening programme must outweigh the physical and psychological harm caused by the test, diagnostic procedures and treatment.[30] The prevalence of unsuspected overt thyroid disease is low, but a substantial proportion of subjects tested will have evidence of thyroid dysfunction, with $\sim$10% with subclinical hypothyroidism and 1% with subclinical hyperthyroidism. 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.[31]

In subclinical hypothyroidism, there is still debate as to what constitutes a normal serum TSH, particularly in older subjects. Although some subjects will progress to overt hypothyroidism, recent data suggest a significant proportion revert to normal without treatment.

Recent meta-analyses have suggested increased cardiovascular risk in younger adults and in those with a serum TSH >10 mIU/l.[32] Other data suggest that mild thyroid failure may be the only reversible cause of left ventricular diastolic dysfunction.[13] Treatment in those who are symptomatic, pregnant or pre-conception, aged ≥ 65 years or evidence of heart failure appears justified.[33]

No consensus exists regarding the treatment of subclinical hyperthyroidism, although it has been strongly argued without any evidence-base that therapy with anti-thyroid drugs or radioiodine may be indicated in view of the long-term risk of atrial fibrillation and loss of bone density.[34] Any potential benefits of therapy in subclinical hyperthyroidism must be weighed against the substantial morbidity associated with the treatment of thyrotoxicosis. For the vast majority of patients adopting a 'wait and see' policy rather than intervention may avoid unnecessary treatment or the potential for harm.

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