DIAGNOSIS, TREATMENT AND LONG-TERM CONSEQUENCES OF HYPERTHYROIDISM: USE OF EXISTING DATA TO GENERATE NEW KNOWLEDGE

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ABSTRACT

Hyperthyroidism is a common endocrine disorder with multiple aetiologies, manifestations and potential therapies. This thesis explores the challenges relating to the diagnosis, treatment and long-term consequences of thyrotoxicosis in real-world outpatient and inpatient settings. We performed a number of epidemiological studies analysing data from large, detailed, routinely collected data sources.

We confirmed that classical manifestations of hyperthyroidism are significantly less prevalent in older patients and established that newly diagnosed thyroid dysfunction is rare in hospitalised subjects despite high volume thyroid function testing in this setting where we found a high proportion of abnormal thyroid tests in those with pre-existing thyroid dysfunction. We determined that thionamides are effective in a half of subjects treated with a prolonged course and that appropriate patient selection improves success rates. We established that treatment of hyperthyroidism with radioactive iodine results in more weight gain than antithyroid drugs and that hyperthyroidism in hospitalised patients is associated with longer hospital stays, higher frequency of admissions and increased mortality.

In conclusion, this thesis provides important new insights into the diagnosis and treatment of hyperthyroidism and highlights that correct evaluation and management of patients may minimise the long-term consequences associated with this common disorder.

For my family.

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PUBLICATIONS AND PRESENTATION OF THE FINDINGS

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B. Torlinska, J. Franklyn, J. Coleman, K. Boelaert. *Increased all-cause mortality, rehospitalisation rate and cardiovascular morbidity in hospitalised hyperthyroid patients — a nested case-control study.* BTA meeting Newcastle 2016: Thyroid Research 2017, 10 (Suppl 1): P1

B. Torlinska, J. Franklyn, J. Coleman, K. Boelaert. *Hyperthyroid but not hypothyroid patients are at higher risk of rehospitalisation and increased cardiovascular morbidity-a matched case-control study.* 15th International Thyroid Congress and 85th Annual Meeting of the American Thyroid Association, Orlando 2015: Thyroid. October 2015, 25(S1): A13-14.

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Boelaert K, **Torlinska B,** Franklyn JA. *Elderly patients presenting with hyperthyroidism have a paucity of symptoms and signs: a cross-sectional study of 3563 UK patients.* Society for Endocrinology BES Harrogate 2009

Torlinska B, Boelaert K, Holder RL, Franklyn JA. *Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study.* BTA meeting London 2009

Publication plans:

The findings from Chapter 4 have drafted as a manuscript, which is being finalised before submission to the Journal of Clinical Endocrinology and Metabolism. The findings of Chapter 5 on weight changes following treatment for hyperthyroidism are currently being drafted into a manuscript with the intention to submit this in the next 3-6 months. Findings from Chapter 6 on thyroid function testing in hospitalised inpatients and from Chapter 7 on all-cause mortality and health system utilisation in hyperthyroid inpatients are complete and we plan to write two separate papers describing the results following submission of papers relating to Chapters 4 and 5.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

131-I	Radioiodine with I-131 isotope
A&E	Accident and Emergency
AOR	Adjusted Odds Ratio
ATA	American Thyroid Association
ATC	anaplastic thyroid carcinoma
BTA	British Thyroid Association
CCI	Charlson Comorbidity Index
CI	confidence intervals
CMZ	carbimazole
ETA	European Thyroid Association
fT3	free triiodothyronine
fT4	free thyroxine
FU	follow up
GD	Graves' disease
GO	Graves' ophthalmopathy
ICD-10	International Classification of Diseases 10th revision
ITU	Intensive Therapy Unit
IQR	interquartile range
LOS	length of stay
L-T4	levothyroxine
NHS	National Health System
NTIS	non-thyroid illness syndrome
OR	odds ratio
PTU	propylthiouracil
RAIU	radioactive iodine uptake
RR	relative risk
SD	standard deviation
SHyper	subclinical hyperthyroidism
SHypo	subclinical hypothyroidism
TD	thyroid dysfunction
TFT	thyroid function testing
TMG	Toxic multinodular goitre
TPOAb	thyroid peroxidase antibodies
TRAb	TSH receptor antibodies
TSH	thyroid stimulating hormone
UHB	University Hospitals Birmingham
WHO	World Health Organization
y	Years

Chapter 1. GENERAL INTRODUCTION

1.1 Thyroid hormones

1.1.1 Synthesis and regulation of thyroid hormones

The synthesis of thyroid hormones (TH), namely thyroxine (T4; 3,5,3',5'-tetraiodo-L-thyronine) and tri-iodothyronine (T3; 3,5,3'-triiodo-L-thyronine), takes place in the follicular cells of the thyroid gland which is the largest endocrine organ (Porterfield and White, 2007). The thyroid gland also produces calcitonin in the parafollicular C-cells. This hormone plays critical roles in calcium homeostasis, but does not form part of the subject of this thesis.

Iodine is the key component of T3 and T4, thyroid hormones being the only iodine containing hormones in vertebrates. Dietary intake of sufficient amounts of iodine is essential for the normal production of the thyroid hormones (Greenspan et al., 2007). This process, illustrated in Figure 1-1, involves several stages (1) active trapping of iodide (I^-) by action of the sodium iodide symporter at the basolateral membrane of follicular thyroid cells; (2) transport of iodide into the colloid lumen; (3) oxidation of iodide into iodine; (4) incorporation of iodine into tyrosine residues within thyroglobulin molecules; (5) conjugation of diiodotyroisine (DIT) molecules

to form thyroxine (tetraiodothyronine, T4) or of monoiodotyrosine (MIT) with DIT to form triiodothyronine (T3) within thyroglobulin; (6) uptake of thyroglobulin from the colloid into follicular cells by a process of endocytosis; (7) fusion of thyroglobulin with lysosomes resulting in proteolysis and release of T4, T3, DIT and MIT; (8) Active transport via the monocarboxylate-8 transporter (MCT-8) resulting in release of T4 and T3 into the circulation (Laycock and Meeran, 2013).

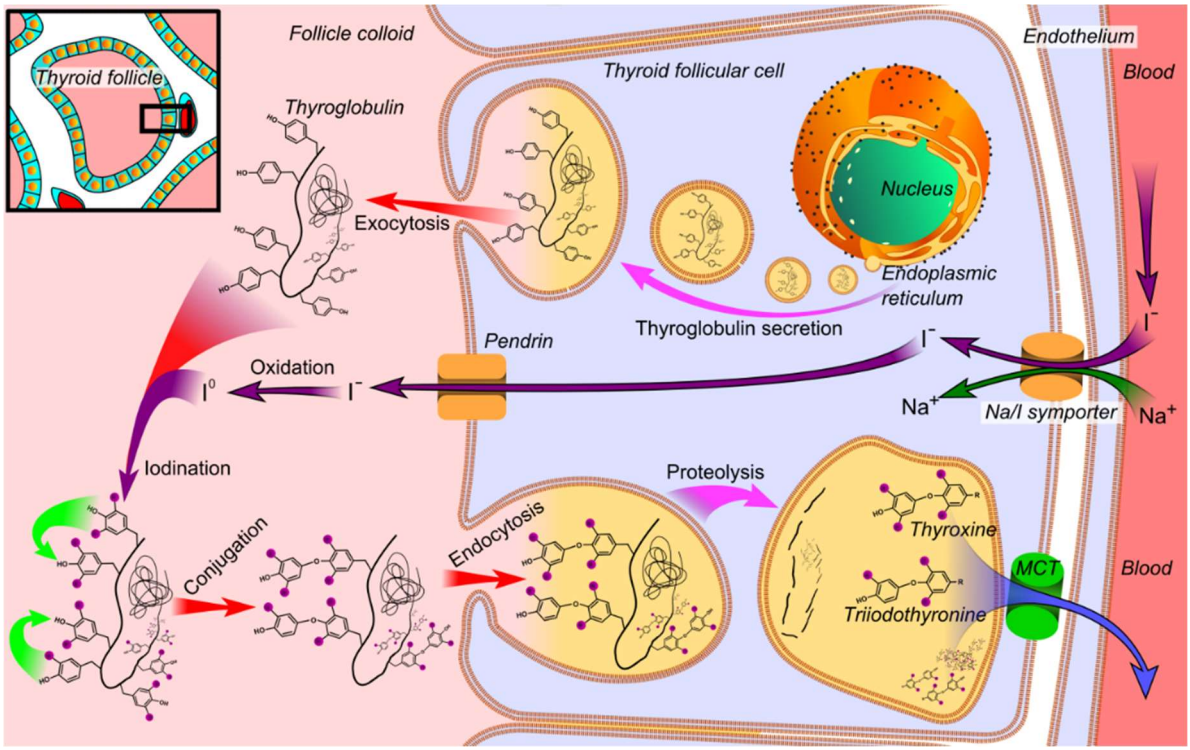

Figure 1-1: Thyroid hormone synthesis. Picture reproduced from: Häggström, Mikael. "Medical gallery of Mikael Häggström 2014". Wikiversity Journal of Medicine 1 (2)

More than 99% of the circulating T3 and T4 is bound to proteins, mainly thyroxine-binding globulin (TBG) and to a lesser extent to transthyretin and albumin. Thyroid hormones can rapidly be released from these proteins, facilitating TH entry into cells. Only about 0.03% of T4 and 0.3% of T3 is free and most modern laboratory assays measure free thyroid hormone concentrations. The half-life of T4 is about

7 days, whereas that of T3 is one day (Nicoloff et al., 1972). Thyroid hormones enter the cells mainly by active transport and investigations during the last decades have identified specific thyroid hormone transporters families including mono-carboxylate (MCT) and organic anion transporters (OAT) (Jansen et al., 2005, Visser et al., 2011).

Typically, a normal thyroid gland secretes about 100 nmol of T4 and only 5 nmol of T3 daily. T3 is the main bioactive thyroid hormone whereas T4 acts mostly as a prohormone that becomes activated upon its conversion to T3. About 80% of T3 is produced from T4 outside the thyroid gland in peripheral tissues by a process of deiodination. There are three different deiodinase enzymes: D1 and D2 are the main activating enzymes converting T4 to T3, whereas D3 is largely an inactivating enzyme degrading T4 into inactive rT3 and T3 into T2 (Gereben et al., 2008). The expression of these enzymes is tissue specific and their metabolic actions may variously create local tissue-specific states of hypothyroidism or thyrotoxicosis even in the setting of systemic euthyroidism.

Thyroid hormones exert their effects through binding to nuclear receptors (TRα and TRβ) thereby mediating changes in gene expression. Thyroid hormone receptors bind to thyroid hormone response elements (TRE, repeats of the sequence AGGTCA) within the DNA as monomers, as homodimers or as heterodimers with the retinoid X receptor (RXR). The heterodimer expresses the highest affinity binding and thus represents the major functional form of thyroid receptors. TRs bind to TREs in the regulatory regions of DNA regardless of whether they are occupied by T3 or unoccupied, however, the subsequent biological effects vary. In general, binding of TR alone to DNA leads to repression of transcription, whereas binding

of the thyroid hormone-receptor complex activates transcription. The extent of thyroid hormone receptor occupancy varies in different tissues, providing a mechanism for alterations in circulating hormone concentrations to modify receptor activity (Mullur et al., 2014, Oetting and Yen, 2007, Yen and Sinha, 2000).

The concentration of circulating thyroid hormones is controlled by the hypothalamo-pituitary-thyroid axis (Figure 1-2). Release of thyroid hormones from the thyroid gland is predominantly regulated by the concentration of the thyroid-stimulating hormone (TSH; thyrotrophin) synthesised and released from the pituitary gland. The secretion of TSH, in turn, is controlled by the stimulatory action of thyrotrophin-releasing hormone (TRH) secreted by hypothalamus. Negative feedback mechanisms are in place whereby high concentration of T3 and T4 inhibit TSH and TRH release in order to maintain homeostasis (Greenspan et al., 2007). Additional mechanisms involved in thyroid hormone metabolism include conjugation with glucuronide and sulfate in the liver followed by excretion in bile, and partial hydrolysis in the intestine (Hays, 1988).

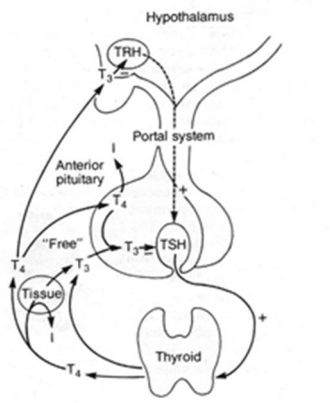

Figure 1-2: Hypothalamic-pituitary-thyroid axis representing regulation of thyroid hormone concentrations through a negative feedback mechanism. Reproduced from Greenspan's Basic and Clinical Endocrinology 8th ed. p. 221

1.1.2 Physiological roles of thyroid hormones in humans

Thyroid hormones affect almost all tissues in the body. They play critical roles in growth and development, thermogenesis, reproduction and metabolism.

1.1.2.1 *Growth and development*

Thyroid hormones exert widespread and complex actions in the skeleton during development and childhood as well as in adult life. Whilst the specific molecular actions of T3 in bone and cartilage have not been fully elucidated, the skeleton is considered to be a T3 target tissue and deficiency of thyroid hormones during development may result in severe growth retardation. Thyroid hormones', and in particular T3's, actions have important roles in bone turnover and maintenance through direct effects on bone-forming osteoblasts and bone-resorbing osteoclasts and abnormalities in circulating thyroid hormones may have significant adverse effects on maintenance of bone health (Williams, 2013).

Thyroid hormones are essential for brain development and maturation, and the developing fetus is dependent on maternal thyroid hormone supply until mid-gestation. The adverse consequences of severe maternal thyroid hormone deficiency on fetal neurocognitive development resulting in cretinism have been well established. More recent evidence indicates that even moderate forms of maternal thyroid dysfunction during gestation may have long-lasting effects on child cognitive and neurological development (Moog et al., 2015).

1.1.2.2 *Thermogenesis and metabolism*

Thyroid hormones control the basal metabolic rate (BMR). They are calorigenic and thus increase oxygen consumption and heat production. BMR decreases in hypothyroidism and increases in hyperthyroidism and this is associated with changes in the numbers and size of mitochondria where a large amount of energy homeostasis occurs at a cellular level. TH stimulate many anabolic and catabolic pathways, thereby affecting protein, lipid and carbohydrate synthesis and degradation (Silva, 2005). Thyroid hormones can increase cholesterol synthesis but they also increase availability of low-density lipoprotein (LDL) receptors, thus allowing higher cholesterol clearance. Blood glucose concentrations are typically normal in patients with thyroid dysfunction, however, TH increase the rate of glucose absorption in the gastro-intestinal tract, and high circulating TH concentrations may both increase insulin resistance and insulin degradation (Silva, 2005). These processes result in altered metabolism in many tissues and organs and may affect the turnover of other hormones, as well as the pharmacokinetics of various medications, resulting in altered half-life of drugs which may therefore require dose adjustment (Porterfield and White, 2007).

Thyroid hormones play a critical role in obligatory and adaptive thermogenesis. In response to environmental factors (such as feeding or temperature) or hormonal stimulation (such as leptin, Figure 1-3), hypothalamic pathways modulate TH secretion through the hypothalamic-pituitary-thyroid axis (McAninch and Bianco, 2014). TH in conjunction with sympathetic output act in multiple organ systems to affect energy metabolism and thus regulate whole-body energy homeostasis. In particular, they

promote adaptive thermogenesis in brown adipose tissue (BAT), regulate cardiovascular functions including blood pressure and heart rate, modulate glucose homeostasis through actions in the pancreas, regulate systemic TH clearance and endogenous glucose production in the liver, and affect other tissues including white adipose tissue and skeletal muscle (McAninch and Bianco, 2014). In the complete absence of thyroid hormones, the resting metabolic rate may be reduced by as much as 30% (Silva, 2003). The use of BAT is regulated by modulation of circulating T3 in response to an environment with low temperatures. During short-term overfeeding, the production of T3 increases and diet-induced thermogenesis takes place. Prolonged fasting reduces serum concentrations of T3 thereby lowering the BMR to save energy (Hadley, 2000).

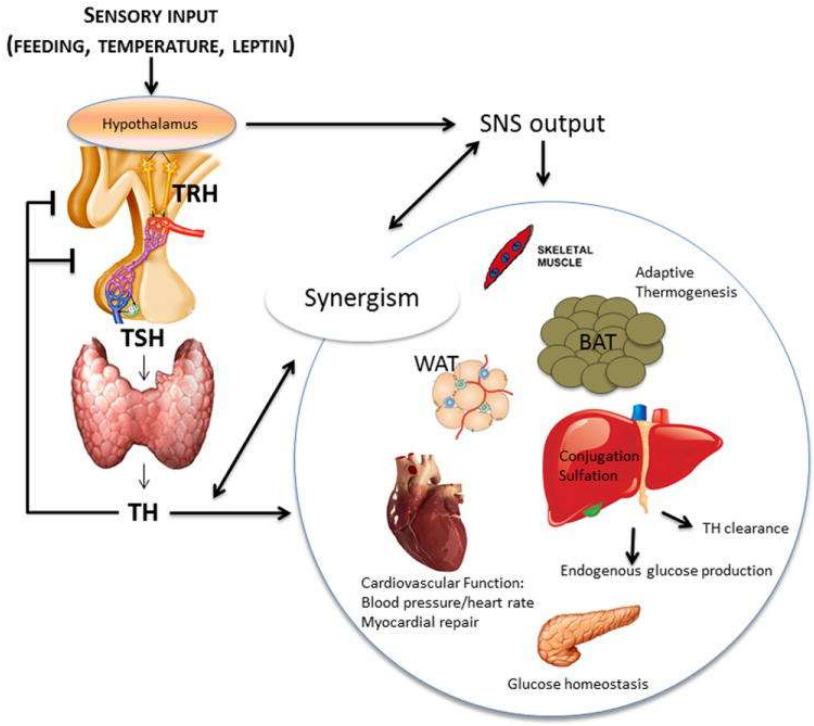

Figure 1-3: The role of thyroid hormone in energy homeostasis. TRH: thyrotropin-releasing hormone; TH: thyroid hormone; SNS: sympathetic nervous system; BAT: brown adipose tissue; WAT: white adipose tissue. Figure adapted from McAninch and Bianco (2014).

Despite direct effects of thyroid hormones on basal metabolic rate, their impact on body weight in the absence of thyroid dysfunction remains unclear. Thyroid function tests in people who are morbidly obese may differ from those in a comparable group of lean people, with higher serum TSH concentrations evident in obese subjects. Interestingly, circulating thyroid hormone concentrations, in particular fT3 (De Pergola et al., 2007), and to a lesser extent fT4 (Reinehr, 2010), may be higher in the obese independent of TSH concentrations, and this is particularly pronounced in children (Reinehr and Andler, 2002). Weight reduction often resolves the mild observed aberrations in thyroid function (Laurberg et al., 2012).

1.1.2.3 *Reproduction*

Thyroid hormones affect the menstrual cycle directly by acting on the ovaries and indirectly through influencing secretion and release of other factors including sex hormone binding globulin, prolactin and gonadotrophin releasing hormone (Doufas and Mastorakos, 2000). It has been found that during the menstrual cycle median serum TSH and thyroid hormones concentration fluctuate in relation to circulating oestrogen levels (Beck et al., 1972), and thyroid volume increases (Rasmussen et al., 1989).

Thyroid dysfunction affects the menstrual cycle (in length and blood flow) and infertility. The prevalence of menstrual abnormalities has been reported at 68% in women with hypothyroidism and 65% with hyperthyroidism compared to 12% in healthy controls. Other reproductive complications such as infertility, pregnancy wastage, and failure of lactation were found in 37.5% of hypothyroid and 36.5% of hyperthyroid subjects and in 16.7% of healthy controls (Joshi et al., 1993). Another

study reported the presence of amenorrhoea in 12% of the hypothyroid group and none among the healthy control subjects, finding an association between the severity of menstrual abnormalities and higher serum TSH concentrations (Krassas et al., 1999). In hyperthyroidism, a 2.5 times higher prevalence of irregular menstrual cycles in female patients with hyperthyroid compared to the healthy population was found (22% vs. 8%) (Krassas et al., 1994).

Treatment of thyroid dysfunction can reverse menstrual abnormalities and thus improve fertility (Poppe et al., 2007). In men, thyroid hormones affect spermatogenesis and thyroid dysfunction may affect testicular size, sperm motility and ejaculate volume (Rajender et al., 2011).

1.1.3 Laboratory assessment of thyroid function

Thyroid function may be assessed by measurement of one or more of the following:

- Serum TSH concentration
- Serum free T4 or T3 concentration
- Serum total T4 or T3 concentration

Serum TSH concentration- Current guidelines recommend the use of highly sensitive third generation TSH assays in UK laboratories (Association of Clinical Biochemistry, 2006). The detection limit of these assays is generally around 0.01 mIU/L (Ross, 2001). Measurement of serum TSH is considered the single most reliable test and hence the most effective to detect the presence of thyroid dysfunction (Ladenson et al., 2000). This represents a good screening instrument due to its high

negative predictive value (Kaplan, 1999). However, serum TSH concentrations alone do not determine the degree of thyroid hormone excess or deficiency (Beckett and Toft, 2003) and for diagnostic purposes serum concentrations of circulating thyroid hormones have to be assessed (Association of Clinical Biochemistry, 2006).

In general, there is an inverse log-linear relationship between serum TSH and thyroid hormone concentrations (Hoermann et al., 2010). This determines that large changes in thyroid hormone concentrations are associated with minor alterations of serum TSH, especially at the lower end of the scale when TSH is undetectable.

There is ongoing controversy regarding normal serum TSH reference ranges. Over the last decades, the upper reference limit for TSH has steadily declined from 10 to approximately 4.0-4.5 mIU/L, which reflects technological advances in laboratory techniques and better understanding of action and metabolism of TSH. Presently most laboratories reference ranges span between 0.3-0.4 and 4.5-5.0 mIU/L. However, it is likely that the upper limit will be reduced further as 95% of rigorously screen euthyroid population have TSH values between 0.4-2.5 mIU/L (Baloch et al., 2003). Additional debate exists regarding the need for age-specific reference ranges for TSH. Many studies report a physiological shift of normal serum TSH concentrations to higher levels with age and application of uniform reference ranges may result in over-diagnosis of thyroid dysfunction and unnecessary treatment in elderly subjects (Surks and Hollowell, 2007, Vadiveloo et al., 2013, Waring et al., 2012). The correct interpretation of thyroid function test results is further complicated by the presence of significant age- and gender-independent inter-individual variations in the set-point of the pituitary-thyroid axis (Meier et al., 1993).

Serum free T4 (fT4) or free T3 (fT3) – free or unbound thyroid hormones are readily available for cellular uptake and are unaffected by changes in the concentration and affinity of thyroid hormone binding proteins. In view of this, measurement of free thyroid hormones is considered to be a much more reliable way of diagnosing thyroid dysfunction than determination of total concentrations. Several commercially available assays are currently used to determine the concentration of free thyroid hormones in serum samples and results from different assays are not always concordant. The use of an equilibrum dialysis method, using undiluted serum, is considered as a reference technique but this is not available on a routine basis (Thienpont et al., 2010a, Thienpont et al., 2010b).

Serum total T4 (TT4) or T3 (TT3) – measures bound and unbound fractions ofserum T4 or T3. Total TH concentrations are abnormal in most patients with thyroid dysfunction but also in those euthyroid individuals in whom the concentrations of, or affinity to, thyroid binding proteins is altered (Thienpont et al., 2010a, Thienpont et al., 2010b). Such situations commonly occur in pregnancy (Glinoer, 1997), in non-thyroidal illness (Economidou et al., 2011) or in patients taking certain drugs such as glucocorticoids, dopamine agonists, somatostatin analogues and rexinoids (Haugen, 2009).

Thyroid function tests (TFT) are used in a variety of clinical settings including diagnosis of, and screening for, thyroid dysfunction, assessing the adequacy of levothyroxine (L-T4) replacement and monitoring the treatment of hyperthyroidism. Basic patterns of TFT and their interpretation are presented in Table 1-1. It has to be pointed out that this table is highly simplified. In order

to diagnose thyroid dysfunction accurately, abnormal results often need to be verified following changes in patients' medical state or concurrent medication. Guidelines for the Use of Thyroid Function Tests (2006) conclude that "measurement of TSH with fT4 should allow the detection of almost all causes of thyroid dysfunction". The guidelines do not recommend a screening policy in a healthy adult population, but they support case-finding strategies in menopausal women or those consulting their GP with non-specific symptoms. Additional groups of patients in whom surveillance for thyroid dysfunction is warranted include those with a past history of post-partum thyroiditis, subjects with diabetes, Down or Turner Syndrome, patients receiving amiodarone or lithium, and those who have undergone ablative treatment in the head and neck area.

Table 1-1: Patterns of thyroid function tests; results may be influenced by concurrent medication and the patients' physiological state. Table adapted from UpToDate service www.uptodate.com/contents/laboratory-assessment-of-thyroid-function.

Serum TSH	Serum free T4	Serum free T3	Assessment
Normal hypothalamic-pituitary function			
Normal	Normal	Normal	Euthyroid
Normal	Normal or high	Normal or high	Euthyroid: hyperthyroxininemia
Normal	Normal or high	Normal or low	Euthyroid: hypothyroxinemia
Normal	Low	Normal or high	Euthyroid: Non-thyroidal illness
Normal	Low normal or low	Normal or high	Euthyroid: thyroid extract therapy
High	Low	Normal or low	Primary hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism
Low	High or normal	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Abnormal hypothalamic-pituitary function			
Normal or high	High	High	TSH- mediated hyperthyroidism
Normal or low*	Low or low-normal	Low or normal	Central hypothyroidism

* In central hypothyroidism, serum TSH may be low, normal or slightly high.

Despite laboratory standardised cut-off points defining euthyroidism, altered health outcomes have been identified in subjects whose thyroid function remains within the normal range. The Birmingham Elderly Thyroid study indicated that in euthyroid individuals aged >65 years with normal serum TSH concentrations, higher fT4 concentrations within the normal range were associated with increased risk of atrial fibrillation (Gammage et al., 2007). Furthermore, large population studies of euthyroid individuals have shown that serum fT4 concentrations at the upper end of the normal reference range are associated with increased fracture susceptibility (Murphy et al., 2010, Lin et al., 2011). Additionally, in a population-based study, low normal TSH and high normal circulating thyroid hormones were associated with development and worsening of depressive symptoms (Medici et al., 2014). A systematic review (Taylor et al., 2013) concluded that higher TSH and lower TH within the reference range were associated with more cardiovascular risks and events and worse metabolic parameters and pregnancy outcomes, whereas lower TSH with higher TH levels were associated with reduced bone mineral density and increased fracture risk. In contrast, recent individual participant data analysis studies have not shown an association between TSH concentrations within the reference range with increased risks of coronary artery events or mortality (Asvold et al., 2015). Moreover, data from the Thyroid Studies Collaboration have indicated that higher TSH concentrations within the reference range may decrease the risk of stroke (Chaker et al., 2016).

1.2 Hyperthyroidism

Hyperthyroidism is a pathological condition in which the thyroid gland produces and secretes increased concentrations of thyroid hormones. The term is often used interchangeably with thyrotoxicosis, which refers to the state of excess circulating thyroid hormone concentrations and which encompasses hyperthyroidism as well as a number of other conditions. Examples of thyrotoxic, but not hyperthyroid, states include leakage of thyroid hormones due to thyroid gland inflammation such as found in thyroiditis or excessive exogenous thyroid hormone intake. Table 1-2 presents common and rare causes of thyrotoxicosis with and without associated hyperthyroidism.

Table 1-2: Causes of thyrotoxicosis with and without over-secretion of thyroid hormones (Franklyn and Boelaert, 2012)

	Type of thyrotoxicosis	Pathogenic mechanism
	Common causes	
hyperthyroidism	**Production of abnormal thyroid stimulator**	
	Graves' disease	TSH-R stimulating antibody
	Thyroidal autonomy	
	Toxic multinodular goitre	Activating mutations in TSH-R or G- proteins
	Solitary toxic adenoma	Focus of functional autonomy Benign tumour
no hyperthyroidism	**Inflammatory disease (thyroiditis)**	
	Silent (painless) thyroiditis (including postpartum)	Release of stored hormones Autoimmune
	Subacute thyroiditis	Probable viral infection
	Extrathyroidal source of hormone	Excess ingestion of thyroid hormone (iatrogenic or factitious)
	Exogenous thyroid hormone	
	Uncommon causes	
hyperthyroidism	**Production of thyroid stimulating hormones**	
	TSH secreting pituitary adenoma	Pituitary adenoma
	Pituitary resistance to thyroid hormone	Mutation in thyroid hormone receptor with greater expression in the pituitary compared with peripheral tissues Thyroid stimulating immunoglobulins
	Neonatal Graves' disease	Human chorionic gonadotrophin secretion
	Choriocarcinoma	Human chorionic gonadotrophin secretion
	Hyperemesis Gravidarum	
	Thyroidal autonomy	
	Congenital hyperthyroidism	Activating mutations in the TSH receptor
	Struma ovarii	Toxic adenoma in dermoid tumour of ovary
	Metastatic follicular thyroid carcinoma	Foci of functional autonomy
	Drug-induced hyperthyroidism	
	Iodine, iodine containing drugs (Amiodarone) and radiographic contrast agents	Jod-Basedow, excess iodine resulting in unregulated thyroid hormone production
no hyperthyroidism	**Inflammatory disease**	
	Drug-induced thyroiditis (amiodarone, interferon-α, lithium)	Destruction of thyroid follicles Direct toxic drug effects
	Acute infectious thyroiditis	Thyroidal infection (bacterial, fungal, etc)
	Radiation thyroiditis	Cell destruction caused by radioactive iodine
	Infarction of thyroid adenoma	Release of stored hormones
	Extrathyroidal source of hormone	
	"Hamburger" thyrotoxicosis	Ingestion of contaminated food

1.2.1 Aetiology of hyperthyroidism

1.2.1.1 *Graves' disease*

The most common cause of hyperthyroidism in iodine sufficient areas, found in 60 to 80% of patients in the UK, is Graves' disease (GD) (Cooper, 2003, Franklyn and Boelaert, 2012, Weetman, 2000). GD is an autoimmune disorder, in which autoantibodies bind to thyrotropin receptors (TSH-R) thereby causing excess production and secretion of thyroid hormones independent of the normal feedback-regulated thyrotropin stimulation. This induces thyroid growth, resulting in a diffuse goitre. TSH receptor autoantibodies (TRAbs) are detectable in almost all patients with Graves' disease when measured using sensitive assays. Studies have shown that in the minority of patients with GD where TRAb was not identified hyperthyroidism was mild (Zophel et al., 2010). In addition, antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) are often present in patients with Graves' disease. Contrary to TRAb, these antibodies do not play a direct role in the pathogenesis of GD but are markers of the presence of thyroid autoimmunity (Wiersinga, 2014).

The pathogenesis of Graves' disease is not yet fully understood (Effraimidis and Wiersinga, 2014). A family history of thyroid dysfunction is present in about 50% of patients with Graves' disease, consistent with a strong genetic influence (Manji et al., 2006). Twin concordance studies suggest that up to 80% of susceptibility can be attributed to genetic factors, whereas the other 20% is associated with environmental influences (Brand and Gough, 2010). Importantly, Graves' disease has been linked with significantly increased risks of associated autoimmune disorders in index cases

as well as their parents (Boelaert et al., 2010a). Recognised environmental factors associated with the development of GD include female gender, infections, stress, cigarette smoking, pregnancy, and excessive intake of iodine or iodine containing drugs such as amiodarone (Hollander and Davies, 2009).

The systemic immune process of the disease driven by TSH-receptor antibodies may lead to extrathyroidal manifestations such as ophthalmopathy (Graves' ophthalmopathy – GO), and less commonly, dermopathy (Graves' dermopathy) and acropachy (Bartalena and Fatourechi, 2014). Since thyroid receptors are present in nearly all tissues in the body, the effects of excess circulating thyroid hormones may have many clinical manifestations and profound effects on cardiac, hepatic and neuromuscular function may be observed (Franklyn and Boelaert, 2012). Since none of the current routinely available treatments for Graves' disease are aimed at the underlying disease process, TRAb may persist after cure of hyperthyroidism (Laurberg et al., 2008). This has been associated with increased likelihood of disease relapse. In pregnant women with a history of GD and who have significant concentrations of TRAb, transplacental transfer may cause foetal and/or neonatal thyrotoxicosis. Current guidelines recommend that TRAb are measured at the end of a prolonged course of antithyroid drugs and around 20 weeks of pregnancy (Ross et al., 2016).

GD is one of the most common autoimmune disorders, with an annual incidence of approximately 20-30 per 100,000 (Burch and Cooper, 2015). As in most autoimmune diseases, it is more common in women than in men and can be found in patients of all ages but its incidence peaks in the fifth and sixth decade of age

(Menconi et al., 2014). Lasting spontaneous remission of mild GD has been reported in up to 30% of patients (Codaccioni et al., 1988).

1.2.1.2 *Toxic nodular hyperthyroidism*

Toxic nodular hyperthyroidism is accountable for up to 50% of cases of thyrotoxicosis in areas with low iodine intake (Laurberg et al., 2001). Whether solitary or multiple, non-neoplastic nodules are the result of glandular hyperplasia. They grow slowly and may remain dormant for years, due to slow proliferation of thyroid cells. These nodules may gain autonomy from serum TSH levels resulting in independent overproduction of thyroid hormones. As a consequence, negative feedback at the level of the hypothalamus and pituitary results in reduced or even undetectable TSH concentrations and suppression of function of the remaining normal thyroid gland (Siegel and Lee, 1998). Once the autonomous secretion of thyroid hormones exceeds normal levels, a patient becomes hyperthyroid.

Toxic adenoma

A toxic adenoma is a solitary autonomous thyroid nodule and varies in prevalence throughout the world; it is higher in Europe (Sweden) than in the US where it accounts for 9% and 5% of all thyrotoxic cases respectively (Reinwein et al., 1988). These differences are considered to be associated with varying degrees of iodine sufficiency, and influenced by the salt iodisation programme in the USA (Siegel and Lee, 1998).

In a study of the natural history of autonomously functioning solitary nodules (Hamburger, 1980), toxic adenomas were found six times more commonly in women

than men and were more prevalent in those over 50 years of age than in younger subjects. Almost all nodules causing overt hyperthyroidism were greater than 3 cm in diameter. Among patients with non-toxic autonomous nodules greater than 3 cm, thyrotoxicosis developed in 20% within 6 years.

Toxic multinodular goitre (Plummer's disease)

Toxic multinodular goitre (TMG) represents the final stage of formation of goitre over time (Siegel and Lee, 1998). Similarly to solitary toxic adenomas, toxic nodules in multinodular goitres develop gradually over years from non-toxic nodules gaining autonomy and progressing to toxic forms and finally resulting in toxic multinodular goitre. Factors affecting this advancement include genetic mutations in the TSH receptor or Gsα genes, iodine deficiency, and possibly other environmental factors (Schroeder and Landenson, 2009).

TMG is the second most common aetiology of hyperthyroidism. Its prevalence is higher in countries with iodine deficiency (Laurberg et al., 1991, Laurberg et al., 2001). The prevalence in the United Kingdom has been reported between 5% and 8% in two studies (Siegel and Lee, 1998), whereas in New Zealand this was 27% (Brownlie and Wells, 1990) and in an iodine deficient region of Northern Italy prevalence of up to 69% (Aghini-Lombardi et al., 1999) have been documented. The introduction of national iodine supplementation programmes has been associated with changes in the incidence of TMG. In Switzerland and in Spain, the incidence of thyrotoxicosis increased during the first year of iodine supplementation, and declined in subsequent years. The first year increase was observed irrespective of underlying aetiology, while the decline was caused mainly by the decrease in TMG incidence (Siegel and Lee,

1998, Zimmermann and Boelaert, 2015) . The incidence of TMG increases with age and is more prevalent among women than men (Abraham-Nordling et al., 2008, Carle et al., 2011).

The incidence of thyroid cancer in toxic adenoma and toxic multinodular goitres is low. Generally, autonomously functioning thyroid tissue rarely harbours malignancy, but cancer may co-exists in the thyroid gland (Sahin et al., 2005).

1.2.1.3 *Differential diagnosis of hyperthyroidism*

Although biochemically thyrotoxicosis with and without hyperthyroidism is indistinguishable, it is important to differentiate between these two forms, and to further identify the correct aetiology, in order to formulate an appropriate management plan. If the diagnosis is not apparent based on the clinical presentation and biochemical evaluation, the American Thyroid Association (ATA) recommends further diagnostic tests including: (1) measurement of TRAb, (2) determination of the radioactive iodine uptake (RAIU), or (3) measurement of thyroidal blood flow on ultrasonography. Moreover, an iodine-123 or technetium-99m pertechnetate scan should be obtained when the clinical presentation suggests a toxic adenoma or toxic multinodular goitre (Ross et al., 2016).

1.2.1.3.1 Isotope Uptake Tests

A radioactive iodine uptake (RAIU) measures the percentage of administered radioiodine that is concentrated into thyroid tissue after a fixed interval, usually 24 hours. Technetium (TcO_4) uptake measurements utilise pertechnetate that is trapped by the thyroid, but not organified and determine the percentage

of administered technetium that remains in the thyroid after a fixed interval, usually 20 minutes (Ross, 1991, Loevner et al., 2008).

Isotope uptake is usually increased in patients with GD and normal or high in toxic nodular goitre. The RAIU will be near zero in patients with painless, postpartum, or subacute thyroiditis, factitious ingestion of thyroid hormone or recent excess iodine intake. The RAIU may be low after exposure to iodinated contrast media or medication with high iodine content such as amiodarone or in subjects consuming a diet very rich in iodine such as seaweed soup or kelp (Ross et al., 2016). The diagnostic utility of uptake measurements can be further enhanced with coincident uptake scans, using a gamma camera to assess potential variability in the concentration of the radioisotope within thyroid tissue. Uptake scans in GD reveal increased, diffuse uptake in the thyroid while in toxic adenoma and in toxic multinodular goitre many "hot" focal points with suppressed uptake in the surrounding thyroid tissue are visible. Additionally, GD and nodular goitre may co-exist resulting in positive TRAb levels and a heterogeneous uptake images as well as the presence of a nodular thyroid on ultrasound (Ross et al., 2016).

1.2.1.3.2 Thyroid directed antibodies

Autoimmunity underlies the major causes of thyroid dysfunction and thyroid autoimmunity is implicated in various conditions including Graves' disease, Hashimoto's thyroiditis and post-partum thyroiditis. Around 10-20% of women and fewer men may have circulating antibodies to thyroglobulin or thyroid peroxidase and TSH receptors (Pedersen et al., 2003). Patients may remain clinically

asymptomatic and serum thyroid hormones concentrations may stay within the normal range for long periods of time.

Anti-TSH receptor antibodies

As discussed before, antibodies to the TSH receptor (TRAb) are present in almost all patients with Graves' disease (section 1.2.1.1). At present third–generation TSH receptor electrochemiluminescence immunoassays with a sensitivity and specificity of 97% and 99%, respectively (Hermsen et al., 2009) are used routinely. Despite these assays having been widely available since the start of the century, until recently, their use was recommended by the national and international guidelines merely as an alternative when thyroid scans and uptake were unavailable or contraindicated (Bahn et al., 2011, Association of Clinical Biochemistry, 2006). Hence, TRAb concentrations have not been routinely performed in the majority of UK thyroid clinics and for many retrospective studies this parameter is not available. In the latest iteration of the ATA guidelines, measurement of TRAb is described as cost-effective and is suggested for initial diagnostic testing in order to confirm the underlying diagnosis, as well as in decision making processes regarding antithyroid drug discontinuation following a prolonged course (Ross et al., 2016).

Anti-Thyroid Peroxidase antibodies

Tests for thyroid peroxidase antibodies (TPOAbs) are less sensitive and specific fo diagnosing GD as they are present in up to 10% of the general healthy population (Fox et al., 2015). The prevalence of TPOAbs is influenced by ethnic and environmental factors such as iodine intake, with higher rates in iodine sufficient areas. TPOAbs are

more commonly found in women than in men and their prevalence increases with age peaking in those 60-69 years old (Pedersen et al., 2003). TPOAbs are detected in approximately 70-80% of patients with Graves' disease and in virtually all patients with Hashimoto's or post-partum thyroiditis (Wiersinga, 2014). Additionally, the presence of serum TPOAbs is considered a risk factor for developing thyroid dysfunction in patients receiving amiodarone, interferon-α, interleukin-2 or lithium therapies, which all may act as triggers for initiating autoimmune thyroid dysfunction in susceptible individuals. Although changes in autoantibody concentrations often occur with treatment or reflect a change in disease activity, serial TPOAb measurements are not recommended for monitoring treatment of autoimmune thyroid diseases (Spencer, 2000).

Anti Thyroglobulin Autoantibodies

Serum thyroglobulin autoantibodies (TgAb) were the first thyroid antibodies to be detected in patients with autoimmune thyroid disorders (Wiersinga, 2014) and they are found usually concurrently with TPOAbs. In those cases of isolated raised TgAbs, no association with abnormal thyroid function tests (Hollowell et al., 2002). Hence, routine diagnostic measurement of serum TgAbs in subjects with thyroid dysfunction is deemed unnecessary (Spencer, 2000).

1.2.2 Epidemiology of hyperthyroidism

Endocrine disorders are among the most common conditions in nutrition-rich populations with advanced screening programmes and they are estimated to occur in at least one in 20 adults in the USA (Golden et al., 2009). Thyroid disorders

are the most common, being present in 30-40% of all subjects seen in endocrinology clinics (Garmendia Madariaga et al., 2014). The prevalence of thyroid disorders varies greatly from area to area depending on availability of iodine in the diet. England was found to be a country of mild iodine deficiency (Vanderpump et al., 2011) but, in contrast to many European countries, no universal programme of iodisation has been implemented.

Large epidemiological studies of thyroid dysfunction in the UK have come from two regions: Whickham in North England, which was originally studied in 1977 and followed up in 1995 (Tunbridge et al., 1977, Vanderpump et al., 1995), and Tayside, Scotland (Flynn et al., 2004, Leese et al., 2008). Overt hyperthyroidism was diagnosed based on the abnormal TFT with undetectable serum TSH and confirmed by clinical evaluation in the Whickham Survey, while in Tayside this was identified based on treatment utilising data linkage techniques. In Whickham, the prevalence of newly diagnosed hyperthyroidism was 0.5% and previously diagnosed and treated cases were found in 20 per 1000 women, rising to 27 per 1000 when potential but unproven cases were included. In men, no new cases were identified and pre-existing hyperthyroidism was prevalent in 1.6 to 2.3 per 1000 men. In the Tayside region, the prevalence of hyperthyroidism in both genders was found to be increasing year-on-year, reaching 1.26% in women and 0.24% in men in 2001.

In a large study from Norway, previously diagnosed hyperthyroidism was reported in 2.5% of women and 0.6% of men (Bjoro et al., 2000). The prevalence increased by age, peaking between 60-79 years, when for men the prevalence was about 1%, compared with women who had a prevalence between 3.1% and 3.6%. In an iodine

deficient community in Northern Italy, where the median iodine excretion was 55 µg/L, the prevalence of hyperthyroidism was 2.9%, when considering the total population and an even distribution was found in women (2.96%) and men (2.86%). Two-thirds of subjects had toxic nodular goitre, which was also more prevalent with age (Aghini-Lombardi et al., 1999).

Newly identified hyperthyroidism was present in 1.2% of women in a study from Denmark (Knudsen et al., 1999) and was found in only 0.4% of the population in Sardinia where both men and women were considered (Delitala et al., 2014). In Norway, the biochemistry of overt hyperthyroidism with undetectable TSH in those with no previous thyroid dysfunction was 0.2%, which rose to 0.3% if low but detectable TSH was included (Bjoro et al., 2000). In a Colorado study, only 0.1% of those not taking thyroid medication had thyroid function tests suggestive of hyperthyroidism (Canaris et al., 2000).

The mean annual incidence of hyperthyroidism in both UK studies was similar in women, being 0.8 per 1000 survivors. However, the Whickham population was aged over 18 years while the Tayside study included all ages. The incidence rate in men was negligible in Whickham and 0.14 per 1000 per year in Tayside. The incidence increased with age, and women were affected two to eight times more than men across the range of ages (Flynn et al., 2004, Leese et al., 2008, Vanderpump et al., 1995).

1.2.3 Manifestations and complications of hyperthyroidism

1.2.3.1 *Clinical features of hyperthyroidism*

The clinical presentation of patients with overt hyperthyroidism may vary widely, ranging from asymptomatic forms to thyroid storm requiring emergency treatment (Ross et al., 2016). Patients with Graves' disease have more pronounced symptoms and signs as they tend to have more severe thyrotoxicosis. In older patients, the presentation of hyperthyroidism may be more occult with fewer classical symptoms and signs (studied in more detail in Chapter 3; (Boelaert et al., 2010b, Nordyke et al., 1988)). The typical clinical features of hyperthyroidism are listed in Table 1-3.

Table 1-3: Typical symptoms and signs of thyrotoxicosis.
Table adapted from Franklyn and Boelaert (2012)

	Clinical features of hyperthyroidism	
	Symptoms	**Signs**
Central nervous system	Fatigue, nervousness, anxiety, hyperactivity, poor concentration	Hyperactivity
Hair	Thinning, hair loss	
Eyes (usually in Graves' disease)	Soreness, grittiness	Stare, eyelid retraction and lag, periorbital oedema, conjunctival injection, ophthalmoplegia
Thyroid	Neck swelling	Goitre
Muscles	Weakness, tremor	Fine tremor, muscle wasting
Skin	Heat intolerance, increased perspiration	Warm, moist skin, increased perspiration
Cardiovascular system	Palpitation, shortness of breath	Tachycardia, atrial arrhythmia, systolic hypertension, high output failure
Gastrointestinal system	Increased appetite, weight loss	Weight loss
Peripheral nervous system		Hyperreflexia
Reproductive system		Oligomenorrhoea, decreased fertility (women); reduced libido (men)

The clinical manifestation of hyperthyroidism and/or subsequent complications may involve one or more organ systems and vary among individuals. In patients with Graves' disease, ocular changes, lymphoid hyperplasia, localised abnormalities of skin and connective tissue (e.g., acropachy) and the goitre itself are caused by the autoimmune reaction (de Groot, 2015). Other pathological changes are due to an excess of thyroid hormones and most often reverse once the euthyroid state is achieved (Fox et al., 2015).

1.2.3.1.1 Thyroid gland

Both Graves' disease and toxic nodular goitre may be associated with enlargement of the thyroid gland (goitre), reflecting thyrocyte hyperplasia. This size increase ranges from minimal to very large and some patients may present with significant compressive symptoms. Diffuse goitre is found mainly, although not exclusively, in Graves' disease patients (Hollander and Davies, 2009). Clinical examination of the neck through palpation may identify one or more nodules associated with solitary toxic adenoma or multinodular goitre, respectively. In some cases, further evaluation through high resolution ultrasound examination is needed to differentiate a solitary nodule from a dominant nodule in a multinodular goitre. Goitre may compress the trachea as well as the oesophagus in some subjects (Sorensen et al., 2014), resulting in upper airways obstruction presenting as shortness of breath, or in swallowing difficulties, or both.

1.2.3.1.2 Cardiovascular system

Thyroid hormones have important effects on the heart, the circulation and the sympathetic nervous system which alters the cardiac haemodynamics patients with hyperthyroidism. Excess thyroid hormones can increase almost all measures of cardiac function, including heart rate, cardiac contractility and output, diastolic relaxation and myocardial oxygen consumption while diastolic pressure and systemic vascular resistance may be reduced (Klein and Ojamaa 2001). These changes are responsible for the observed cardiovascular symptoms and signs in subjects with thyrotoxicosis. These include palpitation, tachycardia, exercise intolerance, exertional dyspnoea, orthopnoea, the presence of a hyperdynamic praecordium, angina-like chest pain, increase in left ventricular mass index and left ventricular hypertrophy, as well as increased ventricular irritability (Biondi et al. 1993; Dorr et al. 2005; Iglesias et al. 2005).

Hyperthyroid patients with normal hearts can develop atrial tachycardia, atrial fibrillation and atrial flutter. Among these arrhythmias, atrial fibrillation (AF) is the most common, occurring in 2 to 20% of patients and may be the main presenting clinical feature (Boelaert and Franklyn 2005). AF is found most commonly in older subjects and in those with underlying organic heart disease (Cooper 2003; Weetman 2000). Although there is a clear association between hyperthyroidism and AF, overt hyperthyroidism is rarely found (<1%) in subjects with new onset AF (Krahn at al. 1996). Thus although hyperthyroidism is a risk factor for AF, it is uncommon in the absence of additional symptoms and signs of thyrotoxicosis (Boelaert

and Franklyn 2005). Atrial fibrillation has been reported to be associated not only with overt thyrotoxicosis but also with subclinical hyperthyroidism (Collet et al., 2012).

1.2.3.1.3 Neuromuscular system

Thyroid hormones have profound effects on the neuromuscular system and the brain. Tremor and cognitive dysfunction of varying severity are the most common neuromuscular signs and symptoms of hyperthyroidism (Gardner, 2005). Tremor occurs in patients of all ages. It usually involves the hands but may be found in different parts of the body such as the face, head, trunk or legs. Typically, the shaking is of high frequency and low amplitude (Kung, 2007). Responsiveness to beta-adrenergic blocking drugs suggests that the tremor in hyperthyroidism is adrenergic in nature (Henderson et al., 1997). Other symptoms of hyperthyroidism affecting the neuromuscular system are muscle weakness, fatigability, muscle pain and cramps, which were reported by 67% of newly diagnosed patients with hyperthyroidism. When measured with electrodiagnostic procedures, myopathy of varying degrees was found in up to 81% of studied patients and its severity correlated with serum fT4 at presentation (Duyff et al., 2000).

1.2.3.1.4 Skin

The skin in subjects with hyperthyroidism is warm and often sweaty due to increased blood flow and accelerated metabolism. It may also seem smooth, which is probably caused by thinning of the keratin layer (Heymann, 1992). In addition, patients may present with thinning and fine hair, softening of the nails or even separation or loosening of finger- or toenails from the nail bed (called Plummer's nails),

and clubbing of the fingers (acropachy) (Jabbour, 2003). Hyperthyroidism may also manifest with reduced pigmentation of the skin in smooth, white patches in the midst of normally pigmented skin or in hyperpigmentation, which may be due to vitiligo, an associated autoimmune disorder (Safer, 2005).

Pretibial myxoedema is an infrequent skin condition specific to Graves' disease and is caused by an autoimmune inflammatory reaction driven by anti TSH-receptor antibodies. Despite its name, it is not restricted to the pretibial area but may spread more widely towards the ankle or back or may be present on the elbows and knees (Fatourechi et al., 1994).

1.2.3.1.5 Graves' ophthalmopathy (GO)

Ocular signs of hyperthyroidism characterise Graves' aetiology and are caused by an autoimmune inflammation that induces expansion of the extraocular muscles and retro-orbital connective and adipose tissues (Dolman, 2012). Ocular signs and symptoms most often occur within 18 months of onset of hyperthyroidism. Approximately 20% to 25% of patients with Graves' hyperthyroidism have clinically obvious GO (Bartalena et al., 2000) which accounts for an annual incidence rate in the US population of 16 women and 3 men per 100,000 per year (Bartley et al., 1995, Bahn, 2010). GO follows a biphasic course, with a progressive or active phase lasting 6–18 months, followed by a stable or inactive phase. GO has been associated with decreased quality of life, which was significantly lower than in patients with hyperthyroidism without GO (Abraham-Nordling et al., 2010). Progression of the condition may result in permanent cosmetic disfigurement and functional visual impairment including restricted ocular motility and double vision, and occasionally

visual loss from compressive dysthyroid optic neuropathy (Dolman, 2012). Thus, despite the self-limiting character of the condition, early appropriate evaluation and treatment is needed to prevent the development of serious consequences.

There are several classification systems designed to accurately assess the activity and severity of orbitopathy. The European Group on Graves' Orbitopathy (EUGOGO) and American Thyroid Association (ATA) recommend an examination assessing activity based on Clinical Activity Score (CAS) (Table 1-4). The severity is classed as (1) mild, when only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment is present, (2) moderate-to-severe, justifying treatment with immunosuppression or surgery, and (3) sight-threatening, when dysthyroid optic neuropathy and/or corneal breakdown is diagnosed (Bartalena et al., 2008, Bahn et al., 2011, Ross et al., 2016).

Table 1-4: Clinical Activity Score (CAS) is the sum of all items present. During the first assessment, only items 1-7 are scored; during follow-up items 1-10 are evaluated. A CAS score ≥3/7 at first examination or ≥4/10 on follow-up visits qualifies the patients for a diagnosis of active Graves' ophthalmopathy. Table adapted from (Campi et al., 2016).

GO activity assessment according to Clinical Activity Score
1. Painful, oppressive feeling on or behind the globe, during the past 4 weeks
2. Pain on attempted up, side, or down gaze, during the past 4 weeks
3. Redness of the eyelid(s)
4. Diffuse redness of the conjunctiva, covering at least one quadrant
5. Swelling of the eyelid(s)
6. Swelling of conjunctiva (chemosis)
7. Swollen caruncle
8. Increase of proptosis of ≥2 mm during a period of 1 –3 months
9. Decrease of eye movements in any direction ≥8° during a period of 1–3 months
10. Decrease of visual acuity of ≥1 line(s) on the Snellen chart (using a pinhole) during a period of 1–3 months

Another very widely used classification system of eye symptoms and signs is based on the mnemonic – NO-SPECS — NO indicating the absence or mild degree of involvement; SPECS the more serious degrees (Villadolid et al. 1995). The severity ranges from class 0 to VI: 0 — No symptoms or signs; I — Only signs, no symptoms (e.g. lid retraction, stare, lid lag); II — Soft tissue involvement; III — Proptosis; IV — Extraocular muscle involvement; V — Corneal involvement; VI — Sight loss /optic nerve involvement. It is noteworthy, that class I signs (lid retraction leading to stare and lid lag) may be caused directly be excess of thyroid hormones and may give the appearance of proptosis, when none exists ("apparent proptosis"). These signs alone do not indicate the presence of ophthalmopathy, and subside when the hyperthyroidism is treated.

A third major diagnostic scoring system, VISA, was introduced in 2006 in Canada and is quickly gaining popularity. It has been adopted by International Thyroid Eye Disease Society (ITEDS). It is a clinical recording form that permits grading of clinical severity and activity based on both subjective and objective inputs. It separates the various clinical features of GO into four discrete parameters: V (vision, dysthyroid optic neuropathy); I (inflammation, congestion); S (strabismus, motility restriction); A (appearance, exposure) (Dolman, 2012, Dolman and Rootman, 2006).

Smoking, stressful life events, a positive family history of ophthalmopathy, radioiodine treatment and poor control of hypothyroidism following radioiodine treatment have been identified as risk factors for developing GO. Additionally, male gender, older age, smoking, and rapid onset of ophthalmopathy have been associated with development

of more severe consequences of GO (Dolman, 2012). Cigarette smoking has been shown by numerous studies to be strongly associated with both the development and more severe consequences of GO (Bartalena et al., 2008).

1.2.3.1.6 Skeletal system

Thyroid hormones directly stimulate bone resorption. In hyperthyroidism, the bone remodelling cycle is shortened by about 50% from 6-7 months to 3-4 months. This increases the ratio of resorption to bone formation causing osteoporosis from new bone loss. In each cycle, there is 10% loss of mineralised bone in patients with hyperthyroidism (Gorka et al., 2013). Moreover, increased bone resorption causes additional release of calcium into systemic circulation and subsequent gastro-intestinal loss. High serum levels of calcium are present in up to 8% of patients with hyperthyroidism (Mosekilde et al., 1990).

A meta-analysis of 25 studies (Vestergaard and Mosekilde, 2003), confirmed consistently decreased bone mineral density (BMD) and increased risk of fractures in untreated hyperthyroidism. Whilst there is a delay in fully reversing the negative consequences of thyroid dysfunction complete disappearance one to four years after initiation of antithyroid treatment has been observed in many studies even if no additional treatment for osteoporosis is administered.

The degree of bone loss and increased risk of osteoporosis are associated with the severity of hyperthyroidism mainly relative to degree of TSH suppression, rather than serum fT4 and fT3 concentrations (Svare et al., 2009). These findings have clinical

implications especially when evaluating risks in patients with subclinical hyperthyroidism. The likelihood of fractures increases also with age and is especially pronounced in post-menopausal women (Vestergaard and Mosekilde, 2003). Importantly, hyperthyroidism was found to be an independent risk factor for hip fractures in older men (>75 years old) increasing the hazard ratio three-fold compared to those with no comorbidity of hyperthyroidism (Cauley et al., 2016).

1.2.3.1.7 Weight and body temperature

Excess thyroid hormones increase metabolism and upregulate thermogenesis, which consequently increases caloric demands. The increased demand for energy may also manifest itself by an insatiable feeling of hunger (Dhillo, 2007). The majority of patients do not balance the new metabolic demand and weight loss is noted in most. However, in some subjects, weight is not affected or may even increase, probably as a consequence of appetite stimulation (Nordyke et al., 1988). Weight changes during the course of hyperthyroidism are studied in more details in Chapter 4.

An accelerated metabolism affects the body temperature. In addition to heat intolerance, intensified sweating and an increased demand for fluid replenishment may be reported by subjects with hyperthyroidism (Tak et al., 1993).

1.2.3.1.8 Gastrointestinal manifestations

Gastrointestinal manifestations in hyperthyroidism are most likely of an adrenergic nature. They include increased bowel movement with or without abdominal pain or vomiting (Ebert, 2010a). A number of studies have documented a negative correlation between transit time from mouth to caecum and serum fT3 concentrations

(Kyriacou et al., 2015). Most gastrointestinal symptoms reverse following successful treatment of hyperthyroidism (Papa et al., 1997).

1.2.4 Treatment of hyperthyroidism

Hyperthyroidism can be managed with multiple treatment approaches. The choice of the therapy requires an accurate diagnosis and is influenced by coexisting medical conditions as well as physician and patient preference. The most common treatment modalities are: (i) a prolonged course of antithyroid drug; (ii) administration of radioiodine I-131; (iii) thyroidectomy. Figure 1-4 represents changes in serum thyroid hormones and TRAb concentrations during each mode of therapy.

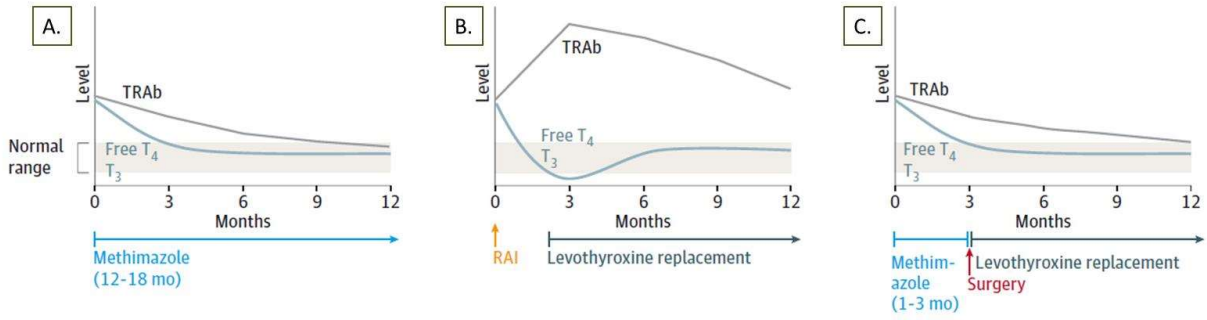

Figure 1-4: Schematic representation of changes in serum thyroid hormones and TRAb concentrations during treatment for hyperthyroidism with thionamides (panel A), I-131 (B) and thyroidectomy (C). Diagram adopted from a review authored by Burch and Cooper (2015)

1.2.4.1 *Antithyroid medication*

Antithyroid drugs (ATD) belong to class of thionamides. In the United Kingdom and large parts of the Commonwealth, propylthiouracil (PTU) and carbimazole (CMZ) are used preferentially. In the USA and in most of Europe and Asia, methimazole (MMI)

is the preferred medication (Cooper, 2005). MMI is an active metabolite of CMZ and, since its conversion is nearly complete, their effects are very similar (Franklyn, 1994). The serum half-life of methimazole and propylthiouracil are 3-5 and 1-2 hours, respectively, however, their therapeutic effectiveness is longer as they accumulate in the thyroid gland (Kampmann and Hansen, 1981).

For years, treatment with antithyroid drugs has been the preferred therapeutic choice for Graves' disease in Europe and Asia and, according to a recent survey, also in the USA (Burch et al., 2012). Methimazole and carbimazole are commonly used, with only 2.7% of doctors preferring PTU (Burch et al., 2012). The primary effect of ATD is to inhibit thyroid hormone synthesis by interfering with thyroid peroxidase mediated iodination of tyrosine residues in thyroglobulin. Additionally, antithyroid drugs may have clinically important immunosuppressive effects. In patients taking ATD, serum concentrations of TSH-receptor antibodies (TRAb) decrease with time (Cooper, 2005). Moreover, PTU but not MMI or CMZ, can block the conversion of T4 to T3 within the thyroid gland and in peripheral tissues, hence the ATA recommendation to use PTU over MMI to secure aggressive inhibition of T4 to T3 conversion in management of thyroid storm (Bahn et al., 2011, Ross et al., 2016).

There are several considerations to be made when prescribing medical therapy for hyperthyroidism: the choice of drug, dose, duration of therapy, addition of levothyroxine and when to discontinue therapy. Whatever the treatment approach, medical therapy has been associated with a high risk (more than 50%) of relapse of hyperthyroidism (Ma et al., 2016, Abraham et al., 2010). To improve the likelihood

of long-term remission, recent ATA guidelines, recommend the assessment of TRAb prior to stopping the thionamide therapy (Ross et al., 2016).

There are two commonly recognised regimens of thionamide treatment: titration and block-and-replace methods. In the titration approach, therapy begins with relatively high doses of thionamides, with the magnitude influenced by the severity of hyperthyroidism and the size of goitre (Garcia-Mayor and Larranaga, 2010). The doses are progressively reduced as the patient improves to the lowest effective dose restoring and maintaining euthyroidism. A meta-analysis (Abraham et al., 2010) has indicated that the optimal duration of antithyroid drug therapy during a titration regimen is 12 to 18 months. The block-and-replace method uses persistently high doses of thionamides concurrent with administration of levothyroxine replacement to avoid hypothyroidism. The optimal treatment duration is 6 months. A meta-analysis comparing both regimens (Abraham et al., 2010) concluded that the efficacy of both approaches was similar, with a 12 month relapse rate for titration and block-and replace regimens being 51% and 54% respectively. Importantly, however, the titration method was associated with fewer adverse effects, probably reflecting lower doses of ATDs.

Treatment with thionamides is associated with a variety of adverse effects from minor to life-threating. Side effects of methimazole are dose-related, whereas those of propylthiouracil are less clearly related to administered dosage (Cooper, 2005, Franklyn and Boelaert, 2012). Table 1-5 presents various adverse reactions to thionamides.

Table 1-5: Side effects of antithyroid drugs. Table compiled from the reviews authored by Franklyn and Boelaert (2012) and Cooper (2005)

	Adverse reaction	Estimated frequency
Major effects	Agranulocytosis	0.1-0.5%
	Hepatitis (especially PTU)	0.1-0.2%; 1% in some series
	Polyarthritis	1-2%
	Cholestasis (especially MMI)	Rare
	Autoimmune disorders (Lupus-like syndrome, ANCA-positive vasculitis)	Rare
	Hypoglycemia due to insulin autoantibodies	Rare
	ANCA-positive vasculitis	Rare
	Hypoprothrombinemia	Rare
	Thrombocytopenia	Very rare
	Aplastic anaemia	Very rare
	Pancreatitis	Very rare
Minor effects	Arthralgia	1–5%
	Fever	Common
	Gastrointestinal effects	1–5%
	Abnormal sense of taste or smell	Rare
	Sialadenitis	Very rare
	Skin reactions	4–6%
	Other hematologic side effects	Very rare

1.2.4.2 *Radioiodine*

Treatment of hyperthyroidism with radioactive iodine (I-131) was first reported in 1942 (Hertz et al., 1942). The technique aims to induce partial destruction of the hyperfunctioning thyroid gland. I-131 is incorporated into thyroid hormones, releasing beta particles that cause ionising damage to thyroid follicular cells. The therapeutic effect depends on the size of the thyroid, the radioiodine uptake, the degree of thyrotoxicosis, and the activity of I-131 administered (Burch and Cooper, 2015). It can be applied in treatment of Graves' disease, toxic adenoma, and toxic multinodular goitre. It is completely contraindicated during pregnancy

and breastfeeding (due to potential effects on the foetal and infant thyroid) and relatively contra-indicated in women planning to become pregnant in the short-term. I-131 requires compliance with radiation safety protocols (De Leo et al., 2016). Additionally, treatment with radioiodine for Graves' disease is contraindicated in those with active moderate to severe ophthalmopathy. Studies have shown radioiodine to be associated with a four-fold increased risk of developing thyroid eye disease or worsening of TED when compared to patients treated with ATD. In the same meta-analysis (Acharya et al., 2008), the use of adjunctive prednisolone prophylaxis was found to be highly effective in preventing the progression of TED in patients with pre-existing TED. Risk factors for developing or worsening of TED following I-131 therapy for Graves' disease include smoking (Traisk et al., 2009), high TRAb titres (Eckstein et al., 2006), high concentrations of total T3 at diagnosis (Tallstedt et al., 1992) and untreated hypothyroidism following radioiodine administration (Stan et al., 2013).

There are two main approaches to I-131 dose required in treatment of hyperthyroidism. Historically, this treatment aimed at avoiding post-therapy hypothyroidism and the dose was calculated based on the weight of the thyroid tissue and iodine uptake. This has proven difficult and often inefficient. With time, many centres have accepted hypothyroidism as inevitable and used fixed doses to ablate the gland. Meta-analyses combining results of different studies found no significant differences in treatment outcomes and in rates of permanent hypothyroidism between the two regimens neither in treatment of Graves' disease nor in toxic nodular hyperthyroidism (de Rooij et al., 2009, Rokni et al., 2014).

Occasionally, I-131 can induce short-term exacerbation of hyperthyroidism (Shafer and Nuttall, 1975, Nakajo et al., 2005). To protect against this effect and to lower the baseline concentrations of thyroid hormones, pretreatment with thionamides is often used. This is especially recommended in patients with severe hyperthyroidism, the elderly, and those with significant co-morbidity that puts them at a greater risk for complications of worsening thyrotoxicosis (Ross et al., 2016). However, pretreatment with thionamides and especially with PTU has been shown to reduce the efficacy of I-131 therapy (Walter et al., 2007). Therefore, discontinuation of thionamide treatment is recommended 3-7 days prior to radioiodine administration (Ross et al., 2016). The risk of long-term hypothyroidism in treatment with radioiodine is estimated at around 60%, and is dose dependent (Boelaert et al., 2009). Pretreatment with antithyroid drugs reduces the risk of hypothyroidism (Walter et al., 2007). Additionally, a number of studies have identified parameters associated with increased risks of 131-I therapy failure: male gender, younger age, high concentrations of circulating thyroid hormones at diagnosis and the presence of a medium to large goitre (Schneider et al., 2014, Andrade et al., 2001, Boelaert et al., 2009, Gupta et al., 2010).

1.2.4.3 *Surgery (thyroidectomy)*

Surgery, as definite therapy for hyperthyroidism, is used to prevent recurrent hyperthyroidism. In Graves' disease, thyroidectomy may be indicated in patients with persistent hyperthyroidism after a prolonged course of anti-thyroid medication, if rapid restoration of euthyroidism is desired, when radioactive iodine treatment

is contraindicated (e.g. in pregnancy) or if the patient prefers this option. In patients with toxic nodular hyperthyroidism, surgery may be the preferred option if radioactive iodine therapy is not feasible, if the patient has a large compressive goitre or if there is uncertainty regarding the presence of thyroid cancer (Ross et al., 2016).

In patients with persistent hyperthyroidism, studies have shown that total thyroidectomy is more cost-effective than radioactive iodine or lifelong anti-thyroid medication (In et al., 2009, Zanocco et al., 2012) although quality of life is significantly reduced when compared to the general population (Al-Adhami et al., 2012). The recommended approach is total or near-total thyroidectomy performed by a "high volume" surgeon for patients with Graves' disease or toxic nodular goitre. Patients should be rendered euthyroid with antithyroid drugs prior to surgery and with additional beta-adrenergic blockade if required. Patients should be counselled regarding the risk of post-operative hypocalcaemia, recurrent laryngeal nerve damage, as well as the need for life-long levothyroxine replacement. In patients with a solitary toxic adenoma, partial thyroidectomy may be sufficient (De Leo et al., 2016, Franklyn and Boelaert, 2012, Ross et al., 2016).

According to a recent meta-analysis (Cirocchi et al., 2015), total thyroidectomy compared with subtotal thyroidectomy conferred a greater risk of permanent hypocalcaemia/ hypoparathyroidism in 8/172 versus 3/221 participants (OR 4.79 [95% CI 1.36 to 16.83]; P = 0.01). There was no significant difference in permanent recurrent laryngeal nerve palsy and regression of Graves' ophthalmopathy between these surgical techniques.

1.2.5 Special forms of thyrotoxicosis with or without hyperthyroidism

1.2.5.1 *Subclinical hyperthyroidism*

Subclinical hyperthyroidism (SHyper) is defined exclusively according to biochemical criteria as a low serum TSH concentration and normal serum free T4 and free T3 concentrations. It was identified as a separate pathological entity in the 1980s as a result of introduction of more sensitive assays allowing measurements of serum TSH concentrations below the normal range (Vanderpump et al., 2011, Wiersinga, 2011). This pattern of biochemistry is not homogenous and may include patients with or without underlying thyroid dysfunction. Table 1-6 presents the aetiology and differential diagnosis of subclinical hyperthyroidism.

Table 1-6: Aetiology and various types of differential diagnosis of persistent subclinical hyperthyroidism (SHyper). Table adapted from Biondi et al. (2015).

Causes of persistent subclinical hyperthyroidism
Endogenous causes
Graves' disease
Toxic adenoma
Multinodular goitre
Exogenous causes
Excessive thyroid hormone replacement therapy
Intentional thyroid hormone suppressive therapy
Causes of transient SHyper
Treatment of overt hyperthyroidism with ATDs or radioiodine
Subacute thyroiditis, painless and silent thyroiditis
Causes of low serum TSH concentrations that are not SHyper
Pituitary or hypothalamic insufficiency
Psychiatric illness
Drugs
Severe non-thyroidal illness
Late first trimester of pregnancy
Can happen in black individuals as a consequence of racial differences
Smoking

Exogenous subclinical hyperthyroidism results from levothyroxine (L-T4) replacement. Typically, the goal of the L-T4 replacement is to achieve and maintain euthyroidism but in many patients this goal is not reached (Somwaru et al., 2009). Subclinical hyperthyroidism is, however, the aim of thyroid hormone therapy in most patients with previous thyroid cancer. Endogenous SHyper most commonly reflects milder forms of hyperthyroid dysfunction; it may be caused by mild or early Graves' disease or toxic nodular hyperthyroidism. Recently, biochemical criteria reflecting the severity of SHyper have been proposed: grade 1 SHyper, which has low but detectable serum TSH concentrations (e.g. TSH 0.1–0.39 mIU/l), and grade 2 SHyper, which has suppressed serum TSH concentrations (<0.1 mIU/l) (Biondi et al., 2015).

In countries where L-T4 treatment is widespread, exogenous SHyper is more common than endogenous (Cooper and Biondi, 2012). Exogenous SHyper was reported in 20-40% of patients taking thyroid hormone (Canaris et al., 2000, Somwaru et al., 2009). Reports on the prevalence of endogenous SHyper in large population studies vary between 0.7% and 1.8% (Vadiveloo et al., 2011, Hollowell et al., 2002). Epidemiological studies have confirmed a higher prevalence of endogenous SHyper with age and higher frequency in women. In young patients, the most common cause of endogenous subclinical hyperthyroidism is Graves' disease, whereas underlying toxic multinodular goitre or solitary autonomous nodules become increasingly common with age. Additionally, SHyper is more common in those with a diagnosis of TNG, toxic multinodular goitre being subclinical in most patients (57%) but in only 6% of those with Graves' disease in a population aged more than 55 years (Diez, 2003).

Subclinical hyperthyroidism may spontaneously revert to euthyroidism (at a rate 5%-12% per year) or, when untreated, may progress to overt hyperthyroidism with yearly conversion rates varying between 0.5%–7% (Ross et al., 2016). The natural history depends on the degree of thyroid dysfunction and the underlying aetiology. Graves' disease has been associated with a higher risk of progression to overt thyroid dysfunction than toxic multinodular goitre (Schouten et al., 2011), although a third of subjects with underlying Graves' disease show reversion of TSH to euthyroidism spontaneously (Zhyzhneuskaya et al., 2016). In toxic nodular goitre, persistent subclinical thyroid dysfunction, lasting for many years, is common. Interestingly, potential progression to overt thyroid dysfunction in patients with nodular hyperthyroidism was noted to be more frequent after iodine supplementation (Vadiveloo et al., 2011). Irrespective of the aetiology, patients with more severe subclinical dysfunction (i.e. lower TSH) are more likely to develop biochemically overt hyperthyroidism (Das et al., 2012, Diez and Iglesias, 2009).

Subclinical hyperthyroidism has been shown to have similar deleterious effects to those seen in overt hyperthyroidism. It has been associated with a 24% increase in risk of overall mortality (Collet et al., 2012), with increased cardiovascular morbidity, especially from heart failure and atrial fibrillation (Gencer et al., 2012, Cappola et al., 2006, Collet et al., 2012) and with decreased bone mineral density in postmenopausal women and older men causing osteoporosis and fractures (Blum et al., 2015). International professional bodies recommend initiation of treatment in older patients (≥65 years of age) with persistent subclinical hyperthyroidism when serum TSH is undetectable (grade 2), as well as in those who are symptomatic or diagnosed with cardiac disease or osteoporosis in whom serum TSH is below normal

but detectable (grade 1). Treatment should be considered in younger patients (<65 years old) when TSH persistently below <0.1 mIU/L in the presence of hyperthyroid symptoms or cardiac or osteoporotic comorbidities. However, younger asymptomatic patients with milder SHyper (grade 1) can be observed without further investigation of the aetiology or treatment (Biondi et al., 2015, Ross et al., 2016).

1.2.5.2 *Thyroid storm*

At the opposite end of the severity spectrum, thyroid storm is a life-threatening manifestation of thyrotoxicosis. It is a very rare disorder with a yearly incidence rate of two cases in 1 million in a Japanese population or occurrence of 0.22% in all patients with hyperthyroidism (5.4% of thyrotoxic subjects admitted to hopsital) (Akamizu et al., 2012). This is a medical emergency with high mortality varying between 8-25%, with multiple organ failure and acute heart failure being the most common causes of death (Angell et al., 2015, Satoh et al., 2016, Swee et al., 2015).

The presentation of thyroid storm does not depend on the concentration of serum thyroid hormones which can be similar to compensated forms of hyperthyroidism (De Leo et al., 2016). Often the reasons triggering thyroid storm are not clear, although irregular use or discontinuation of antithyroid drugs, as well as infections, seem to be common features (Akamizu et al., 2012). Other risk factors include acute illness, thyroid or non-thyroid surgery, trauma, severely stressful life events and pregnancy. The prognosis for survival depends mainly on early intervention.

The diagnosis is made on clinical grounds and is based on the presence of severe and life-threatening manifestations in patients with hyperthyroidism. In 1993, the Burch-Wartofsky scoring system was devised to help making the diagnosis of thyroid storm (Burch and Wartofsky, 1993). It takes into account the severity of symptoms of multiple organ decompensation, including thermoregulatory dysfunction, tachycardia/atrial fibrillation, disturbances of consciousness, congestive heart failure, and gastro-hepatic dysfunction, as well as the role of precipitating factors. The scale differentiates diagnosis into thyroid storm, impending storm and storm unlikely. In 2012, the Burch-Wartofsky scoring system was revised by the Japanese Thyroid Association (JTA) and amendments were proposed (Akamizu et al., 2012). Overall, the two systems are in agreement although thyroid storm defined by the Burch-Warofsky scale seems to select a higher percentage of patients for aggressive therapy than JTA system (Angell et al., 2015, Satoh et al., 2016, Swee et al., 2015).

1.2.5.3 *Hyperthyroidism in pregnancy and postpartum*

In the USA, the average yearly incidence of hyperthyroidism is 5.9 per 1,000 pregnancies (Korelitz et al., 2013). The most common cause is Graves' disease (Carle et al., 2011). In pregnancy, the highest risk of developing hyperthyroidism (Figure 1-5) is during the first trimester and the prevalence is very low in the third. The risk of hyperthyroidism increases significantly during the postpartum period, reaching the highest level at 7–9 months after delivery (Andersen et al., 2015).

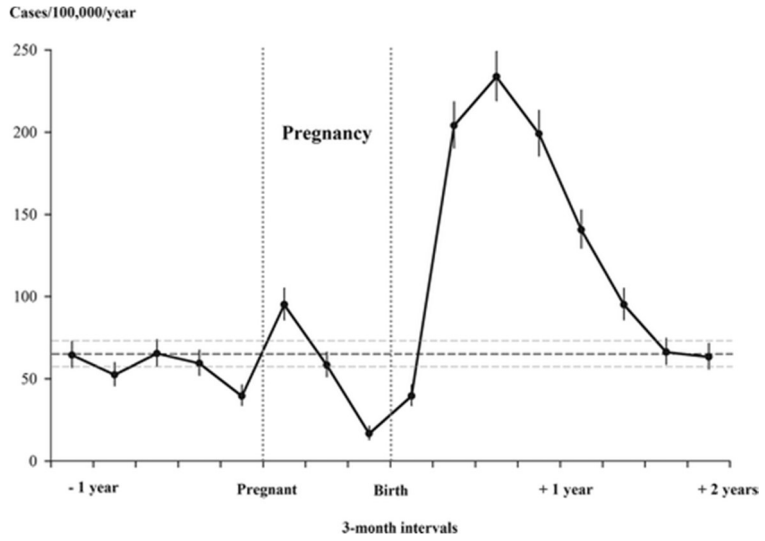

Figure 1-5: Incidence rates of hyperthyroidism around the time of the first pregnancy in 3-month intervals in a Danish nationwide study of 403 958 women (Andersen et al., 2015).

Thyroid function test results of healthy pregnant women differ from those of healthy non-pregnant women due to adaptation processes to meet the needs of increased metabolism. Following conception, circulating total T4 (TT4) and thyroxine binding globulin (TBG) concentrations increase by 6–8 weeks and remain high until delivery (Glinoer, 1997). Consequently, TSH concentrations are lower (often below standardised laboratory reference ranges) and trimester-specific ranges need to be applied. The ATA proposes the use of the following reference cut-offs: first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L; third trimester, 0.3–3.0 mIU/L (Stagnaro-Green et al., 2011). Most studies also report a substantial decrease in serum free T4 (fT4) concentrations associated with progression of gestation, which can be influenced by higher concentration of TBG and needs to be considered as physiological (Baloch et al., 2003).

The differential diagnosis of Graves' hyperthyroidism and transient changes in thyroid biochemistry in the early phases of pregnancy may be difficult. Gestational transient

thyrotoxicosis caused by very high serum human Chorionic Gonadotrophin (hCG) concentrations is most often seen in women with hyperemesis gravidarum. This is usually a self-limiting condition which does not require active treatment (Cooper, 2003, Lo et al., 2015). Importantly, untreated Graves' disease in pregnancy is associated with poor pregnancy outcomes (Millar et al., 1994) and may be also be a risk factor for maternal heart failure (Sheffield and Cunningham, 2004). Hence, treatment of gestational Graves' disease needs to be managed carefully. Moreover, maternal TRAb can cross the placenta and cause fetal or neonatal thyrotoxicosis. Since antithyroid drugs cross the placenta and may induce fetal hypothyroidism, the lowest effective dose controlling maternal hyperthyroidism is to be used (Franklyn and Boelaert, 2012, Laurberg and Andersen, 2015). Use of thionamides during early pregnancy has been associated with an increased rate of birth defects (OR: 1.4-1.8 as compared to mothers not on ATD) including urinary system malformation (following either treatment with MMI/CMZ or PTU), and malformations in the face and neck region (following PTU therapy) (Andersen et al., 2013). Although treatment with either of these ATDs has been found to be teratogenic, the effects of exposure to PTU tend to be less frequent (Yoshihara et al., 2012) and less severe (Andersen et al., 2014). Therefore the use of PTU during the first trimester of pregnancy is recommended (Ross et al., 2016).

Relapse or new onset of thyrotoxicosis during the postpartum period is common (Amino et al., 1999, Andersen et al., 2015). This may be caused either by Graves' hyperthyroidism or postpartum thyroiditis. The latter usually presents as transient hyperthyroidism followed by transient hypothyroidism over a course of 6-12 months. It is important to differentiate the aetiology of post-partum thyrotoxicosis. GD needs

to be treated while thyroiditis usually does not require medical therapy other than symptomatic treatment with beta-blockers (Ross et al., 2016). The differential diagnosis between self-limiting thyroiditis and Graves' hyperthyroidism is based on the presence of ophthalmopathy, positive TRAb, goitre and/or high thyroid uptake of iodine I-123 or technetium, which suggest Graves' disease (Franklyn and Boelaert, 2012). Additionally, differences in the timing onset of both forms have been noted. In a Japanese study, postpartum thyroiditis developed earlier (first three months) after delivery than GD (usually after the first 3 months period), although some overlap existed (Tagami et al., 2007). Postpartum thyroiditis frequently reappears following subsequent pregnancies (up to 80%), which may lead to development of permanent hypothyroidism (Lazarus, 2011).

1.2.5.4 *Thyroiditis*

Thyroiditis is an inflammation of the thyroid gland. The most common forms are subacute thyroiditis, silent thyroiditis, postpartum thyroiditis, and drug-induced thyroiditis (caused by amiodarone, interferon-α, interleukin-2, tyrosine kinase inhibitor (TKI), or lithium). Thyroiditis usually presents with a classic tri-phasic course: a short period of thyrotoxicosis due to release of preformed thyroid hormone that lasts for 1 to 3 months, followed by a more prolonged hypothyroid phase lasting up to 6 months, and finally a return to a euthyroid state (Samuels, 2012).

Subacute thyroiditis (subacute granulomatous or de Quervain's) presents with a painful and tender thyroid, fever and malaise and is characterised by biochemical and clinical thyrotoxicosis (Fatourechi et al., 2003). It may be caused by viral infection of the upper respiratory track. Thyroid isotope uptake is low due to damage of thyroid

cells and release of pre-formed hormone into the circulation. Hence, treatment with ATD is ineffective and patients should be treated with beta-blockers and nonsteroidal anti-inflammatory agents (Ross et al., 2016). The thyrotoxic phase usually lasts 3-6 weeks. In 30% of patients, this is followed by a hypothyroid phase. Normal thyroid function usually returns within 12 months of disease onset, although 5-15% have persistent hypothyroidism (Benbassat et al., 2007, Fatourechi et al., 2003).

Silent (or painless) thyroiditis is caused by lymphocytic infiltration of the thyroid gland. It is associated with positive thyroid peroxidase (TPO) antibodies in 50% of patients (Volpe, 1988) but also with some types of drug-induced thyroid dysfunction, including lithium or cytokine therapy. The postpartum period is the most common time when painless thyroiditis is seen (described in section 1.2.5.3), but it can also occur at any other time in women, as well as in men. During the thyrotoxic phase, free T4 concentrations are elevated often out of proportion to free T3 concentrations and calculation of the fT4 to fT3 ratio may be helpful in establishing the diagnosis. Additionally, low RAIU uptake and the absence of TRAb antibodies help distinguish painless thyroiditis from GD (Kamijo, 2010). Recurrence may be common, being estimated at 5-10% (Mittra and McDougall, 2007). ATD treatment, similarly to the management of subacute thyroiditis, is ineffective, although cases of use of radioiodine or surgery in frequently recurring silent thyroiditis have been reported (Mittra and McDougall, 2007).

1.2.5.5 *Drug-induced thyrotoxicosis*

A number of drugs are associated with the induction of thyrotoxicosis. These include amiodarone, lithium, and new neoplastic- and immunotherapies (Illouz et al., 2014, Dong, 2000).

Amiodarone

Amiodarone is highly effective in the management of dysrhythmias, including atrial fibrillation and flutter. It is very rich in iodine, with a 100 mg tablet containing an amount of iodine that is 250 times the recommended daily iodine requirement (Basaria and Cooper, 2005). Amiodarone-induced thyroid dysfunction occurs in 15-20% of amiodarone-treated patients and its prevalence is influenced by the environmental iodine content. It can present as amiodarone-induced hypothyroidism (AIH) which is more frequent in iodine-sufficient areas, or thyrotoxicosis (AIT), more prevalent in iodine-deficiency (Bogazzi et al., 2012). Monitoring of thyroid function tests before and within the first 3 months following the initiation of amiodarone therapy, and at 3–6 month intervals thereafter has been recommended (Ross et al., 2016).

AIH is easy to control by levothyroxine replacement, and does not require amiodarone withdrawal. AIT occurs in up to 6% of patients taking amiodarone in iodine-sufficient areas of the world and in up to 10% in Europe (Martino et al., 1984). Two distinct mechanisms have been proposed in development of AIT: excess of iodine induced thyroid hormone synthesis in presence of nodular or Graves' hyperthyroidism (type 1) or destructive thyroiditis causing leakage of thyroid hormones from the damaged,

but otherwise healthy gland (type 2). The latter form is more frequent, commonly self-limiting and often does not require discontinuation of amiodarone (Eskes et al., 2012). Treatment of type 1 AIT is with thionamides (Ross et al., 2016) and amiodarone should be discontinued, if this is feasible from a cardiac standpoint. Type 2 AIT is treated with high dose glucocorticoids, often in conjunction with antithyroid drugs. Radioiodine treatment is not effective in AIT due to the low thyroidal iodine uptake. Total thyroidectomy is recommended as an alternative therapy in non-responsive patients (Ross et al., 2016). Often, both forms co-exist or are impossible to distinguish (Martino et al., 2001).

New neoplastic- and immunotherapies

New targeted neoplastic therapies and immunotherapies are often associated with effects on thyroid function. Primary hypothyroidism is one the main potential endocrine complications in patients undergoing treatment with tyrosine kinase inhibitors, radioiodine based cancer therapies as well as a number of immunotherapy agents. Bexarotene rapidly (4-8 hours) induces central hypothyroidism in nearly all of treated patients. The effect reverses within days upon discontinuation of the medication (Hamnvik et al., 2011). Thyrotoxicosis, either caused by autoimmune Graves' disease or destructive thyroiditis, has been associated with treatment with ipilimumab, tremelimumab, alemtuzumab, tyrosine kinase inhibitor, interferon-α and interleukin-2 (Torino et al., 2013).

Interferon-α and Interleukin-2

Interferon-α is a human recombinant cytokine, with antiviral and antitumor activity approved for patients with viral B or C hepatitis, Kaposi-s sarcoma, melanoma, renal cell carcinoma and some hematologic neoplasms (Friedman, 2008). Its effects on thyroid may be autoimmune, causing Graves' disease, Hashimoto thyroiditis, production of thyroid autoantibodies without clinical disease, or non-autoimmune, resulting in destructive thyroiditis or non-autoimmune hypothyroidism (Mandac et al., 2006). The incidence of interferon induced thyroiditis (IIT) vary from 2.4% up to 50% in some trials (Torino et al., 2013) and appears to be more common in patients treated for hepatitis C rather than for malignancies. Pre-existing thyroid autoantibodies result in a four-fold increase in the likelihood of developing hypothyroidism (Roti et al., 1996), which is the most common manifestation of ITT (Tomer et al., 2007). Graves' disease or Graves' ophthalmopathy may develop during the interferon treatment and persist following withdrawal (Hamnvik et al., 2011).

Interleukin-2 (IL-2) activates natural killer cells and antigen-specific T-cell and is approved for treatment in melanoma and renal cell cancer (Hamnvik et al., 2011). An increased incidence of thyroid dysfunction (10-60%) has been observed in patients treated with IL-2, although often there was concurrent administration of interferon-α, lymphokine-activated killer cells or vaccines (Torino et al., 2013). Interleukin-2 may have direct effects on thyrocyte function (Torino et al., 2013, Hamnvik et al., 2011) but a range of autoimmune effects and lymphocyte infiltration have also been described (Vialettes et al., 1993, Krouse et al., 1995, Jiskra et al., 2009).

Alemtuzumab

Alemtuzumab is a humanised monoclonal antibody, approved for treatment of chronic lymphocytic leukaemia and for relapsing-remitting multiple sclerosis (Torino et al., 2013, NICE). Thyroid dysfunction has been reported (22-40%) commonly in patients treated for multiple sclerosis but not for neoplasms (Daniels et al., 2014, Pariani et al., 2017, Coles et al., 2008, Torino et al., 2013). Graves' disease was the most common manifestation of thyroid dysfunction with the risk being 12% at five-year follow-up (Riera et al., 2016). A high proportion of GD patients (20%) had a fluctuating thyroid status. Additionally a number of cases of hypothyroidism, negative for TPOAb and positive for TRAb have been reported, suggesting effects of both blocking and stimulating anti-TSH receptor antibodies (Pariani et al., 2017). The majority cases with thyroid dysfunction occur within 3 years following the most recent dose of alemtuzumab (Daniels et al., 2014, Pariani et al., 2017). Three-monthly monitoring of thyroid function up to four years following the last dose has been recommended (Topliss, 2016).

Ipilimumab/ tremelimumab

Ipilimumab and tremelimumab are monoclonal antibodies (MAb) directed against cytotoxic T-lymphocyte antigen-4 receptor (CTLA-4). Ipilimumab is approved for treatment of advanced cutaneous melanoma and in renal, prostate and bladder cancer. Tremelimumab is being tried for prostate cancer. Rare cases of thyroiditis and euthyroid Graves' ophthalmopathy have been reported with the use of these agents. Central hypothyroidism, due to non-reversible hypophysitis, is more common,

found in 5% of participants in a trial, with onset usually 9-24 weeks following initiation of the treatment.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKI) are now commonly used antithyroid drugs. They are small molecules, usually analogs of ATP, which inhibit the transfer of phosphate from ATP to tyrosine residues of growth factor receptors (Gotink and Verheul, 2010). The effects of TKI on thyroid function vary depending on the agent and include development of new hypothyroidism, thyrotoxicosis (mainly due to destructive thyroiditis) or worsening pre-existing hypothyroidism (Torino et al., 2013). Sunitinib, causing hypothyroidism in more than 50% of subjects and hyperthyroidism in 10% during a phase I/II trial (Desai et al., 2006), has been the most studied agent. The risk of developing thyroid abnormalities increases with time and with the number of cycles of the therapy (Desai et al., 2006, Mannavola et al., 2007, Wolter et al., 2008). Following withdrawal, some patients recover spontaneously, while in others thyroid function remains impaired causing long-term hypothyroidism (Illouz et al., 2014).

Thyroid dysfunction has also been reported during the treatment with other TKI such as sorafenib, motesenib, pazopanib, cediranib, linifarib, imatinib, nilotinib and dastatinib (Torino et al., 2013). In 55 patients treated with nilotinib, thyroid function testing indicated hypothyroidism in 22%, hyperthyroidism in 33% and euthyroidism with thyroid autoimmunity in 7% of patients. Most hyperthyroid subjects became hypothyroid suggesting induction of destructive thyroiditis

by nilotinib (Kim et al., 2010). Similar results were observed during the treatment with dasatanib (Kim et al., 2010).

Additionally, some of TKI are approved for treatment of thyroid cancers (sorafenib, vandetanib, motesanib, cabozantinib). A rise in TSH in these patients, most of whom have been thyroidectomised, has been linked to altered metabolism of levothyroxine, as well as to interference with TSH action, or the pituitary or hypothalamic feedback loop (Verloop et al., 2013, Illouz et al., 2014).

The most recent guidelines on diagnosis and management of hyperthyroidism (Ross et al., 2016) recommend 6-monthly monitoring of biochemical and clinical thyroid function in patients undergoing therapy with lithium, TKI, and interferon-α and interleukin-2. Although, thyroid dysfunction is commonly associated with each of these medication, true hyperthyroidism is less obvious. In a recent large study comparing patients treated with lithium with gender and age-matched controls (Shine et al., 2015), lithium was found to increase risk of hypothyroidism but not hyperthyroidism. This was in line with a meta-analysis (McKnight et al., 2012) investigating the lithium toxicity profile. Other thyroid disorders

1.2.6 Hypothyroidism

Hypothyroidism is a common condition of thyroid hormone deficiency, which is usually readily diagnosed and treated. Overt hypothyroidism is characterised biochemically by an increased serum thyrotrophin (TSH) concentration and a low serum free thyroxine (T4) concentration, whereas subclinical hypothyroidism is defined as a normal free T4 concentration in the presence of an elevated TSH

concentration. The diagnosis of hypothyroidism relies heavily upon laboratory tests because of a lack of specificity of typical clinical manifestations. However, what constitutes "normal" TSH concentrations remains controversial as the reference range varies in different ethnic communities, during pregnancy and by age. Despite increasing evidence that the serum TSH distribution progressively shifts towards higher concentration with age (Surks and Hollowell, 2007), thus far there are few laboratories that use age-specific reference ranges.

Besides the above biochemical classification into overt and subclinical forms, hypothyroidism can also be classified on the basis of its time of onset (congenital or acquired), the nature of the underlying endocrine dysfunction (primary, originating in the thyroid gland, or secondary also called central hypothyroidism, originating in the pituitary or hypothalamus) and the mechanisms of loss of functional tissue (spontaneous and iatrogenic). In the UK, the prevalence of spontaneous hypothyroidism is between 1% and 2%. This condition is more common in older age and about ten times more likely in women than in men (Vanderpump, 2011). In the Western world, the most common aetiology is autoimmune: Hashimotos' thyroiditis caused by high concentrations of antibodies to TPO and Tg. In its severe form this may result in myxoedema coma, a life-threatening medical emergency (Roberts and Ladenson, 2004). Iatrogenic hypothyroidism accounts for the one-third of all cases of hypothyroidism in the UK. This is induced during destructive treatments for benign and cancerous thyroid disorders, malignant tumours of the head and neck and as a consequence of medical therapy with lithium, amiodarone or interferon.

The most common cause of hypothyroidism worldwide is iodine deficiency. Environmental iodine deficiency is typically found in remote mountainous regions and contributes significantly to congenital cretinism in severely deplete areas of the developing world. In many regions, severe iodine deficiency has been successfully eradicated by universal iodine supplementation programmes.

Hypothyroidism is treated by thyroid hormone replacement, usually in the form of levothyroxine. There is ongoing debate regarding the benefits of replacement with liothyronine either in combination with levothyroxine or as monotherapy. Current evidence-based guidelines recommend monotherapy with levothyroxine as the preferred treatment option (Jonklaas et al., 2014, Okosieme et al., 2015). Levothyroxine is the third most commonly dispensed drug in England, reflecting the high prevalence of hypothyroidism (Prescriptions Dispensed in the Community: England 2005-2015).

1.2.7 Thyroid nodules and thyroid cancer

Thyroid nodules represent the most common endocrine disorder worldwide (Hetzel, 1989), diagnosed by palpation in 5% of women and 1% of men (Tunbridge et al., 1977), or by using high-resolution ultrasound in 19-67% of population, with higher proportion in women or in the elderly (Tan and Gharib, 1997, Guth et al., 2009). They are often termed 'nontoxic' or 'sporadic' to differentiate from focal or diffuse enlargements associated with autonomous functioning or underlying inflammatory of autoimmune processes.

The main clinical challenge concerning thyroid nodules is to exclude any form of harboured malignancy, which can be found in 5-15% of subjects with thyroid nodules (Sherman, 2003). The most important diagnostic tool in evaluating thyroid nodules is fine needle aspiration biopsy. Detection of any metastases of thyroid cancer can be performed with a full body scintigraphy using iodine-131. The main risk factors for thyroid cancer include advancing age, female gender, history of radiation exposure and family history (Hegedus, 2004).

Thyroid carcinoma accounts for 1% of all new malignancies in the UK (Cancer Research UK, 2014). In the Western world, its incidence has been increasing over the last decades and in 2014, there were over 3,400 new cases in the UK with men-to-women ratio of 4:10 (Cancer Research UK, 2014, Leenhardt et al., 2004, Davies and Welch, 2006). There is an ongoing debate on the clinical importance of this increase. The prevailing interpretation endorsed by the ATA guidance (Haugen et al., 2016) is that the increase is mostly attributed to the technologically improved detection as most of the tumors are small (<2 cm in 87%) and mortality rates are stable (Davies and Welch, 2006).

Thyroid malignancies are divided into differentiated thyroid cancers (DTC), which includes papillary (80%) and follicular cancers (10%), medullary thyroid carcinomas (MTC; 5-10%), anaplastic carcinomas (ATC, 1-2%), and rarely diagnosed primary thyroid lymphomas and primary thyroid sarcomas (Sherman, 2003). DTCs arise from follicular cells of the thyroid. These slow growing tumors (10-20 years) are TSH sensitive, the feature used therapeutically by inhibition of TSH secretion with thyroxine to improve recurrence and survival rates following completion of treatment.

With aggressive treatment of thyroidectomy followed by radioiodine ablation, prognosis of DTC is excellent with 5 years cure rates of 98%. The 30-year cancer-related death rate of PTC is 6% and for FTC is 15% (Schlumberger, 1998). MTCs develop from the parafollicular, calcitonin producing C cells of the thyroid gland. About 75% of MTCs occur sporadically, and in 25% of cases MTC is hereditary. The overall prognosis for patients with MTC is worse than that of patients with well-differentiated carcinoma. The reported 10-year survival rate is 65%. Low stage of disease at diagnosis, young age, small tumor and early intervention are associated with improved prognosis (Leboulleux et al., 2004). ATC, although rare, is one of the most aggressive solid tumors known to affect humans and carries a poor prognosis, with a median survival of 4 to 12 months from the time of diagnosis. Due to its rapid growth, patients commonly present with associated symptoms of mechanical compression and distant metastases are found in at least a half of patients. The most common metastatic sites are the lungs, bones, and brain (Are and Shaha, 2006). According to the recent statistics, in the UK, 10-year survival for all thyroid carcinomas was 85%. In 2014, there were 376 deaths; papillary thyroid cancer was responsible for 50% of all thyroid cancer-related deaths (Cancer Research UK, 2014).

1.2.8 Non-thyroidal illness syndrome (euthyroid sick syndrome)

Non-thyroidal illness syndrome (NTIS), also called euthyroid sick syndrome (ESS), refers to the biochemical findings of low fT3 and normal or low TSH concentrations in acutely or chronically ill patients. It is seen during starvation, sepsis, surgery, myocardial infarction, cardiac bypass surgery, bone marrow transplantation, and probably in many other severe illnesses (Eber et al., 1995, Holland et al., 1991,

Vexiau et al., 1993, Lee et al., 2016). These findings may occur as a consequence of certain medications used during intensive treatment including amiodarone, glucocorticoids, radiographic contrast agents, propylthiouracil or propranolol (Economidou et al., 2011). However, the main mechanism underlying decrease in T3 concentrations in critically ill subjects is linked to starvation. Carbohydrate deprivation, associated with severe illness, inhibits deiodination of T4 to T3 by the D1 enzyme in the liver, thus decreasing serum T3 concentration (Harris et al., 1978). Starvation induces a decrease in basal metabolic rate and it is suspected that the observed reduction in thyroid hormones represents an adaptive response to conserve calories and protein by inducing some degree of hypothyroidism. Patients who have only a decrease in serum T3 without a decrease in serum T4 concentration represent the mildest form of the NTIS, which usually does not present with clinical signs of hypothyroidism and has not been associated with increased mortality. TSH usually remains normal although during the recovery phase may become raised (Maldonado et al., 1992).

Proportional to the increase of severity of illness and, probably, duration of illness, there may be progression to a more complex syndrome associated with low T3 in the presence of low T4 concentrations. Serum TSH concentration usually remains normal or low. This pattern is often found in very severely ill patients and is associated with greatly increased risks of death (Lee et al., 2016, Maldonado et al., 1992, Langouche et al., 2013). In one study the decline in T3 concentrations significantly correlated with multiple illness severity scores, such as MOF-score, APACHE II and inversely with Glasgow Coma Scale (Schilling et al., 1999).

The management of NTIS remains a matter of a debate. In 2003, de Groot argued that NTIS is a form of secondary hypothyroidism; since serum thyroid hormone concentrations are low, this may be disadvantageous to the patient, and therapy should be initiated if serum thyroxine levels are reduced below an arbitrary cut-off of 4 μg/dL (DeGroot, 2003). However, interventional studies initiating treatment either with thyroxine (Brent and Hershman, 1986) or with low or high doses of T3 (Kaptein et al., 2010) did not show significant effects on outcomes from acute illness. Recent ATA guidelines of treatment for hypothyroidism (Jonklaas et al., 2014) consider thyroid function changes in acute illness to be an adaptive responses and do not recommend institution or adjustment of thyroid replacement treatment. Thyroid function testing is, therefore, not recommended in critically ill patients unless significant underlying thyroid disease is suspected.

1.3 Main aims and objectives of the thesis

Hyperthyroidism is a common endocrine disorder, characterised by increased thyroid hormone synthesis and secretion. Whilst significant advances have been made in diagnosing and managing this condition, further research is needed to improve individual patient care and to influence public health policies.

The overall aim of this thesis is to assess the challenges in diagnosis and treatment of hyperthyroidism, both in the outpatient and inpatient real-world setting, using existing data sources. Furthermore, the long-term consequences associated with hyperthyroid patients treated in hospital as well as in the community

were explored. To achieve these aims we performed a number of epidemiological studies investigating:

- The variability of clinical manifestations of hyperthyroidism in outpatients
- The utilisation of thyroid function testing to confirm or exclude new cases of thyroid dysfunction, as well as to monitor thyroid function in those with pre-existing dysfunction in a hospital setting;
- The effectiveness of treatment of hyperthyroidism with a prolonged course of thionamides and factors predicting relapse;
- Weight changes associated with different modes of treatment for hyperthyroidism
- The characteristics of hospital stay, morbidity and mortality in patients with a history of hyperthyroidism, compared with patients with hypothyroidism, as well as those with no history of thyroid dysfunction.

To achieve our aims, two large data sets were used: the Outpatient Thyroid Clinic Database and the University Hospitals Birmingham NHS Foundation Trust Information System. The specific objectives can be grouped according to these data sources:

Utilising the Outpatient Thyroid Clinic Database:

- To determine the prevalence of symptoms and signs of hyperthyroidism according to patients' age and gender, as well as the severity and type of hyperthyroidism

- To establish the proportion of patients treated for hyperthyroidism with thionamides in an intention-to-treat analysis and to determine treatment outcomes and prognosis
- To determine the extent of weight gain following treatment of hyperthyroidism in subjects presenting with a first episode of overt hyperthyroidism
- To examine the influence of the treatment modality (131-I or ATDs), the development of hypothyroidism, and other factors on the likelihood of weight gain following treatment of hyperthyroidism

Utilising the UHB NHS FT Information System:

- To quantify thyroid function testing in hospitalised patients and to determine the prevalence of newly diagnosed TD in the hospital setting;
- To determine the rate of initiation of treatment in inpatients with newly diagnosed thyroid dysfunction;
- To establish the frequency of finding abnormal thyroid function results in hospitalised patients with pre-existing thyroid dysfunction;
- To compare mortality rates in patients with a history of hyperthyroidism to those with hypothyroidism and those with no history of thyroid dysfunction;
- To assess the differences in hospital utilisation between patients with a history of hyperthyroidism and those with hypothyroidism or with no history of thyroid dysfunction;
- To investigate whether patients diagnosed and treated for thyroid dysfunction are at higher risk of being admitted to hospital due to cardiovascular, respiratory, digestive or mental and behavioural conditions.

Chapter 2. METHODS: RESEARCH USING ROUTINELY COLLECTED DATA

2.1 Introduction

Large amounts of health-related data are collected as part of routine clinical care and operational routines by health providers, insurers and authorities. The value of these data in the analysis of population outcomes, health needs, and operation of the health care system has been long recognised (Acheson and Evans, 1964, Lawrenson et al., 1999). However, the expansion of health information technology systems offers an even greater potential than ever before to use the routinely collected data for health research and population health improvement projects (Foster et al., 2012).

Routine data are generated for the primary purpose of delivering healthcare to individuals, hence their use in research or evaluation is often termed 'secondary' (Jorm, 2015). There are some methodological differences in research based on secondary and primary data (Jorm, 2015, Thygesen and Ersboll, 2014). Use of routinely collected data offers some advantages over primary research data:

- **Population reach** – many datasets offer large sample sizes or even the whole-of-population coverage; they may be more effective in studying rare outcomes, such as selected adverse events, or orphan diseases. Researchers are

also often able to perform complex multivariable analysis due to the large sample size that such routinely collected datasets offer;

- **Longitudinal** – when linked across datasets, routinely collected data enables long-term follow up, possibly identifying causal effects;
- **Completeness of response** – avoids nonresponse, attrition and reporting bias; data is systematically recorded for individual patient benefit, which is likely to be similar across all population demographics;
- **Cost- and time-effectiveness** – additional use of an already existing resource increases return on investment lowering the overall cost of data collection;
- **Real world** – routine data often presents the only way to evaluate the outcomes of care in a real world scenario, which often differs from the highly regulated conditions of clinical trials.

However, there are also a number of limitations, which call for cautious and competent use:

- **Event based** –the collection of data is frequently event driven, such as diagnosis of a disease or death and no information is provided on the health status in-between the events or on those who did not experience such events;
- **Uncertain validity** – requires that accurate information is available and entered correctly, which often requires an additional level of training;
- **Limited data items** – records only contain a set of required information collected for primary reasons, and therefore may not fully satisfy research needs;

- **Linkage or handling error** – non-random bias may easily be introduced if data processing is handled erroneously; due to automated processing the errors may affect relevantly large numbers of data.

By their nature, the routine data collection is not under investigators' control over what and when information is sought from patients (Hripcsak and Albers, 2013). Therefore, appropriate techniques need to be undertaken in the preparation, analysis and interpretation of such data (Deeny and Steventon, 2015).

2.2 Research process using secondary data

The following thesis is based on routinely collected data. During the research process of the studies undertaken, the following elements were followed:

Step 1. Formulating the research question

Step 2. Defining the study design and identifying the databases containing appropriate data

Step 3. Research approval

Step 4. Linking the databases

Step 5. Identifying the variables of interest and the study subjects

Step 6. Extraction of data

Step 7. Data validation, cleaning and transformation

Step 8. Data analysis

Step 9. Reporting of the findings

2.2.1 Formulating the research question

The main ideas and hypothesis of the thesis are described in section 1.3.

2.2.2 Defining the study design and identifying the databases containing appropriate data

The following study designs have been used to find answers to the research questions: cross-sectional study, cohort study and nested, matched case-control study.

2.2.2.1 *Cross-sectional study*

Cross-sectional studies analyse the whole population at a defined point (Coggon et al., 2004). While classically collected data, for practical reasons, usually limits the definition of cross-section to a particular time-specific point (or short period of time) (Levin, 2006), the use of secondary data allows for associating the cross-section with an event. This design was applied in Chapter 3 of our study. The population studied was the cohort of patients with a diagnosis of hyperthyroidism; the analysed point of cross-section was the initial presentation visit to the Thyroid Clinic, which was spread out over the period of more than 20 years.

Cross-sectional studies are descriptive in nature. Many outcomes and risk factors can be assessed at the same time. As the entire population is analysed, they can be used to describe the prevalence, the odds ratios, and the absolute and relative risks (Lee, 1994, Schmidt and Kohlmann, 2008). Since they represent 'a snapshot' of the population any causal interferences can be difficult to draw (Levin, 2006).

2.2.2.2 *Cohort/ longitudinal study*

Routinely collected data is registered to monitor patients' health outcomes over time. This directly corresponds to a cohort (or prospective) study; a design in which subjects are followed over time to monitor their study outcomes. The simplest form of such an approach in classically collected data is the selection of two groups of subjects: those with and those without an attribute of interest followed by the analysis of the frequency of long-term outcomes in both groups. Utilising secondary data, the entire population can be used and categorisation into groups can be done retrospectively (Thygesen and Ersboll, 2014). The record of the characteristics at the study entry (the baseline) is the crucial element of the analysis. The variability between the groups may heavily influence the outcomes, thus the analysis needs a multivariable approach. While classically collected study data for cohort studies may be costly and unsuitable for long-term latency outcomes, the routine collection partially overcomes those issues (Woodward, 2014).

A cohort study design was used for Chapters 4, 5 and 6. In Chapter 4, the population of patients treated with thionamides for hyperthyroidism was followed for relapse; in Chapter 5 weight changes were analysed in patients with hyperthyroidism treated with different modes of treatment; in Chapter 6, a population of hospitalised inpatients was followed for thyroid function testing requests.

2.2.2.3 *Nested, matched case-control study*

A nested case-control study is a type of case-control study embedded in a previously defined and studied cohort. The cases of interest (for example patients with certain

characteristics or a specific disease) are identified from the cohort. For each case, a random selection of corresponding controls from the same cohort is assigned from those who have not developed the disease. As in any longitudinal study, it is important that the time of observing both cases and controls is comparable (Woodward, 2014). Such a design was used in Chapter 7, comparing the hospital utilisation and mortality of patients with hyperthyroidism to those with hypothyroidism or without any form of thyroid dysfunction.

To address the problem of confounding at the design stage of the study, a matching technique was applied i.e. the random pool of corresponding controls was limited by confounding variables. Such a technique of drawing controls provides a more efficient analysis by increasing precision of estimates and by reducing the standard error (Kupper et al., 1981). Additionally to the follow-up time, which is essential, (represented by the calendar year of first hospital admission), the cases and controls were matched on age and gender (description of the process in section 7.2.3). Having a broad pool of matching, we aimed at one to four matching ratio, which is considered a golden standard due to its highest efficiency as studied by Ury (1975). However, there were not enough suitable controls with hypothyroidism and for this pool of patients variable matching was applied.

The matching process has to be reflected in the analysis of the data, as the datapoints are not independent from each other. Cases and controls are more similar to each other than they would have been if independent sampling had taken place (Katz, 2011, Woodward, 2014). For that reason matched data was analysed using Generalised Estimating Equations (GEE), as described in section 7.2.6.

2.2.3 Research approval

In the UK, the collection, processing and use of data is regulated by the Data Protection Act 1998 (DPA) (Chester et al., 1999) underpinned by the European Directive on data protection 95/46/EC, which lays down basic principles and rules for the Member States of the European Union. The DPA stays in close relation with the Human Rights Act 1998 and the Freedom of Information Act 2000 (Singleton, 2005). The issue regarding the use of routinely collected data needs to balance between public and private benefits and protection. On one hand, the use of existing data resources has been identified as a national priority in many countries, England, Scotland and Wales including, on the other hand, patients' privacy needs to be protected (De Lusignan et al., 2016).

Prior to analysis, all of our data was pseudonymised. Due to the observational character of the study, the medical or social care was not affected and therefore individual consent was not sought. All our studies have been approved and registered as indicated in methods section of each chapter.

2.2.4 Identifying the variables of interest and the study subjects

A study cohort and a set of variables were defined separately for each study forming the thesis. The details of these are described within the methods section of each chapter.

2.2.5 Data sources; linking the databases

The following databases were identified as containing data pertinent for the studies: Thyroid Clinic Database, Trust-level Patient Administration System (PAS), and Prescribing, Information and Communication System (PICS), the laboratory information system - Telepath, and the information-exchange system run by the Health and Social Care Information Centre called the Spine.

2.2.5.1 *Outpatient Thyroid Clinic Database*

In the 1990s, a database supporting the collection of clinical, biochemical and demographic findings of patients seen in the Outpatient Thyroid Clinic at University Hospitals Birmingham NHS Foundation Trust was designed. The Clinic itself is a multidisciplinary, secondary/tertiary thyroid referral centre serving a diverse population, supporting mainly urban but also some rural GP practices. The population served varies in terms of ethnic origin, age and gender reflecting the West Midlands demography. Patients are referred to the Clinic in accord with current U.K. guidance, instructing that any patient with abnormal thyroid function tests indicating hyperthyroidism can expect to be referred to a specialist at diagnosis (Vanderpump et al., 1996). The services offered by the Clinic include medical, surgical and radiopharmaceutical treatment.

At presentation, all patients are evaluated by a senior clinician. The findings are recorded in a structured clinic pro-forma collecting information on presenting symptoms and signs, biochemical findings prior to the visit (for example from GP testing), co-morbidities, current medical treatment, history of endocrine disorders,

family history of thyroid dysfunction, smoking habits, and weight and height. During a follow-up visit, weight, current and prescribed treatment, biochemical findings and free-text description of changes in symptoms and signs are recorded. Pathology reports concerning thyroid procedures are also collected.

Historically, until 2012, the system was stand-alone. The clinic pro-forma was completed as a paper document, and laboratory data was sent in as a print-out form. Next, the information was transferred manually by a data clerk into a custom-made database. More recently, data for Thyroid Clinic Database is extracted from the electronic pro-forma based in PICS and merged with the data from the Telepath system and the PAS, to form the Thyroid Clinic information system.

Based on biochemical and clinical findings, patients' data is further aggregated and assigned one or more of the following diagnostic categories: (1) overt or (2) subclinical hyperthyroidism, (3) overt or (4) subclinical hypothyroidism, (5) thyroid nodules or goitre, (6) thyroid ophthalmopathy, (7) transient thyroiditis, (8) euthyroidism, or (9) other. Hyperthyroidism is further stratified into one of the three categories of underlying aetiology: Graves' disease (GD), toxic nodular hyperthyroidism and hyperthyroidism of indeterminate aetiology. GD is defined as hyperthyroidism in the presence of (1) positive titre of serum TRAb concentration or (2) of two of the following: thyroid ophthalmopathy (NOSPECS≥1), a palpable diffuse goitre, significant titre of TPO antibodies and/or thyroglobulin antibodies. Toxic nodular hyperthyroidism was defined as hyperthyroidism with a palpable nodular goitre. Subjects not fulfilling these criteria are categorised indeterminate. Until 2013 TRAb tests were not routinely performed at our Clinic, which prevented

confirmation of diagnosis in up to 50% of patients. In a recently performed internal audit analysing accuracy of the assigned aetiology coding in hyperthyroid patients seen after initiation of routine TRAb testing (in 2013), we found that 58% of patients labelled as indeterminate, using our pre-2013 criteria, were TRAb positive. This allows us to assume that our indeterminate category represent a mixed group of patients mainly with Graves' disease (60% or over), some with toxic nodular hyperthyroidism and some with both, as a clear-cut discrimination is not always possible (Okosieme et al., 2010). We cannot exclude that, despite our best efforts, a diagnosis of hyperthyroidism was made erroneously in some patients with transient thyroiditis who are likely to have been assigned to the category of indeterminate aetiology.

2.2.5.2 *Trust-level data system*

Trust data is collected and coded on one of three levels: patient, spell or episode. According to the NHS Data Model and Dictionary for England (NHS Digital, 2016), a patient is "a person with a specific disease or condition who receives treatment from a Health Care Provider"; a spell is "a continuous period of care or assessment for a patient by one or more care professionals using a hospital bed on the premises of the provider"; and an episode is "a part of a spell when patient is under care of one consultant". The episode level was not analysed in the thesis and any episode-specific data were aggregated into a spell level. For ease of reading, in research chapters (3 to 7), the technical term 'spell' was substituted with a term more commonly used in clinical setting 'hospital admission'; and the technical term 'patient' was used interchangeably either as a subject or a patient.

Health information technology systems need to be interoperable in order for data to flow seamlessly from one system to another; this is done through a Trust Integration Engine (TIE). The TIE works with Trust-level systems and data from Telepath and PAS are fed directly to PICS based on the unique hospital, spell or episode identification number. The sets of data we processed contained demographic information on patient, administrative details of each spell and episode including diagnosis and comorbidity coded according to ICD-10 classification system (WHO, 2016), details on medication prescribed during each spell and thyroid function tests performed in the Trust laboratory for the cohort of patients. Additionally, discharge notes were reviewed for those identified as newly diagnosed with thyroid dysfunction as part of a data validation measure. Mortality data was retrieved from the NHS Spine based on the unique NHS number; this process was conducted by the Trust Informatics department.

2.2.6 Extraction of data

Sets of data, defined by variables of interests and patients within a timeframe, were retrieved according to the submitted requests by the Trust Informatics department. The tables were then transferred into Microsoft Access 2010 (version 14) database where further data processing was undertaken.

2.2.7 Data validation, cleaning and transformation

For quality assurance purposes the data was checked for duplicates, missing values and inconsistency. In the process of cleansing, three main areas of errors were identified:

Human error – typing mistakes or errors resulting from the lack of actual information. Examples of such errors included 53 duplications of records registering either two different surnames or two different dates of birth. Due to the relative small numbers of errors of this type, human errors were considered insignificant for the overall quality of the dataset. Nevertheless, wherever possible, data were corrected to assure the consistency; the latest version of a record was assumed correct.

Data transfer/ data manipulation errors – errors or missing data occurring in the process of manipulation of hospital datasets and extracting the data for the purpose of the study. Examples of such errors include:

- missing data on 1,698 entries with demographic data in the "Spells and Episodes" Table, which resulted from a faulty merge of PAS with the Royal Orthopaedic Hospital database
- duplicates of test results dated on the day of the change of hospital episodes

Errors of this type might significantly affect the results of the study. Hence, all inconsistencies and duplications of this kind were resolved in communication with the Trust Informatics department.

Systematic errors – data, which is not suitable for the purpose of research. In the process of validation, a number of misused fields were identified, which were excluded from the further analyses. An example of such error included the use of "Cause of death" field; in 1,424 (5.4%) cells, the cause of death indicated 'coroner' or its derivatives, which suggested the lack of consistency required for the research purposes.

2.2.7.1 *Dealing with outliers*

There are a variety of definitions of outliers ranging from subjective "an observation dubious in the eyes of the researcher" to the very objective, precise and technical: an outlier is a data point found further then two standard deviations (SD) from the mean, while extreme outliers are those exceeding three SD (Dixon, 1950). Most parametric data, like means or standard deviations and every statistic based on these, are highly sensitive to outliers and interpretation of statistics derived from data sets that include outliers may be misleading. In addition, in the matching design with the big pool of potential matches the outliers are the most likely to be matched with the "more typical" counterparts (with the results closer to the mean). For these reasons the problem of the outliers had to be addressed in each dataset.

During the validation process, a number of outlying data points were identified defined as values exceeding three SD from the mean. Many of these outlying values represented human error and were easily fixable (for example height entered in centimetres when measurement in metres was required). Self-reported variable of weight changes prior to diagnosis of hyperthyroidism (Chapter 4) revealed excessive and not easily fixable variability in the measurement units and had to be

rejected (Anscombe, 1959). The Winsorising technique was applied to smooth the variable 'Number of Hospital Admissions' (Chapter 7), which was generated automatically, hence giving minimal chances for human error, but possibly influencing the results of matched analysis. According to the technique, outlying data were set to the closest "unsuspicious" value (Snyder, 1967, Shorack, 1996). In our study, we predefined the highest value within three SD which was seven hospital admissions. We categorised all patients with eight or more readmissions as outliers and assigned them the value seven. Such transformation was performed across the entire inpatient dataset, prior to the matching process.

2.2.8 Data analysis

P-value, defined as the probability, given that the null hypothesis is true, that the sample estimate, or a more extreme value, could have occurred by chance due to sampling variation was considered significant at the level of 0.05, which value is conventionally accepted in biomedical and social sciences (Nakagawa and Cuthill, 2007). A P-value of less than 0.001 ($P<0.001$) means that, given the null hypothesis is true, the probability of such a result occurring by chance alone is less than 0.1%.

Information on statistical techniques used for analysis of each dataset is described within the method section for each study. Statistical computation was performed using IBM SPSS Statistics versions 19-22 (previously SigmaStat software version 3.2; SPSS Science Software UK Ltd., Birmingham, UK) and Minitab (version 15-17; Coventry UK).

Chapter 3. SYMPTOMS AND SIGNS OF HYPERTHYROIDISM

3.1 Introduction

The clinical manifestations of hyperthyroidism reflect the effects of high concentrations of thyroid hormones in tissues, as well as enhanced β-adrenergic activity (Cooper, 2003, Franklyn and Boelaert, 2012). Typical symptoms include weight loss, tiredness, anxiety, tremor, palpitation and heat intolerance. Common clinical signs comprise tachycardia, the presence of a goitre or thyroid nodules and a fine tremor (Cooper, 2003, de Groot, 2015, Franklyn and Boelaert, 2012). In patients with Graves' disease, extrathyroidal manifestations associated with the autoimmune response may be present, and thyroid ophthalmopathy is most commonly observed (Bartalena and Fatourechi, 2014). In older patients, atrial fibrillation can be found in up to 20%, albeit this is unusual in those aged less than 50 years (Parmar, 2005, Weetman, 2000).

The clinical presentation of patients with hyperthyroidism varies widely, ranging from an entirely asymptomatic form to life-threatening thyroid storm (Angell et al., 2015, Devereaux and Tewelde, 2014). Atypical or subtle presentation may delay diagnosis

and initiation of treatment, potentially resulting in a worse outcome (Nordyke et al., 1988, Tibaldi et al., 1986, Trivalle et al., 1996). Although the prevalence of hyperthyroidism increases with advancing age, it is generally accepted that the diagnosis may be difficult in the elderly. They may present with fewer symptoms or signs resulting in "masked" or "apathetic" hyperthyroidism. Additionally, in this group of patients the subtle and non-specific signs are often attributed to other illnesses, effects of medication or to ageing (Harvard, 1981, Mooradian, 2008, Nordyke et al., 1988, Tibaldi et al., 1986, Trivalle et al., 1996).

Clarity regarding the effects of age on clinical manifestations of hyperthyroidism is of particular importance in view of the ageing population as well as the association of hyperthyroidism with increased morbidity and mortality and reduced quality of life (Watt et al., 2006, Brandt, 2015, Brandt et al., 2011, Dorr and Volzke, 2005). Since population screening for thyroid dysfunction is not recommended in the UK (Association of Clinical Biochemistry, 2006), the identification of specific symptom patterns indicative of hyperthyroidism in older patients is of particular importance in guiding clinicians to perform thyroid function tests.

In addition to patients' age, other factors may also influence clinical presentation of hyperthyroidism (Manji et al., 2006). It has been reported that higher thyroid hormone concentrations and longer duration of symptoms prior to treatment initiation increase the severity of clinical presentation (Motomura and Brent, 1998, Tak et al., 1993). Cigarette smoking has been associated with the induction of Graves' disease (Holm et al., 2005, Bartalena et al., 1995), Graves' ophthalmopathy (Czarnywojtek et al., 2016, Thornton et al., 2007) and development of toxic goitre

(Knudsen et al., 2002, Volzke et al., 2005). Understanding the influence of above mentioned parameters, in addition to other clinical and demographic factors on clinical manifestation of hyperthyroidism, may improve diagnosis and allow earlier therapeutic intervention.

We set out to study the presentation of 3,049 patients with overt hyperthyroidism, simultaneously analysing the effects of patients' age and gender, disease aetiology and severity, duration of symptoms, and smoking habits on clinical diagnostic features of hyperthyroidism. We also investigated whether specific symptoms and signs are more indicative for hyperthyroidism in different age groups. The results of this study were published in the Journal of Clinical Endocrinology and Metabolism (Boelaert, Torlinska et al. 2010).

3.2 Subjects and methods

For the purpose of the cross-sectional study on signs and symptoms in overt hyperthyroidism, the Outpatient Thyroid Clinic Database which records data on patients seen in the clinic was used. This study was registered and approved by the UHB NHS Foundation Trust Research and Development Directorate (South Birmingham LREC CA/2521). Data on adult subjects diagnosed with hyperthyroidism between January 1984 and September 2008 were retrieved. The diagnosis was confirmed biochemically defining overt hyperthyroidism as serum free T4 (fT4) concentration and/or free T3 (fT3) above the reference range (>22 pmol/L and >6.8 pmol/L respectively) and serum TSH concentration below normal

(<0.3 mIU/L). The severity of the ophthalmopathy was classified according to the NOSPECS score (described in section 1.2.3.1.5) into (i) absent (NOSPECS 0) (ii) mild (NOSPECS 1); (iii) moderate (NOSPECS 2-3); or (iiii) severe (NOSPECS 4-6)(Manji et al., 2006). The presence of the atrial fibrillation (AF) was confirmed on electrocardiography.

Patients were divided into quartiles according to their age at presentation: 16-32; 33-44; 45-60 and 61 years or older. The following factors were identified: gender, patient's age at diagnosis, aetiology of hyperthyroidism (as described in section 2.2.5.1), smoking status (current smoker or non-smoker, which including previous smokers), disease severity (defined as presenting serum ft4 concentration) and symptom duration (months). Furthermore, information on treatment with β-blockers or amiodarone was retrieved from clinical records documenting the use of medications at presentation.

3.2.1 Statistical analysis

The Kruskall-Wallis test was used to determine differences between continuous variables; categorical variables were analysed with the Chi square test. Multivariable binary logistic regression analyses were performed to determine the influence of patients' age, gender, disease severity, duration of symptoms, disease aetiology and smoking history on the presence of symptoms of hyperthyroidism and on the presence of signs of AF, tremor and palpable goitre. Multivariable ordinal logistic regression analysis was used to test effects of the various parameters on the severity of ophthalmopathy observed in patients with Graves' disease. Patients'

age was analysed as a continuous variable and as a categorical variable corresponding to the quartiles described. Chi square tests were used to compare the number of symptoms reported by patients in each of the various age categories. Analyses were performed considering all patients and following the exclusion of patients undergoing treatment with β-blockers or amiodarone. Statistical analyses were performed using SigmaStat software (version 3.2; SPSS Science Software UK Ltd., Birmingham, UK) and Minitab (version 15; Coventry UK).

3.3 Results

3.3.1 Characteristics of the patient population

3,049 patients were included into the study, aged between 16 and 88 years (mean 46.65 ±0.32 SE). The details of the clinical and laboratory characteristics of the study population are summarised in Table 3-1. Women comprised 79% of the cohort (N=2,398) overall. The female-to-male ratio varied with age and was highest in the youngest age group, subsequently decreasing with age. A quarter were smokers and smoking was most prevalent in those aged 33-44 years. The proportions of toxic nodular hyperthyroidism increased with advancing age and the proportions Graves' disease patients decreased. The biochemical severity of hyperthyroidism was highest in the youngest and gradually decreased in each age category. The mean duration of symptoms prior to presentation was 8 months and was

similar across age groups. Treatment with β-blockers was most common in those aged 45-60 years, while amiodarone therapy was most frequent in the oldest group of patients.

Table 3-1: Demographic, clinical and laboratory characteristics of 3,049 subjects diagnosed with overt hyperthyroidism. Patients were divided in quartiles according to age. Chi square and Kruskall-Wallis tests were performed to compare prevalences in the different age categories. N: number; NS: not significant.

	All patients N=3,049 Number (%)	Patients aged 16-32 years N=766	Patients aged 33-44 years N=772	Patients aged 45-60 years N=779	Patients aged ≥ 61 years N=732	P value
Gender						
Male	650 (21.3%)	141 (18.4%)	148 (19.2%)	166 (21.3%)	195 (26.6%)	**<0.001**
Female	2,398 (78.6%)	625 (81.6%)	624 (80.8%)	613 (78.7%)	537 (73.4%)	
Smoking history						
Current smoker	852 (27.9%)	218 (28.5%)	265 (34.3%)	231 (29.7%)	130 (17.8%)	**<0.001**
Non-smoker	2,197 (72.1%)	548 (71.5%)	507 (70.2%)	529 (67.9%)	602 (82.2%)	
Underlying aetiology of hyperthyroidism						
Graves' disease	1,189 (39.0%)	418 (54.6%)	381 (49.4%)	294 (37.7%)	96 (13.1%)	
Toxic nodular hyperthyroidism	369 (12.1%)	16 (2.1%)	39 (5.1%)	108 (13.9%)	206 (28.1%)	**<0.001**
Indeterminate aetiology	1,491 (48.9%)	332 (43.3%)	352 (45.6%)	377 (48.4%)	430 (58.7%)	
Free T4 at diagnosis (pmol/l)						
Mean (± SEM)	48.65 ± 0.45	56.56 ± 0.99	51.67 ± 0.92	45.47 ± 0.77	40.61 ± 0.76	**<0.001**
Range	22.1-150	22.1-150	22.1-150	22.1-150	22.1- 150	
Duration of symptoms (months)						
Mean (± SEM)	8.23 ± 0.17	7.90 ± 0.32	8.15 ± 0.34	8.28 ± 0.31	8.64 ± 0.37	NS
Range	1-72	1-48	1-72	1-36	1-48	
Drug treatment						
Patients taking β-blockers	711 (23.3%)	173 (22.5%)	168 (21.8%)	210 (27.0%)	160 (21.9%)	**0.05**
Patients taking amiodarone	60 (2.0%)	5 (0.7%)	7 (0.9%)	11 (1.4%)	37 (5.1%)	**<0.001**

3.3.2 Reported symptoms of hyperthyroidism; influence of demographic, clinical and laboratory characteristics on their prevalence

38.1% of patients presented without any classical symptoms of hyperthyroidism. The most common symptom reported in 60.7% of cases was weight loss (Table 3-2) but 7.2% of patients complained for their weight gain. Symptoms of heat intolerance, tremor, palpitation or anxiety were found in around 50% of subjects. Symptoms of increased bowel movement, enlarged neck and shortness of breath were reported by 20-10% of patients. In the subgroup of patients with Graves' disease, 11.4% complained of eye symptoms.

The results of further analysis, simultaneously testing the effects of patients' age, gender, disease severity, the duration of symptoms prior to presentation, the underlying aetiology of hyperthyroidism and the patients' smoking history on the likelihood of reporting symptoms of hyperthyroidism are presented in Table 3-2. Increasing age, when analysed as a continuous variable, was independently associated with reduced reporting of most of the symptoms, with the exception of weight loss and shortness of breath, which were more likely to be reported by older patients. More severe biochemical hyperthyroidism was associated with increased likelihood of the most common symptoms. However, the reporting of heat intolerance and anxiety was not associated with circulating thyroid hormone concentrations. Weight gain was less likely to be reported by subjects with higher presenting fT4 concentrations. Reporting of weight changes was significantly associated

with duration of symptoms: patients were more likely to report weight gain with shorter- and weight loss with longer duration of symptoms. Women more often presented with palpitation and neck enlargement. Complaints on weight loss were more common in men. Underlying toxic nodular aetiology was associated with a less typical presentation: weight gain was reported more often and weight loss, tremor and anxiety were less likely to be present. Smokers were more likely to report weight loss, tremor, palpitation and anxiety. Symptoms of thyroid ophthalmopathy, analysed only in patients with Graves' disease only, were significantly associated with older age of patients and longer duration of symptoms prior to diagnosis.

Because treatment with β-blockers or amiodarone may affect the presentation of hyperthyroidism (Mooradian, 2008, Nordyke et al., 1988, Tak et al., 1993), the analyses were repeated in the sub-cohort excluding subgroup treated with β-blockers (N=711) or amiodarone (N=60) at the time of presentation to our clinic (Table 3-3). The influence of age, gender, disease severity, duration of treatment and smoking on symptoms of hyperthyroidism was similar following the exclusion of these patients. Additionally, patients with underlying toxic nodular aetiology of hyperthyroidism and not treated with either β-blockers or amiodarone were less likely to present with symptoms of palpitation.

Table 3-2: Frequency of reported symptoms of hyperthyroidism. Multivariable binary logistic regression analysis was performed simultaneously analysing patients' age (continuous variable) and gender, disease severity (defined as the presenting serum fT4 concentration), duration of symptoms, underlying aetiology of hyperthyroidism and smoking history. Displayed values for each variable: adjusted odds ratios (AOR), 95% confidence intervals and P values. GD: Graves' disease

Reported symptom	Total N=3,049	Age (year)	Severity (pmol/L)	Duration of symptoms (month)	Female gender	Toxic Nodular Disease	Smoking
Weight gain	219 (7.2%)	**0.97 [0.96-0.99] P<0.001**	**0.98 [0.97-0.99] P<0.001**	**1.03 [1.01-1.05] P=0.002**	1.51 [0.94-2.41] P=NS	**2.47 [1.45-4.22] P=0.001**	0.86 [0.59-1.25] P=NS
Weight loss	1,850 (60.7%)	**1.02 [1.01-1.02] P<0.001**	**1.01 [1.01-1.02] P<0.001**	**0.97 [0.96-0.98] P<0.001**	**0.68 [0.54-0.86] P<0.001**	**0.51 [0.37-0.70] P<0.001**	**1.42 [1.16-1.75] P=0.001**
Heat intolerance	1,674 (54.9%)	**0.99 [0.98-0.99] P<0.001**	1.00 [1.00-1.00] P=NS	0.99 [0.98-1.00] P=NS	0.94 [0.77-1.16] P=NS	0.86 [0.63-1.15] P=NS	1.08 [0.89-1.30] P=NS
Tremor	1,644 (53.9%)	**0.99 [0.99-1.00] P=0.04**	**1.01 [1.00-1.01] P<0.001**	0.99 [0.98-1.00] P=NS	0.93 [0.75-1.15] P=NS	**0.66 [0.49-0.90] P=0.008**	**1.51 [1.11-1.64] P=0.002**
Palpitation	1,548 (50.8%)	**0.99 [0.99-1.00] P=0.002**	**1.00 [1.00-1.01] P=0.01**	0.99 [0.98-1.00] P=NS	**1.39 [1.13-1.70] P=0.002**	0.75 [0.56-1.01] P=NS	**1.36 [1.12-1.64] P=0.002**
Anxiety	1,249 (41.0%)	**0.99 [0.98-0.99] P<0.001**	1.00 [1.00-1.00] P=NS	1.00 [0.99-1.00] P=NS	1.11 [0.90-1.36] P=NS	**0.70 [0.51-0.96] P=0.03**	**1.20 [1.00-1.45] P=0.05**
Increased frequency of bowel movement	679 (22.3%)	0.99 [0.99-1.00] P=NS	**1.01 [1.00-1.01] P=0.003**	1.00 [0.99-1.01] P=NS	0.98 [0.77-1.28] P=NS	0.70 [0.49-1.02] P=NS	1.10 [0.89-1.36] P=NS
Neck enlargement	664 (21.8%)	**0.97 [0.97-0.98] P<0.001**	**1.01 [1.00-1.01] P=0.001**	1.00 [0.99-1.01] P=NS	**1.75 [1.34-2.29] P<0.001**		0.95 [0.76-1.18] P=NS
Shortness of breath	320 (10.5%)	**1.02 [1.01-1.03] P<0.001**	**1.01 [1.00-1.01] P=0.001**	0.99 [0.97-1.01] P=NS	1.28 [0.91-1.80] P=NS	0.73 [0.45-1.18] P=NS	0.96 [0.71-1.30] P=NS
Eye symptoms (GD subjects N=1,189)	136 (11.4%)	**1.02 [1.01-1.04] P=0.001**	1.00 [0.99-1.01] P=NS	**1.03 [1.01-1.06] P=0.005**	0.93 [0.56-1.55] P=NS		1.24 [0.83-1.86] P=NS

Table 3-3: Frequency of reported symptoms of hyperthyroidism in patients not treated with β-blockers or amiodarone prior to presentation. Multivariable binary logistic regression analysis was performed simultaneously analysing patients' age (continuous variable) and gender, disease severity (defined as the presenting serum fT4 concentration), duration of symptoms, underlying aetiology of hyperthyroidism and smoking history. Displayed values for each variable: adjusted odds ratios (AOR), 95% confidence intervals and P values. GD: Graves' disease

	Total N=2,289	Age (year)	Severity (pmol/L)	Duration of symptoms (month)	Female gender	Toxic Nodular Disease	Smoking
Weight gain	178 (7.8%)	**0.98 [0.96-0.99] P<0.001**	**0.98 [0.97-0.99] P<0.001**	**1.02 [1.00-1.04] P=0.02**	1.39 [0.84-2.31] P=NS	**2.05 [1.13-3.70] P=0.02**	0.89 [0.59-1.35] P=NS
Weight loss	1,340 (58.5%)	**1.02 [1.01-1.03] P<0.001**	**1.02 [1.01-1.02] P<0.001**	**0.97 [0.96-0.98] P<0.001**	**0.68 [0.52-0.90] P=0.007**	**0.56 [0.39-0.81] P=0.002**	**1.30 [1.02-1.65] P=0.03**
Heat intolerance	1,248 (54.5%)	**0.99 [0.98-1.00] P=0.001**	1.00 [1.00-1.01] P=NS	0.99 [0.98-1.00] P=NS	0.96 [0.75-1.23] P=NS	0.80 [0.56-1.13] P=NS	1.12 [0.89-1.40] P=NS
Tremor	1,203 (52.6%)	1.00 [0.99-1.00] P=NS	**1.01 [1.01-1.02] P<0.001**	0.99 [0.98-1.01] P=NS	0.93 [0.73-1.20] P=NS	**0.63 [0.44-0.89] P=0.01**	**1.54 [1.22-1.93] P<0.001**
Palpitation	1,101 (48.1%)	0.99 [0.99-1.00] P=NS	1.00 [1.00-1.01] P=NS	0.99 [0.98-1.01] P=NS	**1.45 [1.14-1.84] P=0.003**	**0.67 [0.47-0.95] P=0.02**	**1.26 [1.01-1.57] P=0.04**
Anxiety	921 (40.2%)	**0.99 [0.98-1.00] P=0.001**	1.00 [1.00-1.01] P=NS	1.00 [0.99-1.01] P=NS	1.03 [0.80-1.31] P=NS	**0.63 [0.44-0.91] P=0.01**	1.07 [0.86-1.33] P=NS
Increased frequency of bowel movement	497 (21.7%)	0.99 [0.99-1.00] P=NS	**1.01 [1.00-1.01] P=0.002**	1.00 [0.98-1.01] P=NS	0.95 [0.72-1.25] P=NS	0.80 [0.53-1.22] P=NS	1.03 [0.80-1.33] P=NS
Neck enlargement	485 (21.9%)	**0.98 [0.97-0.98] P<0.001**	**1.01 [1.00-1.01] P=0.008**	1.00 [0.98-1.01] P=NS	**1.71 [1.24-2.36] P=0.001**		0.82 [0.63-1.07] P=NS
Shortness of breath	231 (10.1%)	**1.02 [1.01-1.03] P<0.001**	1.01 [1.00-1.01] P=NS	0.99 [0.97-1.01] P=NS	1.07 [0.72-1.58] P=NS	0.84 [0.49-1.44] P=NS	0.92 [0.64-1.32] P=NS
Eye symptoms (GD subjects N=877)	100 (11.4%)	**1.02 [1.01-1.04] P=0.004**	1.00 [0.99-1.01] P=NS	**1.03 [1.01-1.06] P=0.02**	1.00 [0.54-1.82] P=NS		0.84 [0.51-1.37] P=NS

3.3.3 Frequency of symptoms according to age

Figure 3-1 represents the prevalence of individual symptoms within the different age categories. The majority of symptoms were reported more frequently with advancing age up to 60 years, followed by a decline in symptom prevalence in patients aged 61 years or older. The likelihood of shortness of breath increased and that of neck enlargement decreased steadily across age categories.

A binary logistic regression analysis, to identify associations between the prevalence of symptoms and age analysed as a categorical variable, was performed. This indicated significant increases in most classical symptoms in those aged 45 to 60 years compared with the youngest subjects, except for weight gain and neck enlargement. In contrast the prevalence of most classical symptoms was reduced in those aged more than 61 years except for weight loss and shortness of breath (Table 3-4). A sensitivity analysis excluding those treated with β-blockers or amiodarone prior to presentation confirmed similar patterns (Table 3-5).

Next we evaluated the number of reported symptoms in different age groups (Figure 3-2). The highest proportions of patients with few symptoms (0/1/2 symptoms) was found in those aged 61 years or older (54.4%, P<0.001) compared with those aged 16-32 years (35.6%), 33-44 years (32.4%) and 45-60 years (29.8%). Similarly the lowest proportion of patients reporting five or more symptoms was found in the patients aged more than 61 years (14.8%, P<0.001) whereas these proportions were similar in younger patients (28.3% [16-32 years], 34.9% [33-44] and 33.9% [45-60], P=NS). When this analysis was repeated excluding those patients receiving

treatment with β-blockers or amiodarone similar patterns of symptom frequencies were evident, with the highest proportion of patients reporting few symptoms evident amongst those aged 61 years or older.

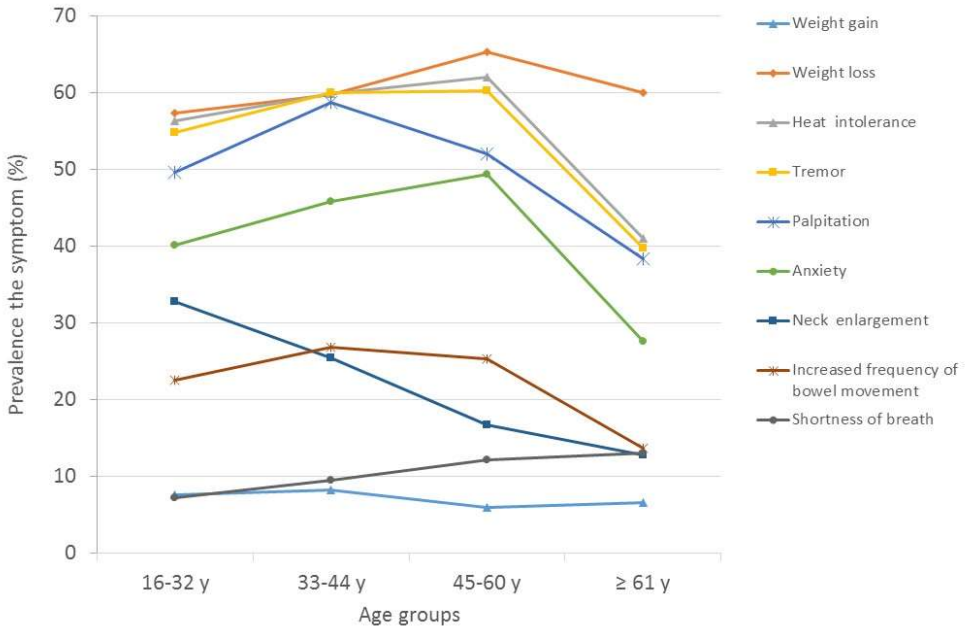

Figure 3-1: Prevalence of symptoms in the age categories; y- year.

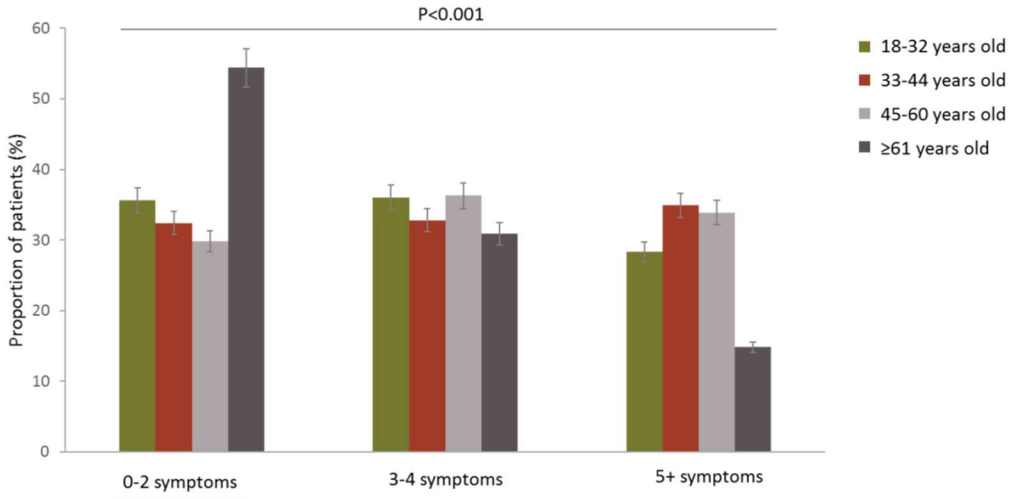

Figure 3-2 Number of reported symptoms according to age groups. Patients aged 61 years or older significantly more often reported fewer symptoms of hyperthyroidism.

Table 3-4: Prevalence of reported symptoms according to age in patients presenting with hyperthyroidism. Binary logistic regression analysis was performed simultaneously analysing patients' age (categorical variable) and gender, smoking history, severity of hyperthyroidism (defined by the presenting serum fT4 concentration), duration of symptoms and underlying aetiology of hyperthyroidism. AOR- adjusted odds ratios, 95%CI- 95% confidence intervals, N- number, y- year.

Reported symptom	16-32 y N=766	AOR	33-44 y N=772	AOR [95%CI] P value	45-60 y N=779	AOR [95%CI] P value	≥61 y N=732	AOR [95%CI] P value
Weight gain	58 (7.6%)	1.00	64 (8.3%)	0.85 [0.55-1.30] P=NS	49 (6.0%)	**0.50 [0.31-0.80] P=0.004**	48 (6.6%)	**0.38 [0.22-0.64] P<0.001**
Weight loss	440 (57.4%)	1.00	462 (59.8%)	1.26 [0.98-1.62] P=NS	509 (65.3%)	**1.82 [1.40-2.37] P<0.001**	439 (60.0%)	**1.73 [1.30-2.30] P<0.001**
Heat intolerance	432 (56.4%)	1.00	459 (59.9%)	1.15 [0.90-1.45] P=NS	483 (62.0%)	**1.29 [1.01-1.65] P=0.04**	300 (41.0%)	**0.56 [0.43-0.73] P<0.001**
Tremor	420 (54.8%)	1.00	463 (60.0%)	**1.34 [1.05-1.71] P=0.02**	470 (60.3%)	**1.46 [1.14-1.88] P=0.003**	291 (39.8%)	**0.74 [0.56-0.96] P=0.02**
Palpitation	381 (49.7%)	1.00	453 (58.7%)	**1.60 [1.27-2.03] P<0.001**	433 (52.1%)	**1.43 [1.12-1.81] P=0.004**	281 (38.4%)	**0.75 [0.58-0.98] P=0.03**
Anxiety	308 (40.2%)	1.00	354 (45.9%)	1.22 [0.97-1.54] P=NS	385 (49.4%)	**1.34 [1.06-1.70] P=0.02**	202 (27.6%)	**0.55 [0.42-0.72] P<0.001**
Neck enlargement	251 (32.8%)	1.00	197 (25.5%)	**0.67 [0.52-0.86] P=0.002**	122 (16.7%)	**0.37 [0.28-0.49] P<0.001**	94 (12.8%)	**0.33 [0.21-0.45] P<0.001**
Increased frequency of bowel movement	173 (22.6%)	1.00	208 (26.9%)	**1.33 [1.03-1.73] P=0.03**	188 (25.4%)	1.27 [0.97-1.66] P=NS	100 (13.7%)	**0.71 [0.51-0.98] P=0.03**
Shortness of breath	56 (7.3%)	1.00	73 (9.5%)	1.49 [0.99-2.23] P=NS	92 (12.2%)	**1.91 [1.27-2.87] P=0.002**	96 (13.1%)	**2.50 [1.62-3.87] P<0.001**
Eye symptoms in patients with GD subjects (N=1,189)	36/418 (8.6%)	1.00	44/381 (11.6%)	**1.85 [1.08-3.15] P=0.03**	45/294 (15.3%)	**2.68 [1.55-4.61] P<0.001**	11/96 (11.5%)	1.89 [0.85-4.18] P=NS

Table 3-5: Prevalence of reported symptoms according to age in patients presenting with hyperthyroidism in the sub-cohort excluding those treated with β-blockers or amiodarone prior to presentation. Binary logistic regression analysis was performed simultaneously analysing patients' age (categorical variable) and gender, smoking history, severity of hyperthyroidism (defined by the presenting serum fT4 concentration), duration of symptoms and underlying aetiology of hyperthyroidism. Adjusted odds ratios and 95% confidence intervals are displayed; N-number, y-year.

Reported symptom	16-32 y N=590	AOR	33-44 y N=598	AOR [95%CI] P value	45-60 y N=562	AOR [95%CI] P value	≥61 y N=539	AOR [95%CI] P value
Weight gain	51 (8.6%)	1.00	51 (8.5%)	0.73 [0.46-1.17] P=NS	39 (6.9%)	**0.48 [0.29-0.81] P=0.006**	37 (6.9%)	**0.40 [0.22-0.71] P=0.002**
Weight loss	319 (54.1%)	1.00	341 (57.0%)	1.30 [0.98-1.73] P=NS	362 (64.4%)	**2.02 [1.50-2.74] P<0.001**	318 (59.0%)	**1.88 [1.36-2.61] P<0.001**
Heat intolerance	324 (54.9%)	1.00	346 (57.9%)	1.15 [0.87-1.51] P=NS	355 (63.2%)	**1.44 [1.08-1.92] P=0.01**	223 (41.4%)	**0.61 [0.45-0.83] P=0.002**
Tremor	309 (52.4%)	1.00	350 (58.5%)	**1.42 [1.07-1.87] P=0.02**	339 (60.3%)	**1.59 [1.19-2.12] P=0.002**	205 (38.0%)	0.74 [0.54-1.01] P=NS
Palpitation	264 (44.8%)	1.00	341 (57.0%)	**1.90 [1.45-2.50] P<0.001**	298 (53.0%)	**1.52 [1.15-2.00] P=0.003**	198 (36.7%)	0.86 [0.63-1.17] P=NS
Anxiety	241 (40.9%)	1.00	263 (44.0%)	1.08 [0.83-1.41] P=NS	277 (49.3%)	1.27 [0.96-1.68] P=NS	140 (26.0%)	**0.51 [0.37-0.70] P<0.001**
Neck enlargement	176 (29.8%)	1.00	144 (24.1%)	**0.72 [0.54-0.97] P=0.03**	94 (16.7%)	**0.47 [0.34-0.66] P<0.001**	71 (13.2%)	**0.38 [0.27-0.55] P<0.001**
Increased frequency of bowel movement	128 (21.7%)	1.00	157 (26.3%)	**1.37 [1.02-1.86] P=0.04**	140 (24.9%)	1.32 [0.96-1.81] P=NS	72 (13.4%)	0.70 [0.48-1.03] P=NS
Shortness of breath	37 (6.3%)	1.00	50 (8.4%)	1.55 [0.95-2.52] P=NS	62 (11.0%)	**1.83 [1.12-3.01] P=0.02**	82 (15.2%)	**3.19 [1.93-5.28] P<0.001**
Eye symptoms (GD subjects N=877)	27/309 (8.7%)	1.00	30/291 (10.3%)	1.67 [0.89-3.14] P=NS	34/200 (17%)	**3.26 [1.72-6.18] P<0.001**	9/77 (11.7%)	1.91 [0.77-4.70] P=NS

3.3.4 Influence of demographic, clinical and laboratory parameters on clinical signs of hyperthyroidism

70% of patients with hyperthyroidism presented with palpable goitre (Table 3-6). Thyroid enlargement was found less frequently in older subjects and more commonly in patients with more severe hyperthyroidism, in those with longer duration of symptoms, in females and in smokers. The presence of a fine tremor was documented in 42% of patients overall and this was more likely in those with more severe disease, smokers and patients with shorter symptom duration. The mean pulse rate was 84.4 beats per minute (bpm) and was higher in younger patients on average. AF was found in 4.1% of subjects and was more prevalent in older patients, those with more severe thyrotoxicosis, men and in the presence of toxic nodular hyperthyroidism.

Similar proportions of clinical signs were documented in the sub-cohort excluding those on treatment with β-blockers or amiodarone (Table 3-7). Increasing age and disease severity were significantly associated with the finding of AF. Details of the independent associations identified in the sensitivity analysis are presented in Table 3-7.

3.3.5 Effect of age on clinical signs of hyperthyroidism

In the analysis of age as a categorical variable (Table 3-8), subjects aged 45-60 years and those 61 years or older had a strikingly increased likelihood of presenting with AF

compared with the younger patients (16-32 y). Although the likelihood of presence of a fine tremor was significantly decreased in those 33-44 years old when compared to the youngest group, there was no significant difference compared to older age groups. The presence of a palpable goitre was significantly reduced in older patients: three-fold in those aged 45-60 and five-fold in those 61 year or older. Graves' ophthalmopathy was more likely to be found in older subjects aged 45-60 years and in those over 61 years when compared with younger ones. Results of the sensitivity analysis following exclusion of those treated with β-blockers or amiodarone, confirmed similar results (Table 3-9).

Table 3-6: Frequency of clinical signs of hyperthyroidism and multivariable binary logistic regression analysing simultaneously patients' age (continuous variable) and gender, disease severity (defined as the presenting serum fT4 concentration), duration of symptoms, underlying aetiology of hyperthyroidism and smoking history. Displayed values for each variable: adjusted odds ratios (AOR), 95% confidence intervals and P values. GD: Graves' disease

Clinical sign at presentation	Total N=3,049	Age (year)	Severity (pmol/L)	Duration of symptoms (month)	Female gender	Toxic Nodular Disease	Smoking
Atrial fibrillation	125 (4.1%)	**1.08 [1.06-1.10] P<0.001**	**1.01 [1.00-1.02] P=0.03**	1.00 [0.97-1.03] P=NS	**0.59 [0.36-0.96] P=0.03**	**3.12 [1.26-7.79] P=0.02**	0.57 [0.29-1.12] P=NS
Tremor	1,275 (41.8%)	1.00 [0.99-1.00] P=NS	**1.01 [1.01-1.01] P<0.001**	**0.99 [0.98-1.00] P=0.05**	0.87 [0.71-1.07] P=NS	0.76 [0.56-1.03] P=NS	**1.24 [1.03-1.49] P=0.02**
Palpable goitre	2,115 (69.4%)	**0.96 [0.96-0.97] P<0.001**	**1.01 [1.01-1.02] P<0.001**	**1.01 [1.00-1.03] P=0.05**	**2.05 [1.63-2.58] P<0.001**		**1.30 [1.04-1.63] P=0.02**
Ophthalmopathy in patients with GD (N=1,189)							
Mild TED (NOSPECS 0-1)	682 (57.4%)	**1.02 [1.01-1.03] P=0.001**	1.00 [1.00-1.01] P=NS	**1.02 [1.00-1.03] P=0.05**	**1.47 [1.04-2.07] P=0.04**		**1.46 [1.12-1.92] P=0.006**
Moderate TED (NOSPECS 2-3)	484 (40.7%)						
Severe TED (NOSPECS ≥ 4)	23 (1.9%)						

Table 3-7: Frequency of clinical signs of hyperthyroidism in sub-cohort of patients without β-blocker or amiodarone treatment and multivariable binary logistic regression analysing simultaneously patients' age (continuous variable) and gender, disease severity (defined as the presenting serum fT4 concentration), duration of symptoms, underlying aetiology of hyperthyroidism and smoking history. Displayed values for each variable: adjusted odds ratios (AOR), 95% confidence intervals and P values. GD: Graves' disease

Clinical sign at presentation	Total N=2289	Age (year)	Severity (pmol/L)	Duration of symptoms (month)	Female gender	Toxic Nodular Disease	Smoking
Atrial Fibrillation	83 (3.6%)	**1.10 [1.07-1.12] P<0.001**	**1.02 [1.00-1.03] P=0.02**	1.01 [0.98-1.04] P=NS	0.69 [0.36-1.31] P=NS	1.76 [0.61-5.01] P=NS	0.56 [0.24-1.29] P=NS
Tremor	977 (42.6%)	1.00 [0.99-1.01] P=NS	**1.01 [1.01-1.02] P<0.001**	0.99 [0.98-1.00] P=NS	0.84 [0.65-1.07] P=NS	0.71 [0.50-1.01] P=NS	**1.33 [1.07-1.66] P=0.01**
Palpable goitre	1,597 (69.8%)	**0.96 [0.96-0.97] P<0.001**	**1.02 [1.01-1.02] P<0.001**	1.01 [1.00-1.02] P=NS	**1.85 [1.41-2.42] P<0.001**		1.10 [0.85-1.47] P=NS
Ophthalmopathy in patients with GD (N=877)		**1.02**	1.01	1.01	**1.61**		1.01
Mild (NOSPECS 0-1)	512 (58.4%)	**[1.01-1.03]**	[1.00-1.01]	[0.99-1.03]	**[1.06-2.44]**		[1.00-1.01] P=NS
Moderate (NOSPECS 2-3)	347 (39.6%)	**P=0.003**	P=NS	P=NS	**P=0.03**		
Severe (NOSPECS ≥ 4)	18 (2.1%)						

Table 3-8: Clinical signs of hyperthyroidism at presentation according to age. Logistic regression analysis was performed simultaneously analysing patients' age and gender, smoking history, severity of hyperthyroidism, duration of symptoms and underlying aetiology of hyperthyroidism. AOR- Adjusted Odds Ratios 95%CI – 95% Confidence Intervals, GD- Graves' Disease, y- years.

Clinical sign at presentation	**16-32y N=766**	**AOR**	**33-44y N=772**	**AOR [95%CI] P value**	**45-60y N=779**	**AOR [95%CI] P value**	**≥ 61y N=732**	**AOR [95%CI] P value**
Atrial fibrillation	1 (0.1%)	1.00	6 (0.8%)	6.17 [0.74-51.61] P=NS	23 (3.0%)	**11.70 [1.51-90.49] P=0.02**	95 (13.0%)	**64.77 [8.78-477.6] P<0.001**
Tremor	365 (47.7%)	1.00	309(40.0%)	**0.74 [0.58-0.93] P=0.01**	321 (41.2%)	0.81 [0.64-1.03] P=NS	280 (38.3%)	0.82 [0.63 -1.08] P=NS
Palpable goitre	645 (84.2%)	1.00	625 (80.9%)	0.87 [0.63-1.21] P=NS	505 (64.8%)	**0.35 [0.26-0.47] P<0.001**	340 (46.4%)	**0.19 [0.14-0.25] P<0.001**
Ophthalmopathy in patients with GD (N=1189)	**N=418**		**N=381**		**N=294**		**N=96**	
None (NOSPECS 0)	179 (42.8%)	1.00	151 (39.6%)	1.26 [0.91-1.74] P=NS	91 (31.0%)	**1.80 [1.26-2.56] P=0.001**	24 (25.0%)	**1.78 [1.06-2.99] P=0.03**
Mild (NOSPECS 1)	84 (20.1%)		72 (18.9%)		58 (19.7%)		23 (24.0%)	
Moderate (NOSPECS 2-3)	149 (35.7%)		152 (39.9%)		139 (47.3%)		44 (45.8%)	
Severe (NOSPECS ≥ 4)	6 (1.4%)		6 (1.6%)		5 (2.0%)		5 (5.2%)	

Table 3-9: Clinical signs of hyperthyroidism at presentation according to age excluding patients receiving treatment with β-blockers or amiodarone. Logistic regression analysis was performed simultaneously analysing patients' age and gender, smoking history, severity of hyperthyroidism, duration of symptoms and underlying aetiology of hyperthyroidism

AOR- Adjusted Odds Ratios 95%CI – 95% Confidence Intervals, GD- Graves' Disease, y- years.

Clinical sign at presentation	16-32 y N=590	AOR	33-44 y N=598	AOR [95%CI] P value	45-60 y N=562	AOR [95%CI] P value	≥ 61 y N=539	AOR [95%CI] P value
Atrial fibrillation	1 (0.2%)	1.00	3 (0.5%)	3.12 [0.32-30.22] P=NS	11 (2.0%)	5.28 [0.61-45.97] P=NS	68 (12.6%)	**63.11 [8.38-475.19] P<0.001**
Tremor	274 (46.4%)	1.00	247 (41.3%)	0.78 [0.59-1.02] P=NS	243 (43.2%)	0.88 [0.66-1.17] P=NS	213 (39.5%)	0.91 [0.67 -1.25] P=NS
Palpable Goitre	491 (83.2%)	1.00	484 (80.9%)	0.99 [0.69-1.44] P=NS	361 (64.2%)	**0.37 [0.27-0.52] P<0.001**	261 (48.4%)	**0.22 [0.16-0.31] P<0.001**
Ophthalmopathy in patients with GD (N=1,189)	**N=309**		**N=291**		**N=200**		**N=77**	
None (NOSPECS 0)	141 (45.6%)	1.00	117 (40.2%)	1.32 [0.90-1.92]	63 (31.5%)	**1.87 [1.22-2.87]**	20 (26.0 %)	1.62 [0.89-2.94]
Mild (NOSPECS 1)	57 (18.5%)		57 (19.6%)	P=NS	37 (18.5%)	**P=0.004**	20 (26.0%)	P=NS
Moderate (NOSPECS 2-3)	106 (34.3%)		113 (38.8%)		95 (47.5%)		33 (42.8%)	
Severe (NOSPECS ≥ 4)	5 (1.6%)		4/291 (1.4%)		5 (2.5%)		4 (5.2%)	

3.4 Discussion

To our best knowledge, this is the first large study to evaluate the influence of age and other clinical, demographic and laboratory parameters on presenting symptoms and signs in patients with overt hyperthyroidism. Our findings indicate that more than half of subjects aged over 61 years presented with entirely, or nearly, asymptomatic forms of hyperthyroidism, while this proportion in younger patients was significantly lower. The prevalence of most symptoms was significantly lower in older patients except for weight loss, which was similar to that of younger patients and shortness of breath, which increased with age. More severe hyperthyroidism and current smoking habits were significantly associated with increased likelihoods of the majority of symptoms. Gender, aetiology of hyperthyroidism and symptom duration prior to diagnosis affected the prevalence of only a minority of symptoms. AF was more commonly found in older patients as well as in those presenting with more severe hyperthyroidism, in males and in subjects with toxic nodular hyperthyroidism. Signs of thyroid ophthalmopathy were more likely to be present in older patients, in those with longer disease duration, in current smokers and in females.

3.4.1 Age and aetiology of hyperthyroidism

Similarly to other studies (Reinwein et al., 1988, Siegel and Lee, 1998), our analysis confirms an increased prevalence of toxic nodular hyperthyroidism in older patients. We also report an association between advancing age and less severe Graves'

hyperthyroidism, which is in accord with other studies from our centre (Manji et al., 2006) as well as others (Aizawa et al., 1989, Kawabe et al., 1979). We confirmed that older patients presented with significantly lower serum fT4 concentrations at diagnosis and the proportion of patients with well-defined Graves' disease according to immunological and clinical criteria decreased with age. The mechanisms behind decreased severity of Graves' presentation among the elderly still need to be elucidated. One of proposed explanations suggested that changes in thyroid hormone economy observed in older subjects including reduced production of thyroid hormones (Bar-Andziak et al., 2012, Clark et al., 2012) may be responsible. Additionally, in older subjects, various age-related forms of thyroid hormone resistance which may alter responses at the tissue level have been proposed (Mooradian, 2008).

Despite the observed reduced severity of presentation of Graves' disease our data revealed an increased severity of thyroid ophthalmopathy in older patients, thus confirming the findings of previous studies (Ben Simon et al., 2015, Lin et al., 2008). Lin et al. established a correlation between the advancing age and severity of Graves' ophthalmopathy score in 210 patients, which was independent from serum TRAb concentrations. Another study analysing the prevalence of symptoms and signs of Graves' ophthalmopathy at diagnosis concluded that younger patients (<40 years old) presented with milder eye problems than patients in the older group, including lower rates of restrictive myopathy and optic neuropathy, despite increased rates of lid retraction and proptosis (Ben Simon et al., 2015).

3.4.2 Classical symptoms of hyperthyroidism

Apathetic or atypical presentation of hyperthyroidism among the elderly has been reported in previous smaller studies and anecdotal reports (Bhattacharyya and Wiles, 1999, Tibaldi et al., 1986, Trivalle et al., 1996). Nordyke et al. (1988) demonstrated little variability in presentation of hyperthyroidism with age until the fifth decade of life after which the prevalence of symptoms gradually started to decrease. The only findings that increased in subjects older than fifty years were weight loss and AF. Our data confirm an increased likelihood of weight loss in patients aged 45 to 60 years old when compared to the youngest group. The prevalence of weight loss in all other age groups, however, was similar. Additionally, we have identified shortness of breath as a symptom increasingly reported with advancing age. These findings were also present in a sensitivity analysis following exclusion of those undergoing treatment with β-blockers or amiodarone and thus more likely to represent patients with co-existing cardiovascular diseases, which might have influenced the symptom of shortness of breath. Importantly our findings indicate associations between advancing age and symptoms of hyperthyroidism independent of disease severity and underlying disease aetiology, factors not accounted for in the above mentioned study (Nordyke et al., 1988).

Our data confirm an increased proportion of entirely, or nearly, asymptomatic hyperthyroidism in patients aged over 61 years, which was found in more than a half of those in this age category and in about 30% in all younger age groups. Whether those patients will benefit from the initiation of treatment remains an open question. However, the evidence associating a significant increase of morbidity and mortality

even with mild or subclinical hyperthyroidism supports the need to promptly diagnose and treat even asymptomatic forms of hyperthyroidism to prevent long-term consequences (Boelaert et al., 2013, Brandt et al., 2013a, van de Ven et al., 2014, Grossman et al., 2016).

3.4.3 Other factors influencing the presentation of hyperthyroidism

Our data from a large cohort of subjects confirm significant relationships between presenting serum free T4 concentration and the presence of a variety of symptoms of hyperthyroidism. These associations were independent of the underlying disease aetiology, patients' age or gender. Our findings are in line with several other studies evaluating the effect of severity of hyperthyroidism on symptoms (Goichot et al., 2016, Motomura and Brent, 1998, Tak et al., 1993).

Our study indicates an overall prevalence of AF in 4.1% of subjects, with the highest rates found in those aged over 61 years (present in 13% of patients in this age category). This is at the lower range of results from other studies of patients with hyperthyroidism, these reporting the presence of AF in 5-20% (Shimizu et al., 2002), and indicating a gradual increase in prevalence with advancing age (Frost et al., 2004). Furthermore, we demonstrated that age is independently associated with an increased likelihood of AF and other independent risk factors were male gender and higher serum free T4 concentrations at presentation. Other studies, including previous reports from our centre (Gammage et al., 2007) and the Danish National Registry study (Frost et al., 2004) confirmed similar findings. Additionally, it has been reported that the risk of arrhythmias is higher in those with toxic nodular

hyperthyroidism when compared with patients with Graves' disease (Vitti et al., 1997). Our study confirmed a three-fold increase in the risk of AF in those with an underlying diagnosis of toxic nodular hyperthyroidism when compared to patients with Graves' disease.

Smoking has been associated with development of Graves' disease (Holm et al., 2005, Vestergaard, 2002) and toxic nodular hyperthyroidism (Knudsen et al., 1999, Volzke et al., 2005). However, the effects of smoking on presentation of hyperthyroidism have not been thoroughly studied. We now show that hyperthyroid patients who smoke are more likely to present with weight loss, tremor, palpitation and anxiety. In keeping with studies suggesting a goitrogenic role for smoking (Ericsson and Lindgarde, 1991, Hegedus et al., 1985), we found an increased frequency of a palpable goitre in current smokers.

3.4.4 Strengths and limitation of the study

The main strength of our study is a large cohort of patients diagnosed with hyperthyroidism in a uniform clinical setting with consistent evaluation of these subjects and the use of standardised reporting procedures. However, we acknowledge the following main shortcomings of our study: (i) presence or absence of goitre was assessed clinically without confirmation of ultrasonography or thyroid scintigraphy, which were not routinely performed, (ii) the underlying disease aetiology was not determined in a large proportion (50%) of subjects. This group of subjects with "indeterminate" aetiology comprised patients with both Graves' disease and toxic nodular hyperthyroidism, although most subjects will have had Graves' disease

reflecting the prevalence of these conditions in England (Tunbridge et al., 1977, Vanderpump et al., 1995).

3.4.5 Conclusions

Hyperthyroidism has been associated with significant long term consequences on various organ systems, especially the cardiovascular system, as well as with increased mortality (Brandt et al., 2011, Singh et al., 2008, Yang et al., 2012). Due to the non-specific symptomatology of hyperthyroidism in some patients, thyroid function testing is required for accurate diagnosis. Population-based screening, however, is not advised by professional guidelines (Association of Clinical Biochemistry, 2006, Bahn et al., 2011, Baloch et al., 2003, Ross et al., 2016). Hence, further clarification of what constitutes 'a suspicious picture' of hyperthyroidism is important for accurate diagnosis and to prompt treatment initiation.

Our data now provide strong evidence that clinicians should have a low threshold for performing thyroid function tests in patients aged over 60 years, especially in those with AF, as well as weight loss and shortness of breath, even in the absence of other significant symptoms.

Chapter 4. OUTCOMES AND LONG-TERM PROGNOSIS OF THIONAMIDE THERAPY FOR HYPERTHYROIDISM

4.1 Introduction

The thionamide antithyroid drugs (ATD), such as carbimazole (CMZ) and propylthiouracil (PTU), have been in clinical use since the 1940s (Cooper, 2005). Next to radioiodine and total thyroidectomy, they remain the key means for management of hyperthyroidism. The latest survey on patterns of treatment of hyperthyroidism (Burch et al., 2012) revealed that ATD therapy is the most popular initial choice of management in Europe, Latin America and Japan. Although in the USA radioiodine is still the most preferred option, the proportion of clinicians initiating a course of thionamides is increasing reflecting many clinical and practical advantages (Brito et al., 2016).

Medical treatment is a suitable option for patients with Graves' disease. Thionamides inhibit the synthesis of thyroid hormones through blocking the action of the enzyme thyroid peroxidase in thyroid cells and hence thyroid hormone synthesis. They help to achieve and maintain a euthyroid state in hyperthyroid patients but do not cure the autoimmune process itself. Hence, those rendered euthyroid by ATD are at high risk of relapse. However, since rates of remission following ATD therapy

are significantly higher than spontaneous remissions we can speculate that these agents may have additional beneficial effects on the dysregulated immune system resulting in long-term remission in certain patients (Laurberg, 2006).

Clinicians have long sought to identify clinical and laboratory predictors to improve the selection of patients likely to be cured following thionamide therapy to increase the efficacy of this intervention. Previous studies identified the factors associated with relapse or poor prognosis as young age (Winsa et al., 1990), male gender (Allahabadia et al., 2000, Magri et al., 2016), large goitre (Allahabadia et al., 2000, Nedrebo et al., 2002), high circulating thyroid hormone concentrations at presentation (Mastorakos et al., 2003, Orunesu et al., 2004), cigarette smoking (Orunesu et al., 2004, Kimball et al., 2002) and thyroid receptor antibody (TRAb) concentrations at diagnosis and at discharge (Cappelli et al., 2007, Dauksiene et al., 2013, Tun et al., 2016).

In 2000, a study analysing outcomes of medical treatment in our clinic was published (Allahabadia et al., 2000). The cohort comprised 536 subjects with Graves' disease who presented between 1975 and 1998. It was identified that men and younger patients are at higher risk of relapse and the use of definitive treatment in these patients soon after presentation was advocated.

In this chapter, we set out to investigate the outcomes and the prognosis of thionamide treatment for hyperthyroidism in a real-life setting where therapeutic decisions were made combining clinical knowledge with patient preference as well as practicalities and challenges associated with various treatment modalities. We performed an intention to treat analysis on patients undergoing full course of antithyroid drugs for hyperthyroidism. Additionally, we compared our current results with those

from the previous study (Allahabadia et al., 2000), determining if the consideration of previous findings impacted on the choice of therapy and if this resulted in improved outcomes overall.

4.2 Subject and methods

4.2.1 Study dataset

We retrospectively assessed the records of patients who had been referred to our institution with newly diagnosed overt hyperthyroidism between 01/01/2005 and 31/12/2013 using the data collected in the Outpatient Thyroid Clinical Database (as described in 2.2.5.1). The project was revised, approved and registered by the University Hospitals Birmingham NHS Foundation Trust (CARMS-12970). Data on all adult hyperthyroid patients (≥16 years old) were extracted (Figure 4-1). The diagnostic code used for hyperthyroidism did not comprise transient thyroiditis. Subjects with a history of previous antithyroid treatment, those with hyperthyroidism induced by medication (amiodarone, lithium and interferon), pregnant women, as well as those within 12 months postpartum, were excluded. Further exclusions encompassed individuals in whom no treatment for thyroid dysfunction was initiated or in whom the only treatment comprised a thionamide course lasting less than 6 months. Next, patients were categorised based on the treatment modality applied during the first 12 months: (i) definitive therapy, if subjects were given radioiodine (131-I) or underwent surgery irrespective of whether pretreatment with ATDs

was given or (ii) medical treatment, encompassing all remaining subjects undergoing treatment with thionamides alone. The final study cohort comprised adult newly diagnosed patients with overt hyperthyroidism treated with a prolonged course of antithyroid drugs and followed up to determine treatment outcomes and relapse rates. A census date of 30th June 2016 was adopted.

4.2.2 Definition of variables

Overt hyperthyroidism was defined as raised serum free T4 (fT4) and/or free tri-iodothyronine (fT3) with undetectable serum thyrotropin (TSH) and euthyroidism as serum fT4 and TSH within the normal range (9.0-22.0 pmol/L and 0.3-4.5 mIU/L, respectively). Cure was defined as achieving euthyroidism with thionamides followed by discontinuation of treatment.

Subjects were categorised into three diagnostic groups: Graves' disease, toxic nodular hyperthyroidism and hyperthyroidism of indeterminate aetiology as described in section 2.2.5.1. Patients' age, gender, smoking history, family history (FH) of thyroid dysfunction, presence of goitre and thyroid eye disease (TED) were recorded during the initial examination. Goitre type was classed as diffuse or nodular; its size was determined clinically as small or medium-to-large. Based on self-reported smoking habits patients were classified as non-smokers, current smokers or previous smokers. The duration of treatment with thionamides was calculated from the commencement of medical treatment until (1) cessation, (2) the administration of ablative therapy, or (3) the last recorded visit in those who were discharged with life-long ATD or lost from follow up. This was stratified into 6-18, 19-24, and 25+ months.

For sensitivity analysis, a subcohort of patients with defined outcomes was identified. These were defined as known outcomes of medical treatment: either successful if patients were cured or unsuccessful if definitive therapy (I-131 or surgery) or reinstatement of treatment with thionamides had to be prescribed. Consequently, patients discharged to GP for long-term, low-dose thionamide treatment and those lost from follow-up were excluded.

In the survival analysis, only patients who achieved euthyroidism followed by cessation of ATD were included. The outcome of interest was the time (in months) to disease relapse. This was counted from time of cessation of thionamide treatment following induction of euthyroidism until re-commencement of thionamide treatment or biochemical reversion to overt hyperthyroidism. The census date was the end of the follow up period (30th June 2016). Patients who died during follow up were censored at their date of death.

4.2.3 Standard medical treatment

After initial evaluation by a senior clinician, a discussion of the main treatment modalities was undertaken. In accord with current guidelines (Ross et al., 2016), all three treatment options were discussed with patients with Graves' disease, while for those with toxic nodular hyperthyroidism definitive treatments with either 131-I or surgery were proposed. In each case the predicted cure rates, safety requirements especially radiation protection, risk of hypothyroidism requiring levothyroxine replacement, complications from surgery and practical implications were discussed.

Regardless of the final therapeutic modality, the initial phase of treatment was typically with antithyroid drugs, aiming to control the thyrotoxic state. Patients intended to be treated with thionamides to induce cure underwent a 12-18 months course with a dose titration regimen as described in section 5.2.3. When the intended duration of drug therapy was completed and antithyroid drug doses had been titrated to small doses (2.5-5 mg of carbimazole or 25-50 mg of propylthiouracil), patients' biochemical and clinical states were reviewed and, if euthyroid, thionamide treatment was discontinued. If administration of thionamides for more than 12 months did not render patients euthyroid or if patients still required high maintenance doses, ablative treatment was advised. Radioiodine was administered as a fixed dose of 600 MBq and surgery consisted of total thyroidectomy performed by a senior surgeon.

4.2.4 Statistical analysis

Categorical data were presented as counts and standardised into percentages. Continuous variables were presented as a mean with standard deviation and as a median with interquartile range. Binary logistic regression was used to identify differences between the groups expressed as Odds Ratio (OR) with 95% confidence intervals (95% CI). In univariate analyses, calculations were done for a specific factor. Multivariable modelling was used to analyse simultaneous impact of covariates applying a backward stepwise regression technique; variables being removed from the model if $P>0.1$.

An intention-to-treat (Gupta, 2011) approach was applied in the main analysis, i.e. all subject intended to be treated with a full course of thionamides were included

into the analysis irrespective of treatment outcomes or of being lost from follow-up status. Since the majority of previous studies in the field excluded those without definitive outcomes, we repeated, where appropriate, the analyses in the sub-cohort of patients with known outcomes to allow for comparison.

Kaplan-Meier curves were used to represent the relapse rate for hyperthyroidism correcting for the length of follow-up in censored data. Cox regression was used to calculate hazard rates (HR) of relapse of hyperthyroidism in those who were rendered euthyroid with thionamides and subsequently the therapy was ceased. Proportional hazard assumption was tested by including the time dependent covariate in the model. Time-dependent covariates were calculated as a product of the time and each variable entered into the model separately. The hazard rates were confirmed proportional ($P>0.05$) for each tested variable.

Similarly to the regression techniques used, the multivariable survival model was built with backward stepwise method eliminating a variable with $P>0.1$. To avoid multicollinearity conflicts, the multivariable model was built twice: (1) introducing all variables and leaving out aetiology of hyperthyroidism; (2) introducing aetiology and other variables but omitting those forming the algorithm to define aetiology, i.e. goitre type, presence of TED and presence of thyroid peroxidase antibodies (TPOAb).

4.3 Results

4.3.1 Identification of study cohort

Figure 4-1 represents the process of identification of the study cohort. Out of 1,695 hyperthyroid patients seen in the Thyroid Clinic, 560 were excluded based on the criteria described above. During the first 12 months after diagnosis, 522 patients were given ablative therapy, in the form of 131-I either with ATD pretreatment or without in 506 and total thyroidectomy in 16 subjects. The final study cohort of the intention to treat analysis consisted of 612 subjects treated with a course of thionamides of minimum 6 month duration.

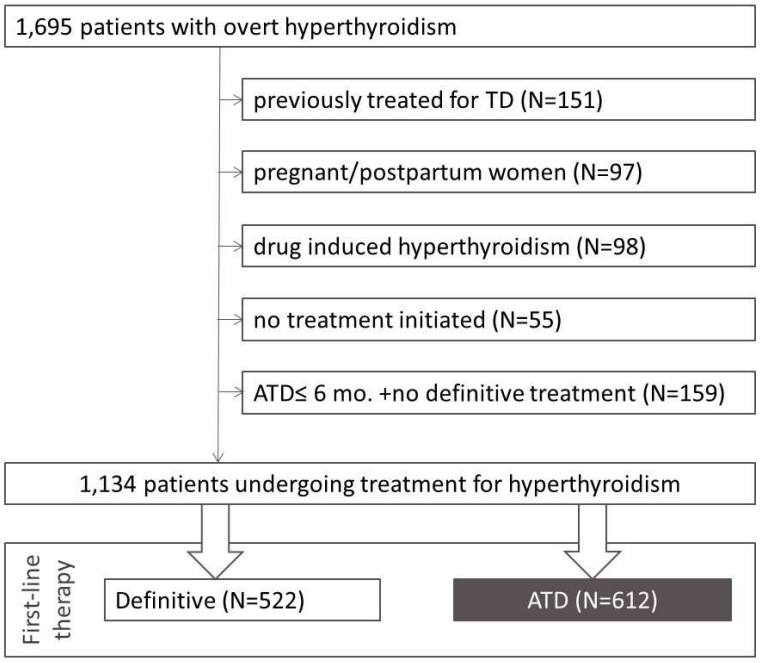

Figure 4-1: Flowchart illustrating the identification of the study patients. ATD, antithyroid drug treatment; N, number; TD, thyroid dysfunction; mo., months

4.3.2 Selection for medical and definitive treatment

The allocation to medical or ablative therapy was not random but based on a decision taking into account clinical factors, patients' preferences and feasibility of adhering to safety measures. Table 4-1 presents the main clinical and demographic differences between the medical and definitive therapeutic groups.

Table 4-1: Differences in patients selected for medical and definitive treatment. Odds ratios (OR) and adjusted odds ratios (AOR) for medical treatment were calculated with binomial univariate and multivariate logistic regression with definitive treatment as a reference category; TNG-toxic nodular goitre; TED- thyroid eye disease

	Treatment		OR (95%CI), P value	AOR (95%CI), P value
	Medical, N=612 (%)	Definitive, N=522 (%)		
Gender				
Female	**491 (80.2)**	377 (72.2)	1.00	1.00
Male	**121 (19.8)**	145 (27.8)	0.64 (0.49-0.85), **0.002**	0.55 (0.39-077), **0.001**
Age, y: mean (±SD)	**43 (±16)**	55 (±16)	0.958 (0.950-0.965), **<0.001**	0.956 (0.946-0.967), **<0.001**
median (IQR: 25-75)	**41 (32-53)**	55 (44-67)		
Diagnostic fT4,				
ml/pmol (±SD)	**48.6 (±23.1)**	43.2 (±23.3)	1.010 (1.004-1.015), **0.02**	NS
median (IQR: 25-75)	**41.5 (30.7-63.0)**	35.8 (26.8-53.1)		
Aetiology				
TNG	**41 (6.7)**	110 (21.1)	1.00	
Graves' disease	**284 (46.7)**	154 (29.5)	4.64 (3.11-6.93), **<0.001**	Not entered into the model
indeterminate	**289 (46.6)**	258 (49.4)	2.73 (1.85-4.03), **<0.001**	
Presence of goitre				
no goitre	**224 (36.6)**	198 (37.9)	1.00	
goitre present	**382 (62.4)**	320 (61.3)	NS	Analysed as type or size of goitre
no data	**6 (1.0)**	4 (0.8)	*excluded from analysis*	
Type of goitre				
diffuse	**340 (55.6)**	210 (40.2)	1.00	1.00
nodular	**41 (6.7)**	91 (17.4)	0.25 (0.17-0.38), **<0.001**	0.46 (0.26-0.82), **0.009**
no goitre	**224 (36.4)**	198 (37.9)	0.70 (0.54-0.91), **0.006**	1.56 (1.09-2.25), **0.02***
no data	**8 (1.3)**	23 (4.4)	*excluded from analysis*	
Goitre size				
small	**277 (45.3)**	205 (39.3)	1.00	1.00
medium to large	**92 (15.0)**	110 (21.1)	0.62 (0.45-0.86), **0.004**	0.62 (0.41-0.94), **0.02**
no goitre	**224 (36.6)**	198 (37.9)	NS	1.56 (1.09-2.25), **0.02***
no data	**19 (3.1)**	9 (1.7)	*excluded from analysis*	
TPO antibodies				
negative or unknown	**367 (60.0)**	354 (67.8)	1.00	
positive	**245 (40.0)**	168 (32.2)	1.41 (1.10-1.80), **0.006**	NS
Presence of TED				
no TED	**453 (76.1)**	445 (86.7)	1.00	1.00
TED	**130 (21.8)**	63 (12.3)	2.03 (1.46-2.81), **<0.001**	1.68 (1.14-2.49), **0.009**
no data	**12 (2.0)**	5 (1.0)	*excluded from analysis*	
Family history of TD				
none	**341 (55.7)**	313 (60.0)	1.00	
known	**249 (40.7)**	180 (34.5)	1.27(0.99-1.62), NS (0.057)	NS
unknown or nor taken	**22 (3.6)**	29 (5.6)	*excluded from analysis*	
Smoking				
never smoked	**334 (54.6)**	226 (43.3)	1.00	1.00
present smoker	**142 (23.2)**	132 (25.3)	0.73 (0.54-0.97), **0.03**	0.70 (0.50-0.99), **0.044**
former smoker	**90 (14.7)**	122 (23.4)	0.50 (3.62-0.69), **<0.001**	0.67 (0.47-1.00), **0.047**
no data	**46 (7.5)**	42 (8.0)	*excluded from analysis*	

Patients with well-defined Graves' disease were five times, and those with indeterminate aetiology of hyperthyroidism three times, more likely to be treated with a prolonged course of thionamides compared to those with underlying toxic nodular hyperthyroidism. Men and older patients were significantly more likely to undergo definitive therapy with radioiodine or surgery. Patients with higher serum fT4 concentrations at diagnosis were more likely to undergo a full course of medical treatment. The presence of goitre did not differ between the therapeutic groups; however, those with medium-to-large goitres were more likely to be treated with definitive treatment when compared to those with small goitres. Patients with diffuse goitre were more likely to undergo a course of thionamides than those with nodular or with no palpable goitre. The presence of TED and of positive TPOAbs were associated with increased likelihoods of medical treatment. Smokers, either current or former, were more often treated definitively. Patients with a family history of thyroid dysfunction were more likely to be treated with thionamides, although this result was of borderline statistical significance.

When the aforementioned factors were analysed simultaneously, gender, age, type and size of goitre, presence of TED and smoking habits had a significant impact on the selection process. Men (AOR=0.55 [95%CI: 0.39-0.77], P=0.001), older patients (0.956 [0.946-0.967], P<0.001), patients with medium-to-large goitres (0.46 [0.36-0.82], P=0.009), and current (0.70 [0.50-0.99], P=0.044) or former smokers (0.67 [0.47-1.00], P=0.047) were less likely to undergo a therapy with thionamides, while the lack of goitre and presence of TED increased the likelihood of medical treatment.

4.3.3 Basic characteristics

Further analysis was conducted using data on 612 medically treated patients including 2,731 persons-years and a median of 3.4 years of follow-up (IQR: 2.0-6.4 years). Nineteen patients died during the study period.

The majority of patients were female (Table 4-1) and the mean age was 43 years. The mean serum fT4 concentration at diagnosis was 48.6 pmol/L and the median was 41.5 (30.7-63.0) pmol/L. Nearly half of patients presented with clearly defined Graves' disease according to our criteria above (N=284, 46.7%) and toxic nodular disease was defined in 44 cases (7.2%); the remainder of the cohort (N=282, 46.1%) had an indeterminate disease aetiology. Goitre was present in two-thirds of patients overall (N=382, 62.4%) and most commonly was diffuse (N=340, 55.6%) and small (N=277, 45.3%). Positive thyroid peroxidase antibodies (TPOAb) were found in 40% of medically treated patients (N=245). 130 (21.8%) subjects presented with thyroid eye disease (TED). Over half of the medically treated patients did not smoke cigarettes (N=334, 54.6%), 142 (23.2%) subjects were current smokers and 90 (14.7%) were former smokers. There was a small proportion of missing data in various categories of patients' records reflecting real-world inaccuracies.

4.3.4 Outcomes of first-line thionamide treatment for hyperthyroidism

Following a prolonged course of ATD, two-thirds of the patients (N=396, 64.7%) were rendered euthyroid and the administration of thionamides was ceased (Figure 4-2). In 132 (21.6%) subjects, euthyroidism was not achieved or maintained with thionamides and they proceeded to "late" definitive therapy (N=104 with 131-I,

N=20 with the surgery, N=8 awaiting ablation at the end of the study). Fifty-seven patients (9.3%) controlled with thionamides were discharged to their GPs with the advice of long-term, continuous, low-dose ATD administration and 27 (3.6%) were lost from follow-up.

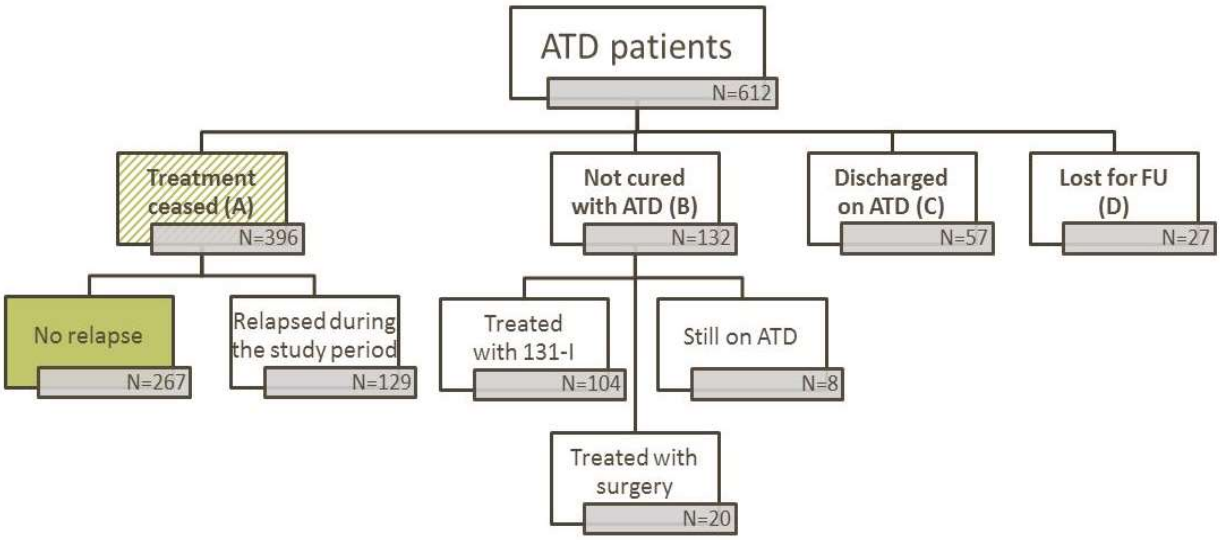

Figure 4-2: Outcomes of treatment with a course of thionamides in 612 hyperthyroid patients. Green colour represents cure with medical therapy.

Table 4-2 presents the differences among the various outcome groups. The gender distribution was similar in all groups. The group of patients in whom thionamides were ceased when euthyroidism was induced (A) comprised proportionally more subjects with small goitres and with indeterminate aetiology than those requiring late ablative treatment (B). Moreover, they (A) had lower presenting serum fT4, a smaller proportion of toxic nodular disease and a lower proportion of patients with TED than those not rendered euthyroid by ATD (B). Those discharged on long-term ATD (C) were the oldest, had the highest proportion of subjects with multinodular goitres

and were less likely to have a family history of TD compared with both those rendered euthyroid with ATD (A) and those requiring late ablative treatment (B). Additionally, Table 4-2 presents differences in duration of therapy with ATD until cessation of treatment, ablation therapy or discharge/lost from FU, which varied across the groups.

Table 4-2: Distribution of various factors in four main outcome groups. Bold font represents significantly higher value compared with an outcome group following the slash sign.

	ATD stopped (A), N=396	Late ablative treatment (B) , N=132	Discharged on long-term ATD (C) , N=57	Lost from FU (D) , N=27	P value
	Count, % mean (±SD)	Count, % mean (±SD)	Count, % mean, (±SD)	Count, % mean, (±SD)	
Gender					
Female	70 (17.7)	31 (23.5)	12 (21.1)	8 (29.6)	NS
Male	326 (82.3)	101 (76.5)	45 (78.9)	19 (70.4)	
Age, y: mean (±SD)	42 (±14)	43 (±15)	**56 (±21)/A,B**	48 (±20)	0.003
Diagnostic fT4, ml/pmol mean (±SD)	47.3 (±22.3)	**54.7 (±26.1)/A**	45.6 (±20.3)	46.4 (±19.4)	0.008
Aetiology					
TN disease	13 (3.3)	**11 (9.8)/A**	**13 (22.8)/A**	**4 (14.8)/A**	<0.001
Graves' disease	181 (45.7)	74 (56.1)	22 (38.6)	9 (33.3)	
indeterminate	**202 (51.0)/B**	45 (34.1)	22 (38.6)	14 (51.9)	
Type of goitre					
diffuse	224 (57.1)	**84 (64.1)/C,D**	23 (41.8)	9 (33.3)	
nodular	13 (3.3)	11 (8.4)	**13 (23.6)/A,B**	4 (14.8)	<0.001
no goitre	155 (39.5)	36 (27.5)	19 (34.5)	13 (48.1)	
Goitre size					
small	**197 (49.7)/B**	48 (36.4)	21 (36.8)	11 (40.7)	
medium to large	33 (8.3)	**45 (34.1)/A,D**	12 (21.1)	2 (7.4)	<0.001
no goitre	155 (39.1)	36 (27.3)	20 (35.1)	13 (48.1)	
TPO antibodies					
negative or unknown	233 (58.8)	74 (56.1)	40 (70.2)	20 (74.1)	0.004
positive	163 (41.2)	58 (43.9)	17 (29.8)	7 (25.9)	
Presence of TED					
no TED	305 (80.7)	85 (65.9)	43 (82.7)	20 (83.3)	0.004
TED	73 (19.3)	**44 (34.1)/A**	9 (17.3)	4 (16.7)	
Family history of TD					
none known	214 (55.6)	66 (52.8)	**44 (81.5)/A,B**	17 (65.4)	0.002
known	171 (44.4)	59 (47.2)	10 (18.5)	9 (34.6)	
Smoking					
never smoked	230 (62.8)	62 (50.0)	29 (55.8)	13 (54.2)	
present smoker	71 (19.4)	46 (37.1)	16 (30.8)	9 (37.5)	0.004
former smoker	65 (17.8)	16 (12.9)	7 (13.5)	2 (8.3)	
Duration of ATD					
≤18 mo.	**197 (49.7)/C**	**59 (44.7)/C**	10 (17.5)	**19 (70.4)/C**	
19 – 24 mo.	**148 (37.4)/C**	24 (18.2)	10 (17.5)	6 (22.2)	<0.001
25+ mo.	51 (12.9)	**49 (37.1)/A,D**	**37 (64.9)/A,B,D**	2 (7.4)	

4.3.5 Characteristics of patients successfully treated with ATD; predictive factors of successful therapy with a course of thionamides

The proportion of patients successfully cured with first-line thionamide treatment, defined as euthyroidism off ATD, continuously decreased over the period of study, reaching 59% (N=361), 53% (N=322) and 48% (N=296) at 6, 12 and 24 months respectively following cessation of therapy, with only 44% (N=267) of subjects remaining in remission at the end of the study. Cure rates in those with well-defined Graves' disease were slightly lower than those in the total cohort: 55% (N=158), 48% (137), 44% (127) and 39% (112), respectively at various time points. Table 4-3 presents the basic characteristics of patients cured at the end of the study compared to those who were not cured i.e. those who required late ablative treatment or were discharged on long-term ATD or were lost from FU or suffered a relapse during the study period.

In univariate analysis (Table 4-3), females, non-smokers, those with less severe hyperthyroidism (lower fT4 concentrations at presentation), those with underlying Graves' disease or an indeterminate disease aetiology, those with no or small diffuse goiters, as well as those without TED, were more likely to be cured after a course of drug therapy. Patients' age and family history of thyroid dysfunction were not different when comparing cured and non-cured patients.

In the multivariable regression model (Table 4-3), independent predictors adversely associated with effective outcome of ATD treatment were current smoking

(AOR: 0.39 [95%CI: 0.25-0.60], P<0.001), presence of medium-to-large goitre (0.23 [0.13-0.41], P<0.001) and older age (0.980 [0.967-0.992], 0.002).

Table 4-3: Characteristics of patients successfully cured with a course of thionamides compared to those not cured with ATD therapy. Odds ratios (OR) and adjusted odds ratios (AOR) for successful ATD treatment were calculated with binary logistic regression; significance was assumed at 0.05 level.

	Outcome of ATD treatment		OR (95%CI), P value	AOR (95%CI), P value
	Cured N=267 (%)	Not-cured N=345 (%)		
Gender				
Female	**224 (83.9)**	267 (77.4)	1.00	1.00
Male	**43 (16.1)**	78 (22.6)	0.66 (0.44-0.99), **0.046**	NS
Age, y: mean (±SD)	**42.1 (±13.8)**	44.5 (±16.7)	0.990 (0.980-1.000),	0.980 (0.967-0.992), **0.002**
median (IQR: 25-75)	**40 (33-51)**	42 (32-54)	NS (0.056)	
Diagnostic fT4,				
ml/pmol (±SD)	**46.2 (±23.1)**	50.6 (±23.3)	0.992(0.985-0.999), **0.02**	NS
median (IQR: 25-75)	**41.5 (30.7-63.0)**	35.8 (26.8-53.1)		
Aetiology				
TN disease	**9 (3.4)**	32 (9.3)	1.00	
Graves' disease	**112 (41.9)**	174 (50.4)	2.29 (1.05-4.98), **0.04**	Not entered into the model
indeterminate	**146 (54.7)**	139 (40.3)	3.74 (1.72-8.11), **0.001**	
Presence of goitre				
no goitre	**112 (41.9)**	111 (32.2)	1.00	
goitre present	**153 (57.3)**	230 (66.7)	0.66 (0.47-0.92), **0.01**	Analysed as type or size of goitre
no data	**2 (0.7)**	4 (1.2)	*excluded from analysis*	
Type of goitre				
diffuse	**144 (53.9)**	196 (56.8)	1.00	1.00
nodular	**9(3.4)**	32 (9.3)	0.38 (0.18-0.83), **0.02**	NS
no goitre	**112 (41.9)**	111 (32.2)	1.37 (0.98-1.93), NS (0.067)	NS
no data	**2 (0.7)**	6 (1.7)	*excluded from analysis*	
Goitre size				
small	**132 (49.4)**	145 (42.0)	1.00	1.00
medium to large	**18 (6.7)**	74 (21.4)	0.27 (0.15-0.47), **<0.001**	0.23 (0.13-0.41), **<0.001**
no goitre	**112 (41.9)**	112 (32.5)	NS	NS
no data	**5 (1.9)**	14 (4.1)	*excluded from analysis*	
TPO antibodies				
negative or unknown	**164 (61.4)**	203 (58.8)	1.00	NS
positive	**103 (38.6)**	142 (41.2)	NS	
Presence of TED				
no TED	**209 (80.7)**	244 (72.6)	1.00	1.00
TED	**44 (17.0)**	86 (25.6)	0.60 (0.40-0.90), **0.01**	NS
no data	**6 (2.3)**	6 (1.8)	*excluded from analysis*	
Family history of TD				
none	**148 (55.4)**	193 (55.9)	1.00	NS
known	**113 (42.3)**	136 (39.4)	NS	
unknown or nor taken	**6 (2.2)**	16 (4.6)	*excluded from analysis*	
Smoking				
never smoked	**160 (59.9)**	174 (50.4)	1.00	1.00
present smoker	**40 (15.0)**	102 (29.6)	0.43 (0.28-0.65), **<0.001**	0.39 (0.25-0.60), **<0.001**
former smoker	**46 (17.2)**	44 (12.8)	NS	NS
no data	**21 (7.9)**	25 (7.2)	*excluded from analysis*	

4.3.5.1 *Sensitivity analysis in patients with defined outcomes*

In order to confirm our findings a subgroup analysis limiting the cohort to those with defined outcomes of treatment (groups A and B) was performed. The cohort consisted of 428 subjects. Ten patients died during the study period. ATD cure rates in this cohort were 68%, 61%, 56% and 51% at 6, 12, 24 months following cessation of therapy and at the study end, respectively. Further limiting this cohort to patients with well-defined Graves' disease revealed cure rates of 62%, 54%, 50% and 44%, respectively at those different time points.

Table 4-4 represents data from the sensitivity analysis. Results were broadly in keeping with those derived from the intention-to-treat cohort. However, on multivariable analysis, patients' age was no longer a predictive factor of cure, whereas the presence of medium-to-large size of the goitre (0.41 [0.26-0.65], P<0.001) and current smoking (0.25 [0.14-0.46], P<0.001) at presentation remained strong independent predictors adversely associated with the success of thionamide therapy.

Table 4-4: Sensitivity analysis of patients comparing patients cured with a course of thionamide with those who needed late ablative treatment or whose hyperthyroidism relapsed during the study period.

	Outcome of ATD treatment		OR (95%CI), P value	AOR (95%CI), P value
	Cured N=267 (%)	Not-cured N=261 (%)		
Gender				
Female	**224 (83.9)**	203 (77.8)	1.00	1.00
Male	**43 (16.1)**	58 (22.2)	0.67 (0.43-1.04), NS (0.075)	NS
Age, y: mean (±SD)	**42.1 (±13.8)**	44.5 (±16.7)	1.000 (1.00-1.00), NS (0.071)	NS
median (IQR: 25-75)	**40 (33-51)**	42 (32-54)		
Diagnostic fT4,				
ml/pmol (±SD)	**46.2 (±23.1)**	50.6 (±23.3)	0.989 (0.982-0.997), **0.004**	NS
median (IQR: 25-75)	**41.5 (30.7-63.0)**	35.8 (26.8-53.1)		
Aetiology				
TN disease	**9 (3.4)**	15 (5.7)	1.00	
Graves' disease	**112 (41.9)**	143 (54.8)	NS	Not entered into the model
indeterminate	**146 (54.7)**	103 (39.5)	2.36 (1.00-5.61), NS (0.051)	
Presence of goitre				
no goitre	**112 (41.9)**	79 (30.3)	1.00	
goitre present	**153 (57.3)**	179 (68.6)	0.60 (0.42-0.86), **0.006**	Analysed as type or size of goitre
no data	**2 (0.7)**	3 (1.1)	*excluded from analysis*	
Type of goitre				
diffuse	**144 (53.9)**	164 (62.8)	1.00	1.00
nodular	**9(3.4)**	15 (5.7)	NS	NS
no goitre	**112 (41.9)**	79 (30.3)	1.62 (1.12-2.33), **0.01**	NS
no data	**2 (0.7)**	3 (1.1)	*excluded from analysis*	
Goitre size				
small	**132 (49.4)**	113 (43.3)	1.00	1.00
medium to large	**18 (6.7)**	60 (23.0)	0.26 (0.14-0.46), **<0.001**	0.41 (0.26-0.65), **<0.001**
no goitre	**112 (41.9)**	79 (30.3)	NS	NS
no data	**5 (1.9)**	9 (3.4)	*excluded from analysis*	
TPO antibodies				
negative or unknown	**164 (61.4)**	143 (54.8)	1.00	
positive	**103 (38.6)**	118 (45.2)	NS	NS
Presence of TED				
no TED	**209 (80.7)**	181 (70.2)	1.00	1.00
TED	**44 (17.0)**	73 (28.3)	0.52 (0.34-0.80), **0.003**	NS
no data	**6 (2.3)**	4 (1.6)	*excluded from analysis*	
Family history of TD				
none	**148 (55.4)**	132 (50.6)	1.00	
known	**113 (42.3)**	117 (44.8)	NS	NS
unknown or nor taken	**6 (2.2)**	12 (4.6)	*excluded from analysis*	
Smoking				
never smoked	**160 (59.9)**	132 (50.6)	1.00	1.00
present smoker	**40 (15.0)**	77 (29.5)	0.43 (0.27-0.67), **<0.001**	0.25 (0.14-0.46), **<0.001**
former smoker	**46 (17.2)**	35 (13.4)	NS	NS
no data	**21 (7.9)**	17 (6.5)	*excluded from analysis*	

4.3.5.2 *Comparison with the previous study from the same centre*

Figure 4-3 represents the various outcomes of treatment in 536 patients with Graves' disease seen in our Clinic between 1975 and 1998 derived from the study of Allahabadia et al. (2000).

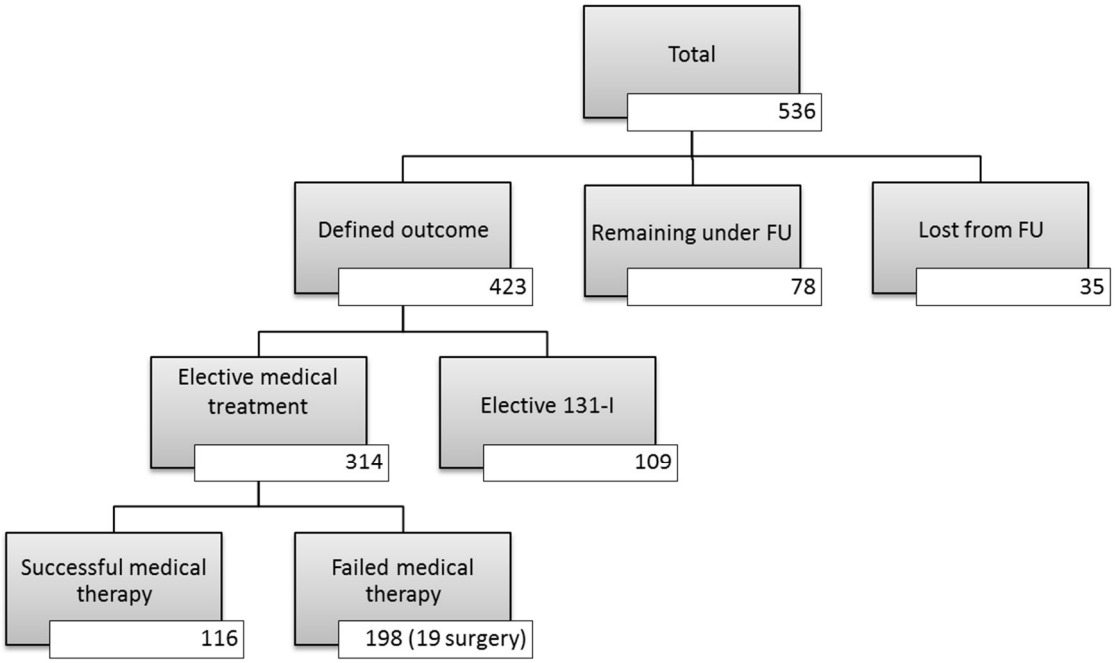

Figure 4-3: Numbers in each outcome category of treatment for Graves' disease of 536 patients seen in the Thyroid Clinic in 1975-1998 derived from Allahabadia et. al study (2000).

In this study outcome after a course of antithyroid drugs was defined as successful when subjects remained euthyroid for at least 6 months after withdrawal of thionamide treatment. 116 out of 314 patients (37%) treated with a prolonged course of antithyroid drugs were cured. In comparison, successful therapy in sub-cohort of our patients with Graves' disease, identified using the same criteria, and with defined outcomes at 6 months following cessation of ATD, was 62% (158/255 subjects). This represents a significant increase (OR=2.78 [95%CI: 1.98-3.91], P<0.001) in present success rate of thionamide treatment compared to the historical cohort from the same centre.

4.3.6 Risk of relapse following the cessation of ATD treatment

Among 396 patients in whom thionamide treatment was ceased after induction of euthyroidism, 129 (32.6%) suffered a relapse during the study period. The highest rate of relapse was seen during the first two years following the discontinuation of ATD and the risk of relapse decreased in subsequent years (Figure 4-4).

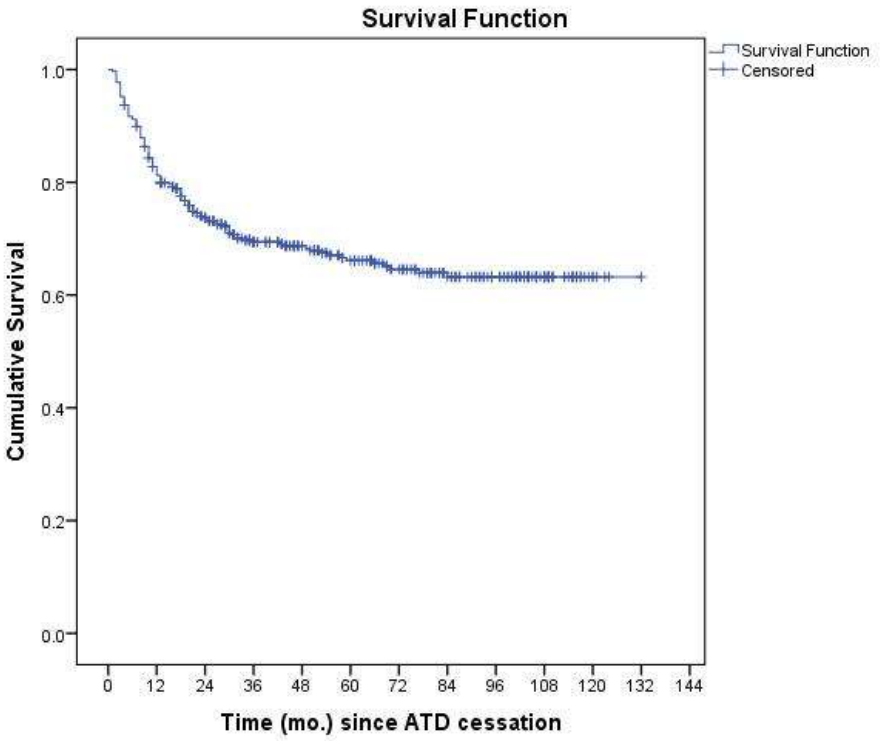

Figure 4-4: Kaplan-Meier survival function estimating the proportion of patients in remission at various time points following cessation of medical treatment

Table 4-5 presents the demographic and clinical characteristics of patients in whom thionamide treatment was withdrawn following a prolonged course. The hazard risk of relapse calculated for each variable in univariate analysis was significantly increased in current smokers (HR=1.59 [95%CI: 1.04-2.43], P=0.03) when compared to those who never smoked and was decreased in those of indeterminate aetiology

of hyperthyroidism (0.61 [0.43-0.86], P=0.005) when compared to patients with well-defined GD.

Table 4-5: Characteristics of patients, in whom thionamide treatment was discontinued following a prolonged course of thionamides, stratified by the finding of relapse during the study. Univariate hazard ratio (HR) and corresponding 95% confidence intervals (95%CI) were calculated using Cox proportional hazard regression. SD - standard deviation, NS – not significant

	ATD treatment ceased		HR (95%CI), P value
	Relapse N=129 (%)	Remission, N=248 (%)	
Gender			
Female	**102 (79.1)**	224 (83.9)	1.00
Male	**27 (20.9)**	43 (16.1)	0.73 (0.48-1.12), NS(0.73)
Age, y: mean (±SD)	**40.8 (±13.7)**	42.1 (±13.8)	0.986 (0.965-1.008), NS (0.21)
median (IQR: 25-75)	**40 (30.5-49.0)**	40 (33.0-51.0)	
Diagnostic fT4,			
ml/pmol (±SD)	**49.4 (±23.1)**	46.2 (±21.2)	1.007 (0.995-1.019), NS (0.27)
median (IQR: 25-75)	**41.0 (30.7-69.5)**	39.9 (30.5-58.1)	
Aetiology			
Graves' disease	**69 (53.5)**	112 (41.9)	1.00
TN disease	**4 (3.1)**	9 (3.4)	0.65 (0.24-1.77), NS (0.40)
indeterminate	**56 (43.4)**	146 (54.7)	0.61 (0.43-0.86), **0.005**
Presence of goitre			
no goitre	**43 (33.3)**	112 (41.9)	1.00
goitre present	**84 (65.1)**	153 (57.3)	1.25 (0.87-1.81), NS (0.23)
no data	**2 (1.6)**	2 (0.7)	*excluded from analysis*
Type of goitre			
diffuse	**80 (62.0)**	144 (53.9)	1.00
nodular	**4 (3.1)**	9 (3.4)	0.83 (0.31-2.28), NS (0.72)
no goitre	**43 (33.3)**	112 (41.9)	0.79 (0.55-1.15), NS (0.21)
no data	**2 (1.3)**	5 (1.9)	*excluded from analysis*
Goitre size			
small	**65 (50.4)**	132 (49.4)	1.00
medium to large	**15 (11.6)**	18 (6.7)	1.49 (0.85-2.62), NS (0.16)
no goitre	**43 (33.3)**	112 (41.9)	0.87 (0.59-1.28), NS (0.48)
no data	**6 (4.7)**	5 (1.9)	*excluded from analysis*
TPO antibodies			
negative or unknown	**69 (53.5)**	164 (61.4)	1.00
positive	**60 (46.5)**	103 (38.6)	1.38 (0.95-1.89), NS (0.10)
Presence of TED			
no TED	**96 (75.6)**	209 (80.7)	1.00
TED	**29 (22.8)**	44 (17.0)	1.41 (0.93-2.14), NS (0.10)
no data	**2 (1.6)**	6 (2.3)	*excluded from analysis*
Family history of TD			
none	**66 (51.2)**	148 (55.4)	1.00
known	**58 (45.0)**	113 (42.3)	1.09 (0.76-1.54), NS (0.65)
unknown or nor taken	**5 (3.9)**	6 (2.2)	*excluded from analysis*
Smoking			
never smoked	**70 (54.3)**	160 (59.9)	1.00
present smoker	**31 (24.0)**	40 (15.0)	1.59 (1.04-2.43), **0.03**
former smoker	**19 (14.7)**	46 (17.2)	0.94 (0.56-1.56), NS (0.80)
no data	**9 (7.0)**	21 (7.9)	*excluded from analysis*
Duration of ATD			
≤18 mo.	**68 (52.7)**	129 (48.3)	1.00
19 – 24 mo.	**46 (35.7)**	102 (38.2)	0.96 (6.6-1.39), NS (0.83)
25+ mo.	**15 (11.6)**	36 (13.5)	0.98 (0.56-1.72), NS (0.95)

A multivariable model of survival using Cox proportional hazard regression was built twice to avoid multicollinearity conflicts as described in the methods section (4.2.4). The first model, excluding aetiology of hyperthyroidism, identified current smoking as the only independent predictor of relapse (HR=1.59 [95%CI: 1.04-2.43], P=0.03). In the second model, including disease aetiology but leaving out goitre type and presence of TED and TPOAb, disease aetiology and smoking habits were both independent predictors of relapse (Table 4-6). Current, but not previous, smoking increased (1.54 [1.01-1.52], P=0.045) and indeterminate aetiology of hyperthyroidism decreased (0.69 [0.48-0.99], P=0.045) risk of suffering a relapse.

Table 4-6: Results of multivariable survival Cox proportional hazard regression predicting development of relapsed hyperthyroidism following cessation of thionamides. HR – hazard rate, CI – confidence interval, NS- not significant

	HR	95.0% CI for HR		P value
		Lower	Upper	
Aetiology				
Graves' disease	1.00			
TN disease	0.70	0.25	1.93	0.72 (NS)
indeterminate	0.69	0.48	0.99	**0.045**
Smoking				
never smoked	1.00			
present smoker	1.54	1.01	2.36	**0.045**
former smoker	0.91	0.55	1.52	0.72 (NS)

4.4 Discussion

This study represents an example of real-world practice of managing hyperthyroidism in a secondary/tertiary care outpatient clinic in a mildly iodine-deficient population (Vanderpump et al., 2011). We found that medical treatment was the most favoured

option as first line-therapy for hyperthyroidism, with surgical intervention being used rarely.

4.4.1 Effects of clinical and biochemical factors on choice of treatment modality

Therapeutic decisions were made jointly by the clinician and the patient. The process took into account various clinical and demographic factors. Our data revealed that patients selected for treatment with ATD were younger, despite several studies reporting higher relapse rates of Graves' hyperthyroidism associated with younger age (Allahabadia et al., 2000, Vitti et al., 1997, Winsa et al., 1990). Hyperthyroidism is significantly less common in men and treatments both with ATD and 131-I are less successful in males (Manji et al., 2006, Allahabadia et al., 2000, Franklyn et al., 1995, Sabri et al., 1999). In our study, men were more likely to be selected for definitive treatment.

Clinical factors affecting the decision process were often those differentiating between Graves' disease and toxic nodular diagnoses such as type of goitre and presence of TED. Interestingly, neither family history of thyroid dysfunction nor the presence of positive TPOAb proved relevant to the selection of therapy when accounting for other factors. Current and former smokers were more likely to be given definitive treatment than those who didn't smoke and this was confirmed on multivariable analysis. Whether these decisions were based on clinicians working on the assumptions that smokers would have worse cure rates with antithyroid drugs or whether smokers were more likely to choose definitive treatment is unclear.

To the best of our knowledge, this is the first study to analyse factors influencing the selection of patients for medical or definitive treatment. Despite numerous studies trying to identify predictors for successful medical treatment in Graves' hyperthyroidism, there are no studies describing if previously identified risk factors for relapse are used in routine clinical practice.

4.4.2 Outcomes following ATD treatment

Analysing the effects of a prolonged course of ATD as initial therapy for hyperthyroidism we identified four main outcomes group: (A) patients rendered euthyroid following a course of ATD in whom medication was discontinued; (B) those in whom thionamides did not achieve or maintain euthyroidism; (C) subjects in whom long-term/indefinite treatment with ATD was advised; and (D) those lost from FU. In any medium to long-term treatment the risk of drop-out has to be taken into consideration. We observed that among those treated with ATD for more than 6 months the proportion of patients lost to follow-up was small (less than 5%). This may be in part due to the therapeutic choice offered to a patient.

Almost 10% of patients treated with thionamides were discharged to the GP with the advice to continue long-term with low doses of ATD (group C). A growing body of evidence advocates this option as a safe and effective way of controlling hyperthyroidism (Azizi et al., 2005, Azizi et al., 2012, Villagelin et al., 2015). Our study confirms a long-term/life-long thionamide regimen occasionally forms part of routine care in a specialist clinic and in the community. The group treated with continuous thionamides was not limited to Graves' patients but included also those with toxic

nodular disease (Table 4-2). In fact, the proportion of nodular hyperthyroidism in this group (C) was significantly higher than in any other outcome group. Furthermore, individuals discharged with continuous ATD were characterised by significantly older age and were unlikely to report a family history of thyroid dysfunction. The first factor is in line with guidelines recommending consideration of life-long medical treatment for hyperthyroidism in patients with limited life-expectancy and increased surgical risks or difficulties in complying with safety regulation after 131-I administration (Ross et al., 2016). The latter may reflect the reduced likelihood of a family history in patients with toxic nodular hyperthyroidism as well as potential difficulties in ascertaining family history data in this elderly group of patients.

In our cohort, subjects who failed to achieve euthyroidism with ATD therapy and who required late ablation (group B) constituted around 20% of all those treated. This proportion was slightly higher than 16% reported in a Graves' disease-only cohort (Magri et al., 2016). The authors reported that patients undergoing 131-I were older and those treated surgically had bigger goitres than those who underwent a prolonged course of ATD. In our study, we did not differentiate between the type of definitive treatment; however those with medium-to-large goitres were less likely to achieve euthyroidism with medical treatment alone, similar to the Magri et al. study.

There is a common belief that the usual cause of failure to control thyrotoxicosis with antithyroid drugs is due to nonadherence to medication (Ross et al., 2016). However, the evidence supporting this is weak and mainly based on a study analysing outcomes in only 9 patients (Cooper, 1985). Our data represent a much bigger group of patients (group B) in whom thionamide administration did not result in control

of thyrotoxicosis. Although the causal effects were not studied, we were able to identify some systematic differences between those who achieved and those who failed to achieve euthyroidism with ATDs. The latter more often had higher concentrations of serum fT4 at diagnosis, had larger goitres and were more likely to have TED or an underlying aetiology of nodular hyperthyroidism. While futility of medical treatment in nodular hyperthyroidism has been recognised (Ross et al., 2016), further studies are needed to explore the associations between failure to achieve euthyroidism with thionamides and the other factors identified as predictors of treatment failure.

The most common outcome of medical treatment for hyperthyroidism, found in two-thirds of patients, was induction of euthyroidism and cessation of treatment (group A). In 50% of patients, the treatment lasted 18 months or less and in 13% more than two years. Some studies reporting outcomes following medical treatment for hyperthyroidism limit analysis of the cohort solely to those who achieved euthyroidism and in whom medication was stopped (Liu et al., 2016, Anagnostis et al., 2013, Mohlin et al., 2014). Such an approach inflates apparent remission rates as it lowers the denominator by excluding the remaining outcomes. When comparing these different studies bias related to patient selection thus needs to be taken into account.

Studies of medical treatment of hyperthyroidism are usually limited to patients with Graves' disease, as toxic nodular goitre is considered incurable with thionamides alone (Ross et al., 2016, De Leo et al., 2016). In our cohort we found 41 patients with toxic nodular hyperthyroidism who were treated with a prolonged course of ATD. A third (N=13) were the subjects discharged to their GPs with advice for long-term, continuous, low-dose ATD treatment (group C). An additional 11 patients were treated

with late ablation as achieving and maintaining euthyroidism was not possible (group B). Thionamide treatment was ceased while euthyroid in 13 individuals with toxic nodular hyperthyroidism (group A) of whom four relapsed and nine remained in remission until the end of the study period. This 30% (4/13) relapse rate in subjects with toxic nodular disease is significantly lower than that reported in two previous studies (van Soestbergen et al., 1992, Laurberg et al., 1986). Discontinuation of thionamide therapy after a minimum follow-up of 2 years since drug withdrawal was associated with nearly 100% relapse in a series studied by van Soestbergen et al. (1992). In the other study of 25 women with TNG, 18 (72%) relapsed within 20 months and 23 (88%) at 60 and 100 months of follow-up (Laurberg et al., 1986). In our cohort scintigraphy scanning, which is often used to confirm the presence of toxic nodular hyperthyroidism, was not routinely undertaken. In addition, thyroid ultrasonography was not performed routinely to determine the size and nature of goitres. Hence, it is hard to confirm if our low rate of relapse represents successful medical treatment or results from difficulties in differentiating patients with Graves' disease from toxic nodular goitre.

4.4.3 Characteristics of patients successfully cured and free of relapse

After a median of 3.4 years of follow-up, the final cure rate with ATD in our intention-to-treat (ITT) cohort was 44%, while in those with defined outcomes, studied in the sensitivity analysis, the rate was 51%. Final cure rate in well-defined Graves' disease was 39% and 44%, respectively.

In multivariable regression analysis, younger age, medium-to-large size of goitre and current smoking were identified as factors independently associated with adverse outcome of medical treatment. Higher concentration of serum fT4 at presentation, the presence of TED and male gender, despite being significant on univariate analysis, did not affect outcomes when adjusted for other variables. The findings of our study confirm previously defined risk factors of successful treatment with thionamides (Abraham et al., 2010, Azizi et al., 2012, Magri et al., 2016, Nedrebo et al., 2002, Orunesu et al., 2004).

When comparing the outcomes with historical data, it is important to appreciate the methodology of cohort selection, as studies in the field vary significantly. Many reports focus on patients with GD only. Some studies, especially those aiming to assess predictors of relapse or remission times, include only those who were rendered euthyroid and in whom ATD prescription was stopped. We assessed successful treatment without relapse in all our patients intended to be treated with thionamides to better understand therapeutic decisions and potential clinical challenges during the treatment process. Additionally, for comparative reasons, a sub-group of patients with defined outcomes was analysed.

Comparison with a previous study from our centre, investigating the outcomes in Graves' disease patients treated between 1975 and 1998 (Allahabadia et al., 2000), demonstrates a significant increase in successful treatment with antithyroid drugs. This may in part be attributed to the practical application of findings from earlier studies determining that male gender (Allahabadia et al., 2000, Magri et al., 2016), larger goitres (Allahabadia et al., 2000, Nedrebo et al., 2002), Graves' aetiology

of hyperthyroidism (van Soestbergen et al., 1992, Laurberg et al., 1986) or smoking (Kimball et al., 2002, Quadbeck et al., 2006) (i.e. factors known to be associated with adverse outcome of treatment with ATDs) had influenced decisions on choice of treatment modality in our cohort. In a recent study from Sweden, comparison to historical data was also performed (Mohlin et al., 2014). The authors acknowledged a decrease in relapse rates between their 2014 study and those from the 1970s and 1980s, even though definitive ablative treatments were used more frequently in previous years (1970-1980). The authors speculated that better outcomes with contemporary use of ATD might reflect improved patient selection.

In our cohort, factors predicting response to treatment, when analysed simultaneously, were current smoking and the presence of medium-to-large goitre. These findings confirmed the results from previous studies highlighting the challenges of medical treatment in patients with large goitres (Dauksiene et al., 2013, de Luis et al., 2002, Winsa et al., 1990) and in smokers (Kimball et al., 2002, Nedrebo et al., 2002, Orunesu et al., 2004). Contrary to some other studies (Allahabadia et al., 2000, Magri et al., 2016), we did not find a significant influence of gender on cure rates. This might have been driven by previous findings of lower rates of cure with ATD in men, who consequently were more than 50% more likely to be treated with definitive treatment.

4.4.4 Relapse risk of hyperthyroidism

In our study, current smoking was strongly associated with a risk of disease relapse in those initially "cured" with thionamides. Both models of analysis confirmed this

as an independent risk factor. A meta-analysis of 25 studies has confirmed that smoking is associated with a 3.3-fold increased risk of development of GD compared with non-smokers (Vestergaard, 2002). It is therefore reasonable to speculate that cigarette smoking also influences recurrence of the disease. This was confirmed by previous studies (Quadbeck et al., 2006, Chowdhury and Dyer, 1998, Nedrebo et al., 2002).

In contrast with these studies, Mohlin et al. (2014) reported better outcomes in previous smokers with no difference in the risk of relapse between current and non-smokers. In our cohort, the risk of the relapse in previous smokers and non-smokers was similar.

Quadbeck et al. (2006) analysed in more detail the impact of smoking on the long-term course of GD after ATD cessation. They investigated the concentration of TRAb in smokers and non-smokers at the end of treatment and four weeks later. They noted that TRAb concentrations were significantly higher at the time of drug withdrawal and rose more rapidly during follow-up in smokers. Additionally, smokers more often relapsed than non-smokers, irrespective of TRAb concentrations. They concluded that smoking alters the course of GD in two independent ways: indirectly, by affecting TRAb concentrations, and directly by modifying the immunological response.
The association of smoking is particularly important because this risk factor is modifiable during the treatment process. We advocate that ATD-treated patients should be strongly encouraged and supported to quit smoking as this may significantly improve the likelihood of successful therapy and lasting remission.

Patients with indeterminate aetiology of hyperthyroidism had an increased likelihood of lasting remission. Indeterminate aetiology in our cohort was defined by algorithmic elimination and consisted of a mixture of subjects with mild Graves' disease, thyroiditis or toxic nodular disease, although based on epidemiological findings they are most likely to have Graves' thyrotoxicosis. Improved outcomes in this subgroup compared with those with well-defined Graves' disease may be explained by better cure rates in those with milder forms of Graves' disease or may reflect the inclusion of patients with thyroiditis in whom thyrotoxicosis resolved spontaneously and who should not undergo long-term drug treatment for hyperthyroidism since this is ineffective. The latter explanation supports the need for carefully establishing the aetiology of hyperthyroidism before treatment decision making. Previous ATA guidelines (Bahn et al., 2011) recommended radioactive iodine uptake (RAIU) in those in whom a diagnosis of Graves' disease was not clinically obvious. However, for many UK centres this procedure is too inconvenient and costly to be used routinely. New ATA guidelines (Ross et al., 2016) have added a TRAb test as an alternative to RAIU, which has already been adopted routinely in our clinic. We expect that in addition to increased use of thyroid scintigraphy we will characterise the underlying disease aetiology better in our patients in future and avoid unnecessary treatment in some.

4.4.5 Study limitations

During the study period, measurement of TRAb antibodies was not part of the clinical decision process either at diagnosis or at the cessation of the treatment; this factor was therefore not included in the analysis. Data relating to new development of TED during follow-up or adverse effects of antithyroid drugs were not readily available.

These factors, if present, may have influenced subsequent treatment decisions. Additionally, goitre type and size were documented clinically and inter-observer variability may have introduced some bias.

Despite these shortcomings, this study provides real-world data regarding outcomes in a systematically documented cohort of patients with hyperthyroidism treated with antithyroid drugs. We have identified certain patient groups who are less likely to be cured by thionamides and in whom early ablative treatment with radioiodine (or surgery) may be indicated. Moreover, we assessed the risk of a relapse of the disease and identified the risk factors for relapse when medical treatment was ceased following achievement of euthyroidism.

4.4.6 Conclusions

We demonstrated a high rate of unsuccessful treatment of hyperthyroidism with thionamides overall with high rates of relapse in patients in whom medical treatment was discontinued following induction of euthyroidism. The proportion of successfully treated patients was, however, larger than in an earlier study from the same centre, a finding which may potentially be attributed to improved selection of patients for medical treatment, based upon application of data from previous studies.

Chapter 5. WEIGHT CHANGES FOLLOWING TREATMENT OF HYPERTHYROIDISM

5.1 Introduction

Weight loss occurs in 60-80% of subjects presenting with hyperthyroidism (Boelaert et al., 2010b, Hoogwerf and Nuttall, 1984) and regain of weight may therefore be expected following normalisation of thyroid function. A few smaller studies have assessed change from premorbid weight, which probably reflects the indolent course of the disease and inaccurate recall by patients. In those who did report such evidence, a high proportion (50-80%) of subjects report that they exceed their premorbid weight following treatment for hyperthyroidism (Jansson et al., 1993, Watts et al., 2002, Berg et al., 1996) The mechanisms underlying this weight "overshoot", however, remain poorly understood. Weight gain often continues after restoration of euthyroidism and the risk of increase in BMI may be particularly marked following induction of hypothyroidism (Brunova et al., 2003, Tigas et al., 2000) which occurs as a consequence of thyroidectomy and in the majority of subjects treated with 131-I (Boelaert et al., 2009, Rotondi et al., 2014). Thus far, only few observational studies have evaluated weight gain following treatment of hyperthyroidism (Alton and Omalley, 1985, Lonn et al., 1998). The reported mean increase in weight with antithyroid treatment ranges from 2.1 to 16.4 kg over 6 months to 5 years. Weight gain occurs principally during the first 6 to 24 months after starting treatment

(Brunova et al., 2003, Dale et al., 2001) and continues for at least 6 months after becoming euthyroid (Rathi et al., 2008).

Thyroid hormones (TH) and weight are linked in two-ways: (1) thyroid hormones regulate use of energy stores, mainly brown and white adipose tissue, as a key component of thermogenesis and metabolism regulation (described in more details in section 1.1.2.2); (2) they act directly or through interaction with other hormones on control of appetite and food intake. The exact mechanism and associations are not yet fully understood. It is hypothesised that T3 concentrations in the hypothalamus directly stimulate food intake, which may be independent of changes in energy expenditure (Kong et al., 2004). This, in turn, can be affected by leptin, a hormone secreted by adipocytes proportionally to the whole-body adipose tissue mass and inhibiting the appetite (Dhillo, 2007). Additionally, the links between TH and the appetite-promoting hormone, ghrelin, have been noted. In most studies, serum ghrelin concentrations were lower in subjects with hyperthyroidism although conflicting results have been found in those with hypothyroidism (Kosowicz et al., 2011, Gimenez-Palop et al., 2005).

Two thirds of the adult population in the US and at least half of the populations of many other developed countries are overweight or obese. In England, the recent data showed that 58% of women and 65% of men were either overweight (BMI>25kg/m^2) or obese (BMI>30kg/m^2) and combined obesity prevalence had increased from 15% in 1993 to 26% in 2014 (HSCIC, 2016). Several large studies have indicated increased mortality in overweight and obese subjects and for every 5 kg/m^2 increase in BMI there is on average an associated 30% higher mortality.

The progressive excess mortality above the optimum BMI of 22.5-25 kg/m^2 is due mainly to vascular disease and is probably causally related (Solomon and Manson, 1997). Hyperthyroidism is also associated with an increased risk of mortality as indicated by large population-based studies from our (Franklyn et al., 1998, Franklyn et al., 2005, Boelaert et al., 2013) and other centres (Metso et al., 2007, Brandt et al., 2013a). These studies, as well as a systematic review (Brandt et al., 2011), have shown that the increased mortality in hyperthyroidism is due largely to an excess in deaths from circulatory causes. Subjects with hyperthyroidism therefore represent a particularly vulnerable group in respect of the cardiovascular consequences of the development of obesity.

Importantly, several studies have indicated that the increased risk of mortality in hyperthyroidism is reversed following induction of hypothyroidism with 131-I (Franklyn et al., 2005, Metso et al., 2007, Boelaert et al., 2013). However, when treatment options are discussed, subjects with hyperthyroidism frequently express concern that the administration of radioiodine will result in excessive weight gain, often determining that this is a less favoured therapeutic option. Few studies have systematically assessed the effects of the chosen treatment modality on weight changes in large cohorts of patients with hyperthyroidism.

We set out to determine the extent of weight gain following treatment of hyperthyroidism in a large hospital cohort presenting with a first episode of overt hyperthyroidism to a single specialist Thyroid Clinic in Birmingham, UK. We examined the influence of the treatment modality used (131-I or antithyroid drugs), the development of hypothyroidism, subjects' age, gender and BMI at presentation

as well as aetiology and biochemical control of hyperthyroidism, on the likelihood of weight gain.

5.2 Subjects and methods

5.2.1 Study dataset

Study data were retrieved from the Outpatient Thyroid Clinic Database at the University Hospitals Birmingham NHS Foundation Trust (described in section 2.2.5.1). The project was revised, approved and registered by the University Hospitals Birmingham NHS Foundation Trust (CARMS-11842). Data from records of all adult patients newly diagnosed with overt hyperthyroidism and treated either with thionamide drugs (ATD), administration of radioiodine (131-I) or a combination of both at the Thyroid Clinic between 1990 and 2010 were extracted. Overt hyperthyroidism was defined as raised serum free T4 (fT4) and/or free tri-iodothyronine (fT3) with undetectable serum thyrotrophin (TSH). Further inclusion criteria encompassed a minimum duration of follow-up of 6 months and a minimum of four recorded weight measurements (with recording of clinic weights at presentation and discharge as mandatory), a measurement of patients' height and a confirmed successful outcome at discharge, which was defined as normal serum TSH concentrations (reference range: 0.3-4.5 mIU/L) off any medication for at least 6 months following discontinuation of antithyroid drugs, following 131-I or following start of levothyroxine replacement therapy for hypothyroidism.

All pregnant women, as well as those within 12 months postpartum, were excluded (N=67). Further exclusions consisted of 30 subjects with transient hyperthyroidism due to thyroiditis and 22 with amiodarone-induced thyrotoxicosis. Thirty four subjects with a history of active cancer and 8 with other co-existing pathologies potentially impacting upon weight (eating disorders, coeliac disease and Crohn's disease) were also excluded. The final study cohort thus comprised 1042 subjects aged between 16 to 89 years.

5.2.2 Variable definitions

Subjects were categorised by simple clinical and immunological criteria into three diagnostic groups: Graves' disease, toxic nodular hyperthyroidism and hyperthyroidism of indeterminate aetiology. Graves' disease was defined as presence of biochemical hyperthyroidism with at least two of: palpable diffuse goitre, significant titre (>1:100) of thyroid peroxidase and/or thyroglobulin antibodies and/or presence of thyroid eye disease. Toxic nodular hyperthyroidism was defined as hyperthyroidism in the presence of palpable nodular goitre. Subjects who did not fulfil either of these criteria were categorised indeterminate, representing a mixed group with Graves' disease, toxic nodular hyperthyroidism or both, the size of this group reflecting our policy of not performing routine radionuclide imaging in subjects presenting with hyperthyroidism during the study years.

The following demographic factors were recorded at presentation: gender, age at diagnosis (divided into quartiles: ≤36 years, 37-47 years, 48-60 years, >60 years), ethnicity (white/non-white) and height (meters). Weight was recorded at presentation

and during each follow-up visit. Body Mass Index (BMI), defined as the weight in kilograms divided by the square of the height in metres (kg/m^2) was calculated for each weight datapoint recorded and divided according to the International Classification (WHO, 1995) into underweight: <18.5kg/m^2; normal weight 18.5-25kg/m^2; overweight 25.1-30 kg/m^2 and obese >30kg/m^2. The underweight and normal weight categories were combined and analysed together due to the small number of underweight patients.

Clinical data collected during the initial examination comprised significant past medical history, current drug therapy, smoking status (current smoker/non-smoker), as well as the presence, size and type of goitre. Patients were requested to assess their weight change prior to presentation, categorised as weight loss, weight gain or unchanged. Laboratory measurements included serial concentrations of serum fT4 (reference range: 10-22 pmol/L) and TSH (0.30-4.50 mIU/L) and serum fT3 (3.5-6.5 pmol/L) at presentation. The serum fT4 concentration at diagnosis (used as a marker of disease severity) was categorised into quartiles: 1st quartile: 22.0-29.6; 2nd quartile: 29.7-39.8; 3rd quartile: 39.9-58.2; 4th quartile >58.2 pmol/L. A fifth category was added to account for subjects with T3 thyrotoxicosis (N=45), whose serum fT4 was within the normal range (<22.0 pmol/L). Comparisons were made to the first fT4 quartile (22.0-29.6 pmol/L). Serum concentrations of fT4 during follow-up were categorised as follows: below normal (<10.0 pmol/L), normal (10.0-22.0 pmol/L), raised (22.1-30.0 pmol/L) and high (>30.0 pmol/L). Serial TSH concentrations were categorised as undetectable (<0.10 mIU/L), low but detectable (0.10-0.29 mIU/L), normal (0.30-4.50 mIU/L), slightly raised (4.51-10.00 mIU/L) and markedly raised (>10.00 mIU/L).

For comparison purposes, gender specific BMI data for the West Midlands background population were obtained. The proportions of patients in different BMI categories at presentation and at discharge were compared with the 2003-2005 dataset at presentation and 2005-2007 background population data at discharge, these time periods corresponding to the median presentation (2004) and discharge year (2006) of the study cohort.

5.2.3 Treatment of hyperthyroidism

Subjects were offered treatment with thionamides or with radioiodine (131-I) according to local and national and international guidelines (Ross et al., 2016). Subjects typically commenced a single dose of 20 mg carbimazole (CMZ) or twice daily doses of 100 mg propylthiouracil (PTU). A dose titration regimen was employed in all, with typical maintenance doses of 5-10 mg carbimazole or 50-100 mg propylthiouracil daily. Subjects were monitored every 6-8 weeks until control of hyperthyroidism and then every 3 months. Graves' disease subjects who relapsed after a 12-18 month course of thionamides were advised to undergo 131-I therapy. Prior to 131-I, subjects received antithyroid drugs (ATD) to control hyperthyroidism; thionamides were stopped at least one week before 131-I and not restarted sooner than one week after. Following 131-I, subjects were seen at 6-8 week intervals and were categorised hypothyroid after starting permanent T4 replacement. Those remaining hyperthyroid 6 months after 131-I were offered a second dose and if they declined, they were treated with antithyroid drugs.

5.2.4 Statistical analysis

Demographic and clinical characteristics of the cohort were described using means and standard deviations (SD) for continuous variables and counts and proportions for discrete variables. Statistical significance was set a *priori* at the 5% level.

The proportions of patients in different BMI categories at presentation and at discharge were compared using the Chi square test. T-test and ANOVA tests were used to analyse difference in weight and BMI changes when comparing findings at presentation and at discharge. These statistical analyses were performed in IBM SPSS Statistics (version 22).

A multilevel multivariable linear regression model was developed by the statistical team (Prof. Mohammed Mohammed and Dr. Linda Nichols) to investigate the relationship between weight and demographic and clinical measurements. Time invariant coefficients were: age at presentation, height, gender, ethnicity, aetiology of hyperthyroidism, self-reported weight change at presentation and serum fT4 concentration at presentation. Time variant covariates were: duration of follow-up (months), serum fT4 and TSH concentration at each clinic visit, 131-I treatment and levothyroxine treatment. The effect of 131-I and levothyroxine were considered to occur at the time of first dose of that treatment and continue until the subject was discharged. A single model was developed to predict weight over time taking into account other covariates considered clinically important. Exploratory plots of weight over time suggested that the weight trajectory might be best described with linear, quadratic and cubic terms for time. A small number of subjects (N=125) remained

under follow up beyond three years; clinical measurements were censored at 36 months for all. The model was built with Stata Statistical Software (version 12).

Due to the number of subjects categorised as having hyperthyroidism of indeterminate aetiology, the sensitivity of the findings was investigated by comparing model coefficients with and without those subjects. Interaction effects of 131-I treatment and levothyroxine (L-T4) replacement on subgroups of subjects were investigated to determine whether this treatment had a different effect on weight between the subgroups. At the outset, the interactions between treatment (131-I or levothyroxine) and gender, aetiology as well as age and BMI category at presentation were considered clinically relevant and were therefore investigated. Since higher serum fT4 concentrations are associated with an increased risk of weight loss prior to presentation, the interaction between treatment and presenting fT4 was also explored. Each interaction term was included in the model separately.

5.3 Results

5.3.1 Characteristics of patient population

Table 5-1 displays the baseline characteristics of 1,042 subjects in the cohort. Two hundred and twenty-nine male (22.0%) and 819 (78.0%) female subjects with a mean age of 48.7 ±16.0 SD (range 16-89) years were followed up for a mean duration of 20.1 (range 6-109) months. Two hundred and fifty-four (24.4%) subjects received thionamide drugs only and 788 (75.6%) underwent treatment

with radioiodine which resulted in permanent hypothyroidism in 613 individuals (77.8% of those undergoing 131-I therapy). At presentation, the mean weight of the cohort was 69.8 ±15.7 kg and 531 (51.0%) subjects had a BMI≤25 kg/m^2. Weight presentation differed significantly based on aetiology of hyperthyroidism, smoking status and presenting severity of hyperthyroidism. Patients aged 37-47 years presented heavier than those in the age quartile of 36 years old or younger. By definition, weight was also different in various BMI categories.

Table 5-1: Baseline characteristics of 1,042 subjects presenting with hyperthyroidism. Categorical data is presented as counts and proportions (%), continuous data as means and standard deviation. Mean weight at presentation were compared using T-test for two and ANOVA for multiple categories of a variable.

Characteristic	Male N=229 (22%)	Female N=813 (78%)	All subjects N=1042	Mean weight (SD) all subjects	P value
Mean (SD) **weight** (kg) at presentation	79.6 (15.7)	67.0 (14.5)	69.8 (15.7)		
Duration of follow-up (months)					
Mean (SD)	18.6 (8.6)	20.5 (8.9)	20.1 (8.8)		
Median (IQR)	17.2 (13.6)	19.3 (14.5)	19.1 (14.3)		
BMI category at presentation (kg/m^2)					
Normal/underweight (≤25.0)	111 (48.5%)	420 (51.7%)	531 (51.0%)	**59.4 (0.3)**	
Overweight (25.1 – 30.0)	78 (34.1%)	246 (30.3%)	324 (31.1%)	**73.3 (0.3)**	**<0.001**
Obese (>30.0)	40 (17.5%)	147 (18.1%)	187 (17.9%)	**91.0 (0.4)**	
Age at presentation (years)					
≤36	64 (28.0%)	195 (24.0%)	259 (24.9%)	**66.8 (0.7)**	
37 – 47	45 (19.7%)	212 (26.1%)	257 (24.7%)	**70.4 (0.9)**	**0.03**
48 – 60	57 (24.9%)	218 (26.8%)	275 (26.4%)	**69.8 (0.9)**	
>60	63 (27.5%)	188 (23.1%)	251 (24.1%)	**68.5 (0.8)**	
Ethnicity					
White	164 (71.6%)	631 (77.6%)	795 (76.3%)	69.3 (0.8)	NS (0.12)
Non-white	65 (28.3%)	182 (22.4%)	247 (23.7%)	67.6 (0.8)	
Aetiology of hyperthyroidism					
Graves' disease	86 (37.6%)	343 (42.2%)	429 (41.2%)	**67.6 (0.7)**	
Toxic nodular hyperthyroidism	31 (13.5%)	159 (19.5%)	190 (18.2%)	**68.1 (0.8)**	**0.007**
Indeterminate aetiology	112 (48.9%)	311 (38.3%)	423 (40.6%)	**70.1 (0.9)**	
Smoking status					
Non-smoker	162 (70.7%)	624 (76.8%)	786 (75.4%)	**69.6 (0.8)**	**0.012**
Smoker	67 (29.3%)	189 (23.3%)	256 (24.6%)	**66.9 (0.8)**	
Serum fT4 at presentation (pmol/L)					
<22.0	8 (3.5%)	37 (4.6%)	45 (4.3%)	**73.5 (0.8)**	
22.0 - 29.7	54 (23.6%)	195 (24.0%)	249 (23.9%)	**70.1 (0.8)**	
29.8 - 39.9	50 (21.8%)	201 (24.7%)	251 (24.1%)	**69.5 (0.9)**	**0.03**
40.0 - 58.3	60 (26.2%)	190 (23.4%)	250 (24.0%)	**68.2 (0.9)**	
>58.3	57 (24.9%)	190 (23.4%)	247 (23.7%)	**67.0 (0.7)**	
Treatment administered					
ATD only	41 (17.9%)	213 (26.2%)	254 (24.4%)	67.7 (0.8)	
131-I treatment (± ATD)	37 (16.2%)	138 (17.0%)	175 (16.8%)	70.6 (0.9)	NS (0.14)
131-I (± ATD) and L-T4	151 (65.9%)	462 (56.8%)	613 (58.8%)	68.9 (0.8)	

5.3.2 Weight changes during the follow-up of the entire cohort

Seven hundred and two subjects (67.4%) reported weight loss prior to presentation, with reported weight increase in 80 (7.7%) subjects. During the period of follow-up, the mean weight gain of the cohort was 6.9 (±6.5 SD) kg. In 723 subjects (69.4%) a minimum 5% (range 2.4-34.7 kg) and in 448 subjects (43.0%) a minimum of 10% (range 4.7-34.7 kg) increase was observed when comparing body weight at discharge and at presentation. Weight did not increase in all subjects and 20 (1.9%) subjects lost 5% or more of their presenting body weight during follow-up. Figure 5-1 illustrates the mean percentage weight change in all subjects during follow-up. Weight gain was most pronounced during the first 6 months following presentation, when a mean increase of 5.8% was observed. Weight gain continued throughout the period of follow-up and reached a mean of 13.1% increase at 36 months after presentation.

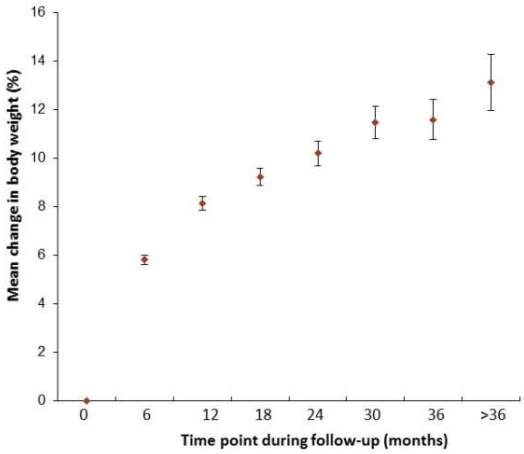

Figure 5-1: Percentage of mean weight change in the study cohort during the follow-up period in six-monthly intervals; whiskers represent confidence intervals

Table 5-2 illustrates the changes in weight from presentation to discharge according to baseline characteristics and treatment administered, using univariate regression

analysis. Men gained more weight than women and those with an underlying aetiology of Graves' disease gained more than subjects with toxic nodular hyperthyroidism or those with indeterminate aetiology. Older subjects gained less than younger patients did and weight gain was most pronounced in those with the highest fT4 concentrations at presentation. Weight gain was similar in subjects who were euthyroid following 131-I administration but was higher following 131-I induced hypothyroidism, compared with those treated with antithyroid drugs.

Table 5-2: Mean weight change (from the initial visit to discharge) by baseline characteristics.

	N	Mean weight change at discharge (kg)	(95% CI)	P-value
Gender				
Male	229	8.98	(8.14 to 9.82)	
Female	813	6.33	(5.92 to 6.77)	**<0.001**
Aetiology				
Graves'disease	429	8.60	(7.93 to 9.37)	
Toxic nodular hyperthyroidism	190	5.37	(4.56 to 6.17)	**<0.001**
Indeterminate aetiology	423	6.01	(5.42 to 6.45)	**<0.001**
Ethnicity				
Non-white	247	6.65	(5.89 to 7.42)	
White	795	6.99	(6.57 to 7.50)	0.47
Age at presentation (years)				
≤36	259	7.97	(7.04 to 8.90)	
37 - 47	257	6.76	(6.04 to 7.68)	**0.03**
48 - 60	275	6.75	(6.11 to 7.57)	**0.03**
>60	251	6.13	(5.48 to 6.79)	**0.001**
BMI category at presentation				
Normal/underweight (≤25.0 kg/m^2)	531	6.83	(6.35 to 7.37)	
Overweight (25.1 – 30.0 kg/m^2)	324	6.93	(6.25 to 7.69)	0.82
Obese (>30.0 kg/m^2)	187	7.09	(6.07 to 8.26)	0.63
Smoking status				
Non/ex-smokers	786	6.72	(6.32 to 7.72)	
Current smokers	256	7.49	(6.71 to 8.33)	0.10
Treatment				
Thionamide drugs only	254	5.90	(5.21 to 6.59)	
131-I treatment (± thionamides)	175	6.48	(5.52 to 7.39)	0.36
131-I (± thionamides) and LT-4	613	7.45	(6.96 to 8.02)	**0.001**
Serum fT4 at presentation (pmol/L)				
<22.0	45	3.27	(2.31 to 4.70)	0.17
22.0 - 29.7	249	4.63	(4.11 to 5.34)	
29.8 - 39.9	251	6.22	(5.50 to 6.96)	**0.004**
40.0 - 58.3	250	8.20	(7.52 to 8.88)	**<0.001**
≥58.3	247	9.27	(8.30 to 10.24)	**<0.001**

5.3.3 Comparison of the weight status to the background population

Table 5-3 and Figure 5-2 present the proportions of female and male subjects by BMI category at presentation and at discharge compared to the background population of the West Midlands. That comparison with the 95% confidence intervals for the cohort shows that for both male and female subjects there was a lower percentage of the cohort in the overweight/obese categories at baseline than in the West Midlands population. On discharge, the proportion of obese patients in the cohort was higher than that of the West Midlands population.

Table 5-3: Proportion of hyperthyroid patients by BMI category at presentation and at discharge: comparison with West Midlands population

	Presentation			Discharge		
BMI	Hyperthyroid cohort	(95% CI)	West Midlands	Hyperthyroid cohort	(95% CI)	West Midlands
Males						
Underweight/normal	48%	(42% to 55%)	27%	22%	(16% to 27%)	31%
Overweight	34%	(28% to 40%)	44%	41%	(35% to 47%)	44%
Obese	17%	(13% to 22%)	27%	37%	(31% to 43%)	25%
Females						
Underweight/normal	52%	(48% to 55%)	39%	33%	(30% to 36%)	39%
Overweight	30%	(27% to 33%)	33%	35%	(32% to 38%)	34%
Obese	18%	(15% to 21%)	27%	32%	(29% to 35%)	27%

Of the 531 subjects with a BMI <25 kg/m^2 at presentation, 201 (37.9%) become overweight and 20 (3.8%) obese at discharge. Almost half (N=145, 44.6%) of 324 subjects who were overweight at presentation became obese, however, 16 overweight patients (5.0%) lost weight and moved to the normal weight category. 185 out of 187 (98.9%) subjects who were obese prior to treatment

for hyperthyroidism remained obese; their median BMI increased from 33.37 [IQR: 31.21-36.52] to 36.19 [IQR: 33.89-39.37] kg/m^2.

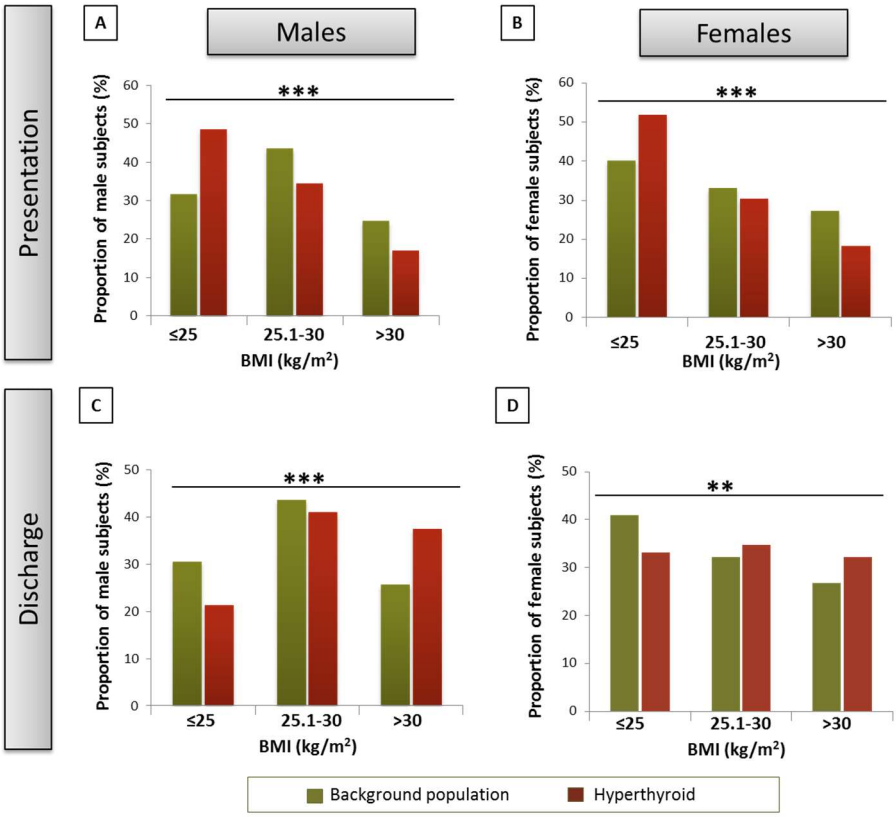

Figure 5-2: Proportion of hyperthyroid patients by BMI category at presentation and at discharge: comparison with West Midlands background population

5.3.4 Weight changes based on the administered treatment

Among those treated with I-131, 37.2% (293/788) gained over 4 kg following I-131 administration and 14.5% (89/613) among those who developed hypothyroidism. A multilevel model was developed to investigate the relationship between the weight of subjects and treatment modality whilst controlling for other covariates. Table 5-4 displays the coefficients of all covariates used in the model. The coefficients

in this model indicate weight change (in kg), when all other covariates are kept constant. This analysis demonstrated that 131-I treatment was associated with a small but significant increase in weight (model coefficient: 0.61, P<0.001), compared with thionamide treatment alone. Slightly or markedly raised serum fT4 concentrations during follow-up were associated with a weight decrease compared with serum fT4 concentrations within the reference range (-0.67, P<0.001 and -1.39, P<0.001, respectively). Similarly, undetectable serum TSH (-1.01, P<0.001) and below normal serum TSH concentrations (-0.72, P<0.001) during follow-up were associated with weight decrease, whereas slightly (0.35, P<0.001) or markedly raised TSH measurements (0.87, P<0.001) were associated with significant weight increase compared with serum TSH within the normal range during follow-up. Hence, induction of hypothyroidism during the treatment, indicated by serial serum TSH concentration, was associated with an additional significant weight increase. On the contrary, prolonged thyrotoxicosis, indicated by high serial concentrations of serum fT4, was associated with reduced weight gain. When corrected for fluctuation in serum concentrations of fT4 and TSH, treatment with levothyroxine itself was not affecting the weight change (0.17, NS).

It can be predicted that a typical subject, whose hyperthyroidism would be easily controlled with ATD pre-treatment and who would undergo 131-I therapy and become overtly hypothyroid requiring levothyroxine replacement would, therefore, weigh 1.48 kg more than the same subject treated with thionamides not becoming hypothyroid. Figure 5-3 illustrates the prediction of weight change for an average white, non-smoking female patient with Graves' disease depending on the treatment administered.

Table 5-4: Multilevel model coefficients to predict weight change. The coefficients in this model indicate weight change (in kg), when all other covariates are kept constant.

	Coefficient	(95% CI)	P-value
Duration of follow-up (months)	0.37	(0.34 to 0.40)	**<0.001**
Age at presentation (years)			
≤36	0		
37 - 47	1.93	(0.81 to 3.04)	**0.001**
48 - 60	0.57	(-0.58 to 1.72)	0.334
>60	-0.50	(-1.78 to 0.77)	0.440
Gender			
Male	0		
Female	-2.05	(-3.26 to -0.85)	**0.001**
Ethnicity			
Non-white	0		
White	1.19	(0.23 to 2.16)	**0.016**
Aetiology			
Graves disease	0		
Toxic nodular hypothyroidism	-0.69	(-2.03 to 0.65)	0.313
Indeterminate	-0.06	(-0.97 to 0.86)	0.903
BMI category at presentation			
Underweight/Normal	0		
Overweight	13.91	(13.01 to 14.80)	**<0.001**
Obese	32.24	(31.15 to 33.34)	**<0.001**
Smoking status			
Non/ex-smokers	0		
Current smokers	-1.21	(-2.14 to -0.28)	**0.011**
Serum fT4 at presentation (pmol/L)			
<22.0	0.40	(-1.80 to 2.60)	0.721
22.0 - 29.7	0		
29.8 - 39.9	0.54	(-0.60 to 1.68)	0.355
40.0 - 58.3	0.07	(-1.09 to 1.22)	0.907
>58.3	0.79	(-0.39 to 1.97)	0.187
Serial serum fT4 during FU (pmol/L)			
<10.0	0.15	(-0.03 to 0.34)	0.098
10.0 - 22.0	0		
22.1 - 30.0	-0.67	(-0.85 to -0.49)	**<0.001**
>30.0	-1.39	(-1.61 to -1.17)	**<0.001**
Serial serum TSH (mU/L)			
<0.10	-1.01	(-1.17 to -0.85)	**<0.001**
0.10 - 0.29	-0.72	(-0.94 to -0.50)	**<0.001**
0.30 - 4.50	0		
4.51 -10.00	0.35	(0.16 to 0.55)	**<0.001**
>10.00	0.87	(0.67 to 1.08)	**<0.001**
Treated with 131-I			
No	0		
Yes	0.61	(0.42 to 0.80)	**<0.001**
Treated with levothyroxine			
No	0		
Yes	0.17	(-0.07 to 0.41)	0.172
Time after iodine (months)	0.04	(0.00 to 0.08)	**0.040**
Height (cm)	0.83	(0.78 to 0.88)	**<0.001**
Time squared (months)	-0.01	(-0.01 to -0.01)	**<0.001**
Constant	61.44	(59.75 to 63.13)	<0.001

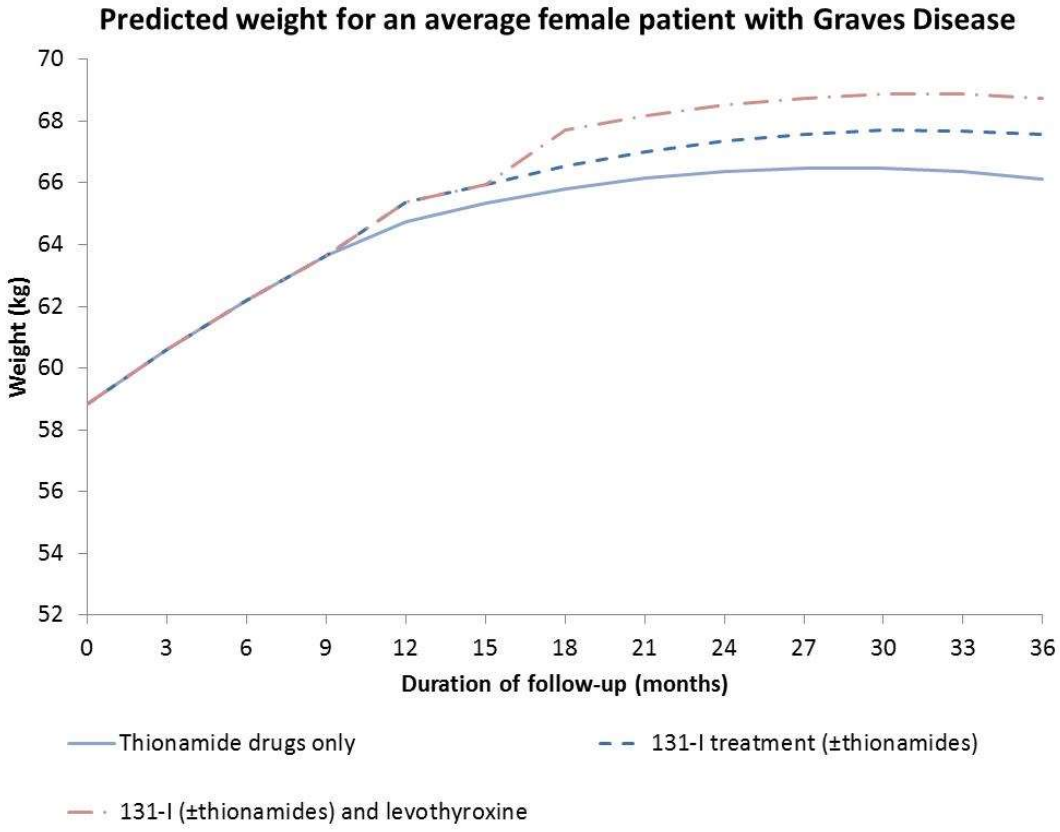

Figure 5-3: Predicted weight gain of an average white, non-smoking female patient with Graves' disease (produced by Prof Mohammed Mohammed and Dr Linda Nichols)

5.3.4.1 *Sensitivity analysis comparing defined diagnoses of Graves' disease with toxic nodular goitre excluding those with indeterminate aetiology*

A sensitivity analysis (Table 5-5) was undertaken to test the model in patients with defined diagnoses of Graves' disease or toxic nodular hyperthyroidism and excluding those with hyperthyroidism of indeterminate aetiology. This analysis revealed similar findings and confirmed weight increase in subjects treated with radioiodine compared with those receiving antithyroid drugs (0.74, P<0.001). Raised serum fT4 concentrations during follow-up (-0.61, P<0.001 for fT4 22.1-30.0 pmol/l;

- 1.60, P<0.001 for fT4>30 pmol/l) and below normal TSH concentrations (-0.95, P<0.001 for TSH<0.1 mIU/l; -0.70, P=0.05 for TSH 0.1-0.3 mIU/l) were associated with significant weight decrease whereas raised serum TSH (0.40, P<0.001 for TSH 4.51-10 mIU/l; 0.86, P<0.01 for TSH>10 mIU/l) was associated with significant weight increase. Adjusted for weight changes associated with fluctuation in thyroid hormone concentrations, there was no additional significant weight gain if 131-I resulted in permanent hypothyroidism requiring treatment with levothyroxine (0.08, P=NS).

Table 5-5: Sensitivity analysis: Multilevel coefficients to predict weight change in patients with defined diagnoses of Graves' disease or toxic nodular hyperthyroidism.

	Coefficient	(95% CI)	P-value
Duration of follow-up (months)	0.40	(0.36 to 0.44)	**<0.001**
Age at presentation (years)			
≤36	0		
37 - 47	2.17	(0.80 to 3.54)	**0.002**
48 - 60	0.74	(-0.68 to 2.15)	0.307
>60	-0.86	(-2.61 to 0.89)	0.336
Gender			
Male	0		
Female	-2.34	(-3.89 to -0.78)	**0.003**
Ethnicity			
Non-white	0		
White	0.96	(-0.26 to 2.18)	0.125
Etiology			
Graves disease	0		
Toxic nodular hypothyroidism	-0.66	(-2.07 to 0.75)	0.357
BMI category at presentation			
Underweight/Normal	0		
Overweight	14.07	(12.95 to 15.18)	**<0.001**
Obese	31.34	(29.91 to 32.76)	**<0.001**
Smoking status			
Non/ex-smokers	0		
Current smokers	-1.36	(-2.47 to -0.25)	**0.016**
Serum fT4 at presentation (pmol/L)			
<22.0	0.56	(-1.62 to 2.73)	0.616
22.0 - 29.7	0		
29.8 - 39.9	0.31	(-1.24 to 1.85)	0.695
40.0 - 58.3	-0.56	(-2.08 to 0.96)	0.469
>58.3	0.43	(-1.07 to 1.92)	0.575
Serial serum fT4 during FU (pmol/L)			
<10.0	0.18	(-0.06 to 0.43)	0.141
10.0 - 22.0	0		
22.1 - 30.0	-0.61	(-0.85 to -0.38)	**<0.001**
>30.0	-1.60	(-1.87 to -1.32)	**<0.001**
Serial serum TSH (mU/L)			
<0.10	-0.95	(-1.17 to -0.74)	**<0.001**
0.10 - 0.29	-0.70	(-0.99 to -0.42)	**<0.001**
0.30 - 4.50	0		
4.51 -10.00	0.40	(0.13 to 0.66)	**0.003**
>10.00	0.86	(0.58 to 1.13)	**<0.001**
Treated with 131-I			
No	0		
Yes	0.74	(0.49 to 0.98)	**<0.001**
Treated with levothyroxine			
No	0		
Yes	0.08	(-0.23 to 0.40)	0.603
Time squared (months)	-0.01	(-0.01 to -0.01)	**<0.001**
Time after iodine (months)	0.03	(-0.02 to 0.09)	0.193
Height (cm)	0.80	(0.73 to 0.87)	**<0.001**
Constant	62.18	(60.08 to 64.27)	**<0.001**

5.3.5 Factors influencing weight change according to treatment administered

The same multi-level model was used to investigate interaction effects of the treatment administered and development of 131-I-induced hypothyroidism, with a number

of clinical and biochemical parameters at presentation (Table 5-6). Radioiodine treatment was associated with a different effect on males and females: weight gain associated with 131-I administration in men was 0.58 kg higher than in women (P=0.004). The effect of radioiodine-induced hypothyroidism did not significantly differ between genders.

The effect of radioiodine administration was different in patients depending on the underlying aetiology of hyperthyroidism and was more pronounced in those with Graves' disease who gained 0.94 kg on average, compared to those with TNG who gained 0.45 (P=0.036) as well as to subjects with indeterminate aetiology, who were predicted to gain 0.34kg (P=0.002). The effect of induction of hypothyroidism on weight gain did not differ among patients with varying disease aetiology.

131-I administration and subsequent hypothyroidism differently affected patients within the normal and the overweight BMI category at presentation. Overweight patients were predicted more weight gain, which was an additional 1 kg following radioiodine treatment and a further 0.5 kg associated with levothyroxine replacement. In comparison, subjects within the normal BMI category were predicted to gain 0.4 kg (p=0.005) following radioiodine and to lose 0.1 kg following subsequent induction of hypothyroidism. Effects of 131-I and hypothyroidism on obese patients were similar to those with normal BMI at presentation.

Patients with higher presenting serum fT4 were more affected by 131-I administration than those with less severe thyrotoxicosis. Weight gain following the induction of hypothyroidism affected T3 toxic patients significantly less than those with increased serum fT4 concentration at presentation. Age was not associated with

different weight responses, either following radioiodine treatment or following the induction of hypothyroidism (Table 5-6).

Table 5-6: Interaction effects of treatment administered and development of hypothyroidism with clinical and biochemical parameters

	Interaction with 131-I treatment			Interaction with 131-I induced hypothyroidism		
Interaction	**Coefficient**	**(95% CI)**	**P-value**	**Coefficient**	**(95% CI)**	**P-value**
Gender						
Male	1.05	(0.70 to 1.40)		0.04	(-0.37 to 0.46)	
Female	0.47	(0.26 to 0.69)	**0.004**	0.21	(-0.06 to 0.47)	0.478
Etiology						
Graves' disease	0.94	(0.66 to 1.21)		0.27	(-0.06 to 0.60)	
Toxic nodular hypothyroidism	0.45	(0.07 to 0.83)	**0.036**	-0.30	(-0.85 to 0.24)	0.064
Indeterminate	0.34	(0.05 to 0.63)	**0.002**	0.22	(-0.12 to 0.56)	0.814
BMI category at presentation						
Underweight/normal	0.43	(0.17 to 0.68)		-0.10	(-0.41 to 0.20)	
Overweight	0.99	(0.67 to 1.31)	**0.005**	0.56	(0.18 to 0.94)	**0.004**
Obese	0.52	(0.12 to 0.91)	0.696	0.30	(-0.20 to 0.80)	0.153
Serum fT4 at presentation (pmol/L)						
<22.0	0.13	(-0.65 to 0.91)	0.938	-1.23	(-2.40 to -0.06)	**0.010**
22.0 - 29.7	0.16	(-0.20 to 0.52)		0.41	(-0.04 to 0.87)	
29.8 - 39.9	0.43	(0.06 to 0.79)	0.298	0.00	(-0.42 to 0.42)	0.169
40.0 - 58.3	0.97	(0.62 to 1.32)	**0.001**	0.46	(0.06 to 0.86)	0.882
>58.3	0.93	(0.58 to 1.27)	**0.002**	-0.02	(-0.44 to 0.40)	0.153
Age at presentation (years)						
≤36	0.43	(0.06 to 0.80)		0.08	(-0.34 to 0.51)	
37 - 47	0.83	(0.46 to 1.20)	0.121	0.09	(-0.36 to 0.54)	0.984
48 - 60	0.60	(0.27 to 0.93)	0.484	0.21	(-0.17 to 0.59)	0.643
>60	0.60	(0.27 to 0.93)	0.480	0.26	(-0.17 to 0.69)	0.556

5.4 Discussion

5.4.1 Weight gain as observed in the overall cohort

Our study of more than 1,000 patients treated for hyperthyroidism confirms significant weight gain following antithyroid treatment, especially during the initial 6 months

of follow-up but continuing for more than 36 months (Figure 5-1). Further detailed analysis indicated a small but significant excess weight gain after treatment with 131-I compared with antithyroid drugs and further additional weight gain following the induction of hypothyroidism. We determined that weight changes were significantly associated with alterations in thyroid hormone concentrations during treatment. Moreover, we demonstrated that men, those with Graves' disease and those with more severe hyperthyroidism at presentation are at particular risk of weight gain following administration of 131-I.

Thyroid hormones regulate energy metabolism (Reinehr, 2010) and thyroid dysfunction is associated with changes in body weight and composition as well as total and resting energy expenditure (Biondi, 2010). We determined that the proportion of subjects who were underweight or had normal weight was higher than the background population matched in time and geographical location, consistent with the catabolic effects of high levels of circulating thyroid hormones. Our finding that the proportion of obese men and women was significantly higher than the background population of West Midlands following cure of hyperthyroidism supports the hypothesis that treated hyperthyroidism is a risk factor for obesity and that restoration of euthyroidism is associated with the gain exceeding simple replenishment of the pre-morbid weight.

The replenishment of weight lost at the onset of hyperthyroidism was studied in a cohort of military patients, 84% of which were men, with recorded premorbid weights during regular health check-ups (Hoogwerf and Nuttall, 1984). Patients, generally, regained previously lost weight to achieve pre-morbid levels during the first

24 months following treatment initiation. However, body weight gain subsequently continued to increase past the pre-morbid set-point. Whilst the evidence is compelling, the Hoogwerf and Nutall study cohort is atypical and demographically quite different from community-diagnosed hyperthyroidism. Therefore, the findings have to be interpreted with caution. Similar conclusions of weight overshoot following antithyroid therapy, although based on much less precise patient-recalled data, were confirmed later in the community setting. Two to five years following treatment for toxic diffuse goitre, 50-80% of women reported weight gain (Berg et al., 1996, Jansson et al., 1993).

We determined that weight gain was most pronounced during the initial 6 months following start of treatment (Figure 5-1), consistent with other reports in adults (Dale et al., 2001, Hoogwerf and Nuttall, 1984, Rathi et al., 2008, Watts et al., 2002) and children (van Veenendaal and Rivkees, 2011). The timing corresponds to the greatest change in thyroid function associated with biochemical resolution of hyperthyroidism. The greatest amount of weight gain was observed in adults in whom circulating thyroid hormones normalised quickly (Hoogwerf and Nuttall, 1984) and a strong correlation between thyroid hormone concentration changes and changes in body weight were found in children (van Veenendaal and Rivkees, 2011).

5.4.2 Factors affecting weight gain during the treatment for hyperthyroidism

When comparing presentation and discharge weights, we established that men, younger subjects, those diagnosed with GD, subjects with more severe hyperthyroidism and patients who developed radioiodine-induced hypothyroidism gained significantly more weight. Additionally, our multilevel model established time-varying changes in serum concentrations of thyroid hormones as significant factors influencing total weight change at the end of the study. In particular, excess of circulating fT4 resulted in less weight gain, while the association with serum TSH was significant when TSH was abnormal, either below or above the normal range. Low TSH or undetectable TSH were associated with decrease in body weight, while raised TSH concentrations were positively linked to final weight. The extend of TSH rise or suppression was directly correlated with the amount of observed weight change.

Thus far, our model is the most complex analysis exploring and quantifying associations of various contributing factors with weight change following antithyroid treatment. Results of similar smaller studies following antithyroid treatment have been inconsistent. Jansson et al. (1993) compared various clinical and metabolic factors in women to those without self-reported weight problems at an average of 4 years following treatment for hyperthyroidism. They found no significant differences between the groups in regard to pretreatment thyroid hormone concentrations, method of treatment, smoking habits or levothyroxine therapy replacement. Post-treatment serum concentrations of TH, TSH, cortisol, procollagen III

peptide, cholesterol, HDL or triglycerides were similar in both groups. However, the study was small, comparing the effects on 20 women in each group. Pre-morbid weight, which was based on recall from 4 years, and the self-definition of "weight problems" are both very bias-prone elements of the study and therefore the results have to be interpreted with caution.

Studies based on more robust data have postulated that consequent hypothyroidism (Dale et al., 2001, Brunova et al., 2003), aetiology of Graves' disease (Dale et al., 2001, Rathi et al., 2008) and male gender (Ariza et al., 2010) increased the likelihood of weight gain, which was also found in our investigation. Furthermore, the protective effect of smoking, noted in our study, was demonstrated by Rathi et al. (2008). Importantly, we demonstrated that the control of thyroid function during follow-up significantly influenced the total amount of weight gain. Prolonged increases in serum fT4 and/or prolonged presence of below normal TSH reduced the predicted weight gain at 36 months of follow-up. An increase of serum TSH above the normal range was associated with additional weight gain. Our findings confirm those of Hoogwerf and Nuttall (1984) who reported that the return to baseline weight was delayed in subjects who remained hyperthyroid for prolonged periods of time following initial treatment.

Increased basal metabolic rate and an overall increase in protein degradation and lipolysis as well as fat malabsorption have been proposed as factors contributing to weight loss from hyperthyroidism (Silva, 2003). However, studies evaluating body composition changes during hyperthyroidism and following treatment have revealed conflicting results. Some have shown reduction in lean body mass at presentation

with regain of lean mass and not fat after achievement of euthyroidism (Acotto et al., 2002, de la Rosa et al., 1997, Dutta et al., 2012), whilst others show increases in both fat and fat-free mass (Greenlund et al., 2008, Lonn et al., 1998).

Hunger/satiety signals are altered in patients with hyperthyroidism and hence weight loss, despite increased appetite and food intake, being documented in subjects with high circulating thyroid hormone concentrations (Abid et al., 1999, Rojdmark et al., 2005). Alterations in the neurophysiology of food intake regulation with marked hyperphagia and craving for carbohydrates was found in subjects with untreated Graves' disease (Pijl et al., 2001). Further studies have revealed conflicting results regarding concentrations of appetite controlling hormones, including leptin and ghrelin, during hyperthyroidism and following restoration of euthyroidism. Reduced leptin concentrations were found at diagnosis of hyperthyroidism and increased following treatment with antithyroid drugs (Iglesias et al., 2003) and radioiodine (Obermayer-Pietsch et al., 2001), whereas others documented increasing leptin concentrations in patients who went from a hypothyroid to a subclinically hyperthyroid state following treatment for differentiated thyroid cancer (Hsieh et al., 2002). Reduced ghrelin concentrations were found to markedly increase following treatment of hyperthyroidism (El Gawad et al., 2012, Rojdmark et al., 2005), although a more recent study found that hyperphagia and alterations in weight homoeostasis associated with hyperthyroidism were independent of circulating leptin and ghrelin levels (Dutta et al., 2012).

Excess weight gain following antithyroid treatment may be due to a mismatch between appetite and changes in metabolic rate. Reductions in metabolic rate associated

with food energy intake which was initially greater than required to maintain the premorbid weight were observed when thyroid hormone concentrations decreased in radioiodine-treated hyperthyroidism (Abid et al., 1999). Similarly subnormal levels of energy expenditure and spontaneous physical activity caused by lowering of thyroid hormones during antithyroid treatment have been documented (Jacobsen et al., 2006) and positive correlations between serum fT4 concentration and resting energy expenditure have been demonstrated (Klieverik et al., 2011).

5.4.3 Weight changes in relation to the modality of treatment

The other focus of our study was to estimate the effects of 131-I treatment on long-term weight change in comparison to treatment with thionamides. In our model, we demonstrated that there was an overall modest (on average just 0.61 kg) but significant increase in weight gain in those treated with 131-I as compared to medical therapy alone. An additional small but significant increase was noted with development of hypothyroidism, indicated by an increase in time-varying serum TSH concentrations. The start of levothyroxine replacement following the induction of hypothyroidism was not found to be significantly associated with weight change. Altogether, the average expected weight increase in those with hypothyroidism induced by 131-I treatment was around 1.5 kg as compared to patients treated with adequate titration of thionamides. Our calculations were confirmed when considering the crude means of weight changes in the various therapeutic groups (Table 5-2), accounting for 5.9 kg in those treated with thionamides only, 6.5 kg in those administered 131-I and remaining euthyroid, and 7.5 kg in those treated with 131-I followed by levothyroxine replacement for induced hypothyroidism.

A similar prediction of weight gain following treatment for thyrotoxicosis was confirmed in the sub-cohort of those with a defined aetiology of hyperthyroidism. Administration of 131-I and development of hypothyroidism, expressed as a time-variant factor of raised serial TSH, was significantly associated with higher expected weight gain. The start of treatment with levothyroxine did not significantly affect weight change in this group of patients either. Other factors associated with weight gain following antithyroid treatment were similar to those of the total cohort with the exception of ethnicity, which was not significantly associated with weight change in the sensitivity analysis.

Only a few smaller studies have compared the effect of different treatment modalities on weight gain in univariate analyses. After one year of follow-up analysing 65 patients undergoing one of three modes of treatment of hyperthyroidism, Pears et al. (1990) found the highest increase in body weight of 7.4 kg in patients administered 131-I, which was 2 kg more than those treated with ATDs and 1.1 kg higher than those treated with thyroidectomy. Very different results were found by Dale et al. (2001), who demonstrated that there was no difference in weight gain comparing thionamides with 131-I (5.2 vs. 4.8 kg) but patients treated with surgery gained significantly more (10.5 kg). In our study, analysing a much bigger cohort, we were able to find a small but significant increase in weight gain in those treated with 131-I in comparison to medical treatment.

The observed excess weight gain following 131-I therapy was not distributed equally within the cohort (Table 5-6). We identified that patients with underlying Graves' disease and treated with 131-I were more affected by weight gain than those

with hyperthyroidism of any other aetiology. Similarly, those presenting with more severe hyperthyroidism (serum fT4 above 40 pmol/L) gained more weight following 131-I therapy than those with less severe forms of hyperthyroidism. Also, men gained more weight than women and overweight patients more than those within the normal/underweight BMI category. This can possibly be explained by a bigger biological "capacity" of weight gain due to the larger body size in these patients. Interestingly, obese patients were expected to have similar weight gain after 131-I compared to those with normal BMI. Radioiodine administration did not significantly influence the weight gain in relation to the age of patients at presentation. These results are similar to a study of 111 patients treated with 131-I and requiring levothyroxine following induction of hypothyroidism which demonstrated increased weight gain in men but no association with age (Ariza et al., 2010). In this study, there were no significant effects of aetiology of hyperthyroidism on weight gain at any point studied. Higher concentration of fT3 at diagnosis significantly predicted more weight gain at 24 months following 131-I administration, although effects of serum fT4 at presentation were not analysed.

5.4.4 Clinical implications

One of the clinical issues addressed by the study was patients' concern that "radioiodine treatment would make them fat". Although we did find a significant increase in weight associated with the 131-I administration, the average added absolute increase of 0.6 kg does not seem likely to be clinically important. An additional small increase in weight of less than 1 kg associated with induction of hypothyroidism should not outweigh the potential benefits of definitive treatment (Boelaert et al.,

2013). By identifying those patient groups at particular risk of additional weight gain, our study helps to facilitate the individualisation of treatment and to support the decision makers, both physicians and patients. Having established the association between more excessive weight gain and increased serial TSH, we would like to propose that expedited diagnosis and treatment of hypothyroidism following I-131 may potentially reduce the risk of excessive weight gain and further studies to confirm this would be useful.

In those who lost weight prior to presentation, replenishment of body mass may be desirable. Studies on changes in body composition following treatment for hyperthyroidism are conflicting. Lonn at al. (1998) found that during the first three months of treatment a considerable part of the initial weight gain consisted of an increase in lean body mass, mainly muscles. Later, the proportions of lean to fat mass were changing and by 12 months the gain was mostly caused by accumulation of fat. Similar results were also confirmed by de la Rosa et al (1997). However, Jacobsen et al. (2006) claimed that the entire weight gain during the first year can be attributed to fat accumulation. Although weight regain may be desirable, efforts should be directed towards limiting unnecessary fat build-up due to associated morbidity and diminished quality of life (Kelderman-Bolk et al., 2015).

Our study demonstrates excessive weight gain in some patients undergoing treatment for hyperthyroidism and identifies particular 'at risk' groups. We advocate controlled randomised studies to test appropriate interventions to limit unwanted weight gain.

5.4.5 Limitation of the study

Although the present study is the biggest and one of the most complex in this area, there are a number of shortcomings. Firstly, our analysis is limited to two out of three treatment modalities for hyperthyroidism. This is due to differences in systematic collection of data on thyroid patients between medical and surgical clinics, which made common analysis impossible. Additionally, we did not have enough data to analyse either total or free serum T3 levels, which have previously been associated with differences in energy expenditure and weight changes.

Moreover, establishing pre-morbid weight proved impossible in our study. That was mainly due to three factors: the indolent disease course, inaccurate recall of premorbid weight by patients as well as varying use by patients and clinicians of units measuring weight (stones, kilos or pounds) which was not always clearly indicated.

A further shortcoming of our study is the large proportion of patients with indeterminate underlying aetiology of hyperthyroidism. This is in part due to the lack of routine testing for TSH receptor antibodies, which would allow for better identification of Graves' disease. However, our sensitivity analysis including only patients with well-defined underlying diagnoses lends further support to the validity of our data.

Due to the retrospective nature of the study, other data clinically relevant to this research, such as concentrations of fT3, insulin, cholesterol and hormones involved

in appetite regulations, have not been systematically recorded and were hence not available for analysis.

5.4.6 Conclusions

We demonstrated that the weight re-gain and weight 'over-shoot' following restoration of euthyroidism is associated with treatment for hyperthyroidism. We observed significant associations between serial serum concentration of TSH as well as fT4 outside the reference range with weight changes during the follow-up. We established that radioiodine treatment was associated with a small but significant increase in weight compared to treatment with a course of thionamides and additional increase following induction of hypothyroidism. The mean small amount of weight gain following radioiodine treatment compared to antithyroid drugs does not seem to be clinically relevant. However, based on the increased risk of obesity at discharge observed in comparison with background population, we postulate that the risk of excess weight gain should form part of the process of informed decision when discussing therapy for hyperthyroidism with patients. It would be interesting to evaluate if life-style interventions may prevent excessive weight gain in patients with hyperthyroidism and efforts are underway in our group to obtain funding for a randomised trial assessing the potential benefits this.

Chapter 6. THYROID FUNCTION TESTING IN HOSPITALISED PATIENTS

6.1 Introduction

Laboratory testing is in general a common and expensive diagnostic activity. The costs of diagnostic testing account for more than 10% of all health care costs and this fraction is rapidly increasing with the advent of better and more sophisticated tests. In addition to financial considerations, blood testing burdens patients with anxiety, and the risk of false-positive results, causing unnecessary treatment initiation or intensification (Koch et al., 2013, Salisbury et al., 2011, McCoy et al., 2015). Only a third of tests ordered influence clinical decision making (Miyakis et al., 2006). Despite all those costs, diagnostic errors are frequent, with recent estimates suggesting that in the USA, more than a million patients per year are harmed by diagnostic errors (Newman-Toker and Makary, 2013), encompassing incorrect, missed or grossly delayed diagnoses, which differ in severity of consequences from very mild to fatal (Graber, 2013).

Laboratory testing is the cornerstone for diagnosing and managing thyroid dysfunction. The clinical picture of hypo- or hyperthyroidism is incomplete without biochemical confirmation. Furthermore, non-specific or completely asymptomatic forms of hyperthyroidism are common, especially among the elderly (as discussed

in Chapter 3), and laboratory investigations are especially needed to confirm the diagnosis in this patient group. At the end of the 20th century, there were an estimated 10 million requests for Thyroid Function Test (TFT) per annum (Association of Clinical Biochemistry, 2006), resulting in annual costs of £30 million taking into account only reagent costs and not including costs of laboratory staff and equipment (Beckett and Toft, 2003).

The UK Guidelines for the Use of TFTs (Association of Clinical Biochemistry, 2006) do not support a population screening policy for thyroid dysfunction. Primary care physicians are advised to limit testing to those patients where clinical suspicion of thyroid dysfunction is high. Additionally, a case-finding strategy is proposed as part of assessment in patients with clinical evidence of goitre, AF, dyslipidaemia, osteoporosis and subfertility. Surveillance is recommended for patients with a history of neck irradiation and in those with type-1 diabetes mellitus, Down or Turner Syndromes as well as those treated with amiodarone or lithium.

In patients who are diagnosed with thyroid dysfunction, monitoring of TFTs is required (Association of Clinical Biochemistry, 2006, Jonklaas et al., 2014). During treatment of hyperthyroidism determination of thyroid function is recommended at one to three monthly intervals and following completion of treatment annual testing is required to check for disease recurrence or to monitor development of hypothyroidism. Once an appropriate dose of levothyroxine replacement has been established in patients with hypothyroidism, the dose usually remains constant (Jonklaas et al., 2014). Current recommendations advise long-term follow-up with at least one annual measurement of serum TSH to check compliance

and dosage, taking into account variations caused by concomitant drug treatment (Association of Clinical Biochemistry, 2006).

Despite guidelines advising on appropriate testing strategies, an audit of general practitioners' TFT requesting patterns revealed high variability in test ordering between practices (Vaidya et al., 2013). The estimated annual rate for TSH requests varied from 6.2 to 355.8 per 1,000 population registered with the practice. Only a small proportion of this variation (24%) could be explained by differences in prevalence of thyroid dysfunction or socioeconomic deprivation. The rationale behind the decisions to thyroid function testing and the consequences of potentially abnormal results on individual patient care remain unknown.

In the hospital setting, interpretation of TFT is even more challenging and current national and international recommendations (Association of Clinical Biochemistry, 2006, Baloch et al., 2003) therefore advise against routine thyroid function testing unless there is a high level of clinical suspicion. This is mainly due to alteration in thyroid function as a response to acute non-thyroidal illness or as an effect of co-existing drug administration as discussed in sections 1.2.5.5 and 1.2.8. However, in view of the high prevalence of thyroid dysfunction (TD), there may be a need to check thyroid function in hospitalised patients and vigilance for new case finding may be appropriate in certain risk groups.

In the current economic environment, resources are not unlimited and are often subject to cuts. Judicious use of the laboratory testing, whether for diagnostic or monitoring reasons, needs to be implemented in a proper and cost-effective manner. However, the evidence regarding the appropriate utilisation of laboratory

panels, including thyroid function testing, remains scanty. We therefore set out (i) to assess the volume of thyroid function testing in a large secondary/tertiary centre; (ii) to determine the prevalence of newly diagnosed thyroid dysfunction and to establish the rate of initiation of treatment in inpatients with newly diagnosed thyroid dysfunction, and (iii) to evaluate the frequency of finding abnormal thyroid function results in hospitalised patients with pre-existing thyroid dysfunction.

6.2 Subjects and methods

6.2.1 Study setting

A retrospective, observational study of the laboratory testing of thyroid function in hospitalised patients was carried out at the Queen Elizabeth Hospital, Birmingham, which is an academic teaching hospital with approximately 1,250 beds covering all specialties except obstetrics, paediatrics and mental health. Data on admissions between 1st January 2007 and 31st December 2011 were retrieved from the hospital IT system. The dataset contained information on patients' demographics and details of each hospital stay including ICD-10 coded diagnosis, type of admission and admitting specialty, medication prescribed and laboratory thyroid function tests. Exclusions comprised admissions to the Accident and Emergency (A&E) department without further hospitalisation (N=6,220), admissions of military patients for general check-up (N=3,019) and patients aged less than 16 years (N=38). We also excluded patients treated for the thyroid cancer (N=249) as the pathophysiology, monitoring

and treatment goals are different in patients with this condition compared with those with thyroid dysfunction. The study was approved and registered by the University Hospitals Birmingham NHS Foundation Trust (CARMS-12523).

6.2.2 Variables and stratification of data

Patients' age was calculated at the first admission and divided into intervals based on decades (initial interval covering ages 16-29; the final 80 years and over). Length of hospital stay (LOS) was calculated and divided into same day discharges (1 day), and admissions lasting 2-7, 8-21 or longer than 21 days.

Information on prescribed and dispensed medication was retrieved from the Prescribing, Information and Communication System (PICS) (section 2.2.5) including medication for treatment of thyroid dysfunction (carbimazole (CMZ), propylthiouracil (PTU), levothyroxine (L-T4)) and medication associated with increased risk of hyper- and hypothyroidism, namely amiodarone and lithium, as stated in the UK guidelines for the use of TFT (Association of Clinical Biochemistry, 2006). "One-off" or intravenous prescriptions were excluded. Admitting specialties were grouped into (1) general and (2) specialty medicine, (3) general and (4) specialty surgery, (5) a fifth category was created for patients treated at Intensive Therapy Units (ITU) during the admission irrespective of admitting specialty.

6.2.2.1 *Morbidity*

During the entire study period, admissions to the hospital were coded with one primary diagnosis and one or more secondary diagnoses using the International Classification of Diseases 10th edition (ICD-10) (WHO, 2010).

The primary diagnosis for admission was collated based on the chapters of ICD-10 publication (see Appendix Table 1). The exemption was Chapter 13 (R00-R99 codes) not describing the diagnosis but presenting signs and symptoms instead. These were grouped within the chapters for the corresponding disorders. The subchapter "Signs and Symptoms of General Malaise" (R50-R69) remained as separate category due to its potential clinical relevance to the diagnosis of thyroid dysfunction. Admissions for injuries and traumas were assumed to be least likely related to thyroid dysfunction and were therefore chosen as the reference category.

ICD-10 coding was also used to adjust for patient's co-morbidity. That was achieved using the Charlson Comorbidity Index (CCI), a predicting model for one-year survival (Charlson et al., 1987). It has also proved to be useful for assessing severity of comorbidities in broader setting and it is widely utilised in many cohort studies broadening their comparability (Sundararajan et al., 2004, Schneeweiss and Maclure, 2000). CCI scores were computed for each admission. ICD-10 codes defining each of 17 conditions applied to calculate CCI are listed in Appendix Table 2. Severity of comorbidities was categorised as low (CCI score=0), medium (CCI score = 1-2) or high (CCI score ≥ 3) (Sogaard et al., 2016).

The ICD-10 coding system was also utilised to identify comorbidities associated with increased risk of thyroid dysfunction and recommended for screening (atrial fibrillation [AF, ICD-10 code: I48], osteoporosis [M80-M82], dyslipidaemia [E78] and diabetes mellitus [E10-E14]) or surveillance (Down [Q90] or Turner Syndromes [Q96]) of thyroid function by the UK guidelines (Association of Clinical Biochemistry, 2006). Due to small numbers of inpatients coded with Down or Turner

syndromes, these co-morbidities combined are presented in baseline descriptive data but excluded from further analysis.

6.2.3 Admissions with and without history of thyroid dysfunction

Each hospital admission was coded for TD history if there was an assigned thyroid dysfunction diagnostic code (E02-03 for hypo- or E05 for hyperthyroidism) and/or if treatment relating to thyroid dysfunction was prescribed (L-T4 without thionamides for hypothyroidism and CMZ or PTU for hyperthyroidism). The first admission of a patient coded for thyroid dysfunction was verified for new diagnosis through review of biochemical test results and clinical notes. A patient was newly diagnosed with TD during the hospital admission when overt biochemical TFT was confirmed and the clinical notes did not state otherwise. Any subsequent admission following a diagnosis of TD was assigned to the "pre-existing TD" category. Inpatients developing thyroid dysfunction during the study period swapped categories: from "no TD history" prior to diagnosis to "pre-existing TD" thereafter.

The stratification was performed to enable analyses of two different testing strategies: (i) the approach towards new case finding and (ii) monitoring of those with thyroid dysfunction aiming to assure treatment adequacy. The frequencies of testing between these two approaches were significantly different (section 6.3.1). The data of those with known and unknown TD history were analysed separately. The main focus of analysis of the cohort with no TD was on a patient characteristic (case-finding approach) while in cohort with pre-existing TD on characteristic of an admission (monitoring approach). This was achieved collapsing data of no TD history admissions

into a patient-level and leaving admission-level data in patients with known history of TD.

6.2.4 Thyroid function tests

Thyroid function tests (TFT) were all evaluated in the hospital laboratory using Roche immunoassays. The normal reference ranges were: TSH 0.3-4.5 mIU/L, fT4 10.0-22.0 pmol/L, fT3 3.1- 6.8 pmol/L. The test results were stratified into euthyroidism (normal TSH, normal fT4), overt hyperthyroidism (TSH<0.3 and fT4>22.0), subclinical hyperthyroidism (0.3<TSH and normal fT4), overt hypothyroidism (TSH>4.5 and fT4<10.0), subclinical hypothyroidism (TSH>4.5, normal fT4) and other. Overt and subclinical dysfunction were further stratified based on the degree of TSH abnormality reflecting the clinical relevance: hyperthyroidism grade 1 was defined as detectable serum TSH (≥0.1 and <0.3) and grade 2 as undetectable (TSH<0.1) and similarly, hypothyroidism grade 1 was defined as TSH above normal but below 10 mIU/L (>4.5 and ≤10 mIU/L) and grade 2 as TSH >10.0 mIU/L (Biondi et al., 2015, Wiersinga, 2015).

6.2.5 Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 21. 95% confidence intervals (95% CI) were calculated for prevalence and odds ratios. Uni- and mulivariate binary logistic regression analyses were performed to identify odds ratios of factors predicting probability of being tested for thyroid dysfunction during the baseline admission in a cohort of inpatients with no TD history. Cumulative

variables of numbers of admissions or number of emergencies as well as length of stay (LOS) followed the Poisson distribution and were analysed accordingly.

Accounting for the effect of clustering admissions in patients with pre-existing TD, a Generalised Estimating Equation (GEE) was used to identify the factors predicting probability of being tested for thyroid dysfunction during any hospital admission of patients with TD history.

6.3 Results

6.3.1 Characteristics of thyroid function testing in the hospital

A total of 269,235 hospital admissions were analysed, representing a cohort of 147,693 patients of whom 19,047 (12.9%) had thyroid function measured during at least one hospital stay. Altogether 26,384 thyroid function tests were performed. Of these 3,103 (11.7%) were repeats in patients who had already been tested earlier during the same hospital admission. There were three patterns of TFT requests: measurement of TSH alone, TSH+fT4, or TSH+fT4+fT3. The most common thyroid function test request consisted of serum TSH and serum free T4 measurements (N=24,058, 91.2%). An additional request for serum fT3 was made for 1,749 patients (N=2,236 tests); serum TSH only was requested rarely (N=55 tests).

There was a significant decrease in the proportions of tested admissions per calendar year ($P<0.001$) as presented in Figure 6-1. The average number of admissions with thyroid function requests per calendar year was 4,601 (±321 SD).

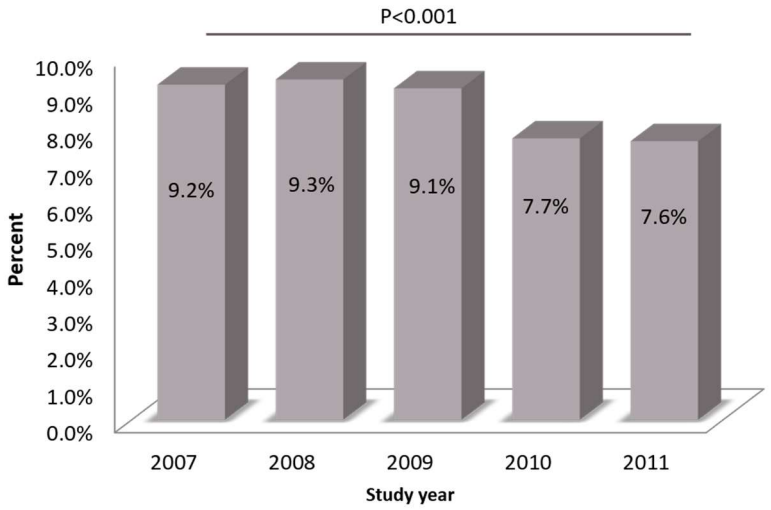

Figure 6-1: Proportions of hospital admissions with thyroid function test requests in calendar year indicating a significant decrease during the 5 years of study (P<0.001)

We identified a total number of 251,914 (93.6%) admissions of 140,176 (95.0%) patients with no TD history. We assumed that if TFTs were requested in those subjects, the intent was for finding new cases or excluding TD. 8,494 (5.7%) inpatients with pre-existing TD were admitted to hospital in 17,321 (6.4%) admissions. TFTs ordered for those patients were, presumably, for monitoring of adequacy of thyroid dose medication.

Thyroid function tests were requested three-fold more frequently for patients with pre-existing TD compared to those with no history of TD (Figure 6-2) whether measured on a patient-level (P<0.001) or admission-level (P<0.001), reflecting the variation in testing approach between the two cohorts. Data were further analysed separately for each cohort to capture the nature of these two strategies.

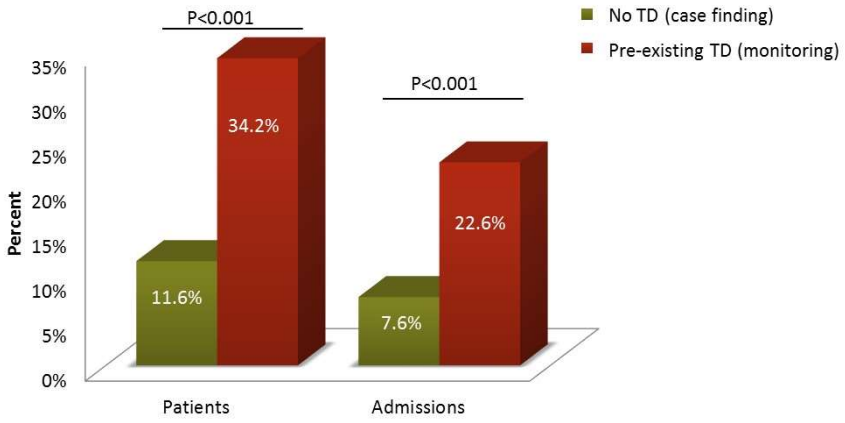

Figure 6-2: Frequency of TFT in patients and admissions in those with no previous history of TD compared to those with a pre-existing TD

6.3.2 Thyroid function testing in patients with no history of TD

In the population with no TD history, 21,476 (81.4% of all TFTs requested during the time period of the study) tests were requested in 16,291 (11.0% all inpatients; 11.6% of the cohort) inpatients. TFTs were requested once in 12,738 subjects (78.2%) and more frequently in 3,553 patients, resulting in a mean number of requests of 1.32 ±0.74 SD in those undergoing testing. Almost half the tests (N=9,061, 42.2%) were ordered during the first day of the hospital stay and 75% of TFTs had been requested by the end of day five.

6.3.2.1 *Basic characteristics of inpatients without known thyroid dysfunction*

Table 6-1 (column 1) presents the basic characteristics of inpatients without a known history of thyroid dysfunction. There was a slightly higher prevalence of men (55.4%). The age distribution was bimodal, peaking around 21 and 62 years and the median was 53 years (interquartile range IQR: 35-69). During the baseline admission, two-thirds of the patients were admitted as emergencies and 3% were treated in intensive care

units (ITU). The most common reason for admission was for circulatory diseases (19.2%), followed by injuries and trauma (17.8%). Co-morbid AF, dyslipidaemia or diabetes mellitus was found in 6.3–7.4%, while osteoporosis was found in less than 1% of subjects. Low comorbidity scores were assigned to two-thirds of individuals. Treatment with drugs known to be associated with increased risk of TD was rare; amiodarone was prescribed in less than 2%, of which the majority (75%) were admitted for cardiovascular causes, and lithium in 0.1% of inpatients admitted for variety of reasons. A third of inpatients returned to hospital for subsequent admissions.

A comparison of the baseline characteristics of those in whom TFT was obtained to those with no TFTs taken while in hospital is presented in Table 6-1 (columns 2-4). In general, patients undergoing thyroid function testing were older, were hospitalised more often and had a higher comorbidities burden compared with the not-tested cohort. TFTs were requested more frequently in those prescribed lithium (33.7%) or amiodarone (28.1%), and in subjects diagnosed with AF (34.3%), osteoporosis (30.0%), diabetes mellitus (20.5%) and dyslipidaemia (12.2%). A quarter of those in whom thyroid function was tested were admitted for cardiovascular disorders, which comprised 16.3% of all CVD admissions. The most commonly tested were inpatients admitted for endocrine disorders (N=539; 28.7%), general malaise (N=1,423; 27.4%) and nervous and mental conditions (N=1,826; 26.1%).

Table 6-1: Basic characteristics of patients without TD. Baseline admission for the non-tested patients was the first admission to hospital during the study period; for the tested – first admission with TFT requested. In bold– significant difference at 0.05 level

	Patient characteristics	All, N=140,176	No TFT requested, N=123,885 (88.4%)	TFT requested, N=16,291 (11.6%)	OR (95% CI)	P value
Baseline admission	**Sex:** Male	77,591 (55.4%)	**69,814 (56.4%)**	**7,777 (47.7%)**	**1.00**	
	Female	62,585 (44.6%)	**54,071 (43.6%)**	**8,514 (52.3%)**	**1.41 (1.39-1.46)**	**<0.001**
	Age					
	16-29	26,332 (18.8%)	**25,138 (20.3%)**	**1,189 (7.3%)**	**1.00**	
	30-39	17,238 (12.3%)	**16,159 (13.0%)**	**1,079 (6.6%)**	**1.41 (1.30-1.54)**	**<0.001**
	40-49	20,155 (14.4%)	**18,466 (14.9%)**	**1,687 (10.4%)**	**1.93 (1.79-2.09)**	**<0.001**
	50-59	20,391 (14.5%)	**18,144 (14.6%)**	**2,244 (13.8%)**	**2.61 (2.43-2.81)**	**<0.001**
	60-69	21,645 (15.4%)	**18,918 (15.3%)**	**2,718 (16.7%)**	**3.04 (2.83-3.26)**	**<0.001**
	70-79	19,381 (13.8%)	**16,073 (13.0%)**	**3,311 (20.3%)**	**4.36 (4.06-4.67)**	**<0.001**
	≥80	15,034 (10.7%)	**10,987 (8.9%)**	**4,063 (24.9%)**	**7.82 (7.30-8.37)**	**<0.001**
	mean (SD)	52.3 (20.8)	**50.8 (20.5)**	**63.6 (19.6)**	**1.383 (1.370-1.395)**	**<0.001**
	Severity of comorbidity (CCI score):					
	Low (0)	83,792 (59.8%)	**77,265 (62.4%)**	**7,103 (43.6%)**	**1.00**	
	Medium (1-2)	43,238 (30.8%)	**36,486 (29.5%)**	**6,665 (40.9%)**	**2.19 (2.11-2.27)**	**<0.001**
	High (≥3)	13,145 (9.4%)	**10,133 (8.2%)**	**2,523 (15.5%)**	**3.52 (3.36-3.69)**	**<0.001**
	Primary reason for admission:					
	Injuries	25,022 (17.9%)	**23,707 (19.1%)**	**1,192 (7.3%)**	**1.00**	
	Cardiac	26,823 (19.1%)	**22,586 (18.2%)**	**4,396 (27.0%)**	**3.86 (3.61-4.13)**	**<0.001**
	Digestive	19,272 (13.7%)	**17,001 (13.7%)**	**2,129 (13.1%)**	**2.48 (2.31-2.67)**	**<0.001**
	Cancer	15,896 (11.3%)	**14,715 (11.9%)**	**1,090 (6.7%)**	**1.47 (1.35-1.60)**	**<0.001**
	Respiratory	9,521 (6.8%)	**8,048 (6.5%)**	**1,497 (9.2%)**	**3.69 (3.41-4.00)**	**<0.001**
	Endocrine	1,813 (1.3%)	**1,336 (1.1%)**	**539 (3.3%)**	**8.08 (7.20-9.07)**	**<0.001**
	Nervous and mental	6,798 (4.8%)	**5,166 (4.2%)**	**1,826 (11.2%)**	**7.03 (6.49-7.60)**	**<0.001**
	Genitourinary	8,785 (6.3%)	**7,977 (6.4%)**	**696 (4.3%)**	**1.74 (1.58-1.91)**	**<0.001**
	Musculoskeletal	9,084 (6.5%)	**8,614 (7.0%)**	**373 (2.3%)**	**0.86 (0.76-0.97)**	**0.013**
	General malaise	5,033 (3.6%)	**3,777 (3.0%)**	**1,423 (8.7%)**	**7.44 (6.84-8.10)**	**<0.001**
	Other	12,129 (8.7%)	**10,958 (8.8%)**	**1,130 (6.9%)**	**2.05 (1.89-2.23)**	**<0.001**
	Presence of:					
	Dyslipidaemia	9,753 (7.0%)	8,568 (6.9%)	1,185 (7.3%)	1.06 (0.99-1.13)	NS (0.09)
	Diabetes mellitus	10,402 (7.4%)	**8,266 (6.7%)**	**2,136 (13.1%)**	**2.11 (2.00-2.22)**	**<0.001**
	Atrial fibrillation	8,838 (6.3%)	**5,810 (4.7%)**	**3,028 (18.6%)**	**4.65 (4.43-4.87)**	**<0.001**
	Osteoporosis	1,056 (0.8%)	**739 (0.6%)**	**317 (30.0%)**	**3.30 (2.89-3.76)**	**<0.001**
	Down or Turner Syndrome	20 (0.0%)	16 (0.0%)	4 (20.0%)	1.90 (0.64-5.69)	NS (0.25)
	Treated with:					
	Amiodarone	2,494 (2.5%)	**1,795 (1.4%)**	**702 (4.3%)**	**3.05 (2.79-3.33)**	**<0.001**
	Lithium	232 (0.2%)	**130 (0.1%)**	**66 (0.4%)**	**3.87 (2.88-5.21)**	**<0.001**
During the study period	**Hospital admissions**:					
	1	94,097 (67.1%)	**87,597 (70.7%)**	**6,500 (39.9%)**	**1.00**	
	2-4	37,932 (27.1%)	**31,193 (25.2%)**	**6,739 (41.4%)**	**2.91 (2.81-3.02)**	**<0.001**
	≥5	8,147 (5.8%)	**5,095 (4.1%)**	**3,052 (18.7%)**	**8.07 (7.67-8.50)**	**<0.001**
	mean (SD)	1.8 (1.3)	1.6 (1.3)	3.1 (1.8)		
	Emergencies:					
	None	39,442 (28.1%)	**37,887 (30.6%)**	**1,555 (9.5%)**	**1.00**	
	1	72,126 (51.5%)	**65,510 (52.9%)**	**6,616 (40.6%)**	**2.44 (2.30-2.56)**	**<0.001**
	2-3	21,159 (15.1%)	**16,269 (13.1%)**	**4,890 (30.0%)**	**7.37 (6.94-7.82)**	**<0.001**
	≥4	7,449 (5.3%)	**4,219 (3.4%)**	**3,230 (19.8%)**	**18.51 (17.29-19.82)**	**<0.001**
	mean (SD)	1.2 (1.1)	1.0 (1.0)	2.5 (1.6)		
	Cumulative length of stay (days):					
	1	19,620 (14.0%)	**18,867 (15.2%)**	**753 (4.6%)**	**1.00**	
	2-7	67,659 (48.3%)	**64,133 (51.8%)**	**3,526 (21.6%)**	**1.41 (1.30-1.26)**	**<0.001**
	8-21	30,594 (21.8%)	**26,348 (21.3%)**	**4,246 (26.1%)**	**4.12 (3.80-4.47)**	**<0.001**
	≥22	22,303 (15.9%)	**14,537 (11.7%)**	**7,766 (47.7%)**	**13.69 (12.65-14.82)**	**<0.001**
	mean (SD)	12.9 (3.6)	10.0 (3.2)	34.7 (5.9)		

6.3.2.2 *Factors influencing TFT testing*

Table 6-2 presents factors independently associated with likelihood of having TFT requested. We noted that women and those admitted for emergencies had an approximately 33% higher testing probability. The chance of being tested increased with each age decade and in patients aged over 80, the odds were doubled compared with subjects aged 16-19 years. In comparison to patients admitted for injuries and trauma, those admitted for endocrine or nervous and mental health reasons were the most likely to have TFTs requested, while increased probabilities were also noted in those admitted with general malaise, digestive and cardiovascular diseases. Individuals hospitalised for musculoskeletal causes were less likely to be tested. Those admitted by general medical specialties were most likely to have TFTs measured, with 2–5 times higher odds in comparison with any other specialty. Longer hospital stays were associated with significantly increased probabilities of testing, as was the severity of comorbidity, expressed as CCI scores categories. When analysing co-administered medication, we noted that patients prescribed lithium, but not those treated with amiodarone, were more like to have TFTs measured, compared with those not taking these treatments. While looking at specific co-morbidities we found increased odds for testing in those with AF, osteoporosis and diabetes mellitus. Interestingly, individuals who were diagnosed with dyslipidaemia had lower odds of having TFTs checked.

Table 6-2: Results of multivariable binary logistic regression analysis identifying factors associated with request of TFT in patients with no TD history

Parameter	AOR	95% CI	P -value
Sex: **Female**	1.30	(1.25- 1.35)	<0.0001
Age (y): **16-29**	1.00		
30-39	1.23	(1.13- 1.35)	<0.0001
40-49	1.44	(1.33- 1.56)	<0.0001
50-59	1.75	(1.61- 1.89)	<0.0001
60-69	1.73	(1.60- 1.87)	<0.0001
70-79	1.74	(1.61- 1.88)	<0.0001
≥80	1.89	(1.75- 2.05)	<0.0001
Admission type: **Emergency**	1.28	(1.21- 1.36)	<0.0001
Primary diagnosis: **Injuries**	1.00		
Cardiac	1.64	(1.52- 1.78)	<0.0001
Digestive	2.05	(1.89- 2.23)	<0.0001
Cancer	0.75	(0.67- 0.83)	<0.0001
Respiratory	1.20	(1.10- 1.32)	<0.0001
Endocrine	3.90	(3.41- 4.48)	<0.0001
Nervous and mental	3.02	(2.76- 3.31)	<0.0001
Genitourinary	1.23	(1.10- 1.37)	<0.0001
Musculoskeletal	0.83	(0.73- 0.95)	0.006
General malaise	2.60	(2.35- 2.86)	<0.0001
Other	1.60	(1.45- 1.76)	<0.0001
Speciality: **General medicine**	1.00		
Specialty medicine	0.59	(0.59-0.62)	<0.0001
General surgery	0.16	(0.15-0.17)	<0.0001
Specialty surgery	0.23	(0.22-0.25)	<0.0001
ICU	0.32	(0.29-0.36)	<0.0001
Length of stay: **1 day**	1.00		
2-7 days	1.72	(1.62- 1.83)	<0.0001
8-21 days	4.56	(4.25- 4.88)	<0.0001
≥ 22 days	9.34	(8.63-10.10)	<0.0001
Severity of comorbidity (CCI):			
Low (0)	1.00		
Medium (1-2)	1.21	(1.16-1.27)	<0.0001
High (≥3)	1.90	(1.78-2.03)	<0.0001
Presence of:			
Dyslipidaemia	0.67	(0.62-0.72)	<0.0001
Diabetes mellitus	1.08	(1.01-1.15)	0.02
Atrial fibrillation	2.34	(2.20-2.45)	<0.0001
Osteoporosis	1.57	(1.34-1.83)	<0.0001
Treatment with:			
Amiodarone	1.11	(0.99- 1.23)	NS (0.07)
Lithium	1.97	(1.40-2.77)	<0.0001

6.3.2.3 *Biochemical findings of TFT results in patients with no TD history*

In the cohort with no TD, there were 36 subjects in whom serum TSH only was measured, of which 31 had serum TSH concentration within the normal reference range. An additional four subjects had mildly abnormal results and one was identified

as having overt hypothyroidism (TSH=12.25 mIU/L). These results were not acted upon subsequently.

In 16,255 patients with serum TSH measured simultaneously with serum fT4, the majority of tests (81.0%) indicated biochemical euthyroidism (Table 6-3). Overall, the prevalence of hyperthyroidism was 3.5% and of hypothyroidism 9.2%. Discordant TFT results were found in 6.0% (N=990) of tested subjects. The majority of these consisted of serum TSH concentrations within the reference range while measurements of serum fT4 were either raised (hyperthyroxinaemia) or decreased (hypothyroxinaemia). Findings of TSH outside the reference range with discordant fT4 were rare and accounted for less than 0.4% of all TFT results.

Table 6-3: Baseline TFT of simultaneously measured serum TSH and fT4 in patients with no history of TD

	TFT outcome	TFTs N, (%)
Hyperthyroid	Overt hyperthyroidism (TSH<0.1)	158 (1.0)
	Overt hyperthyroidism with detectable TSH (0.1-0.3)	57 (0.4)
	Subclinical hyperthyroidism grade 2 (TSH<0.1 and fT4 normal)	125 (0.8)
	Subclinical hyperthyroidism grade 1 (TSH 0.1-0.3 and fT4 normal)	255 (1.6)
Euthyroid		13,176 (81.0)
Hypothyroid	Subclinical hypothyroidism grade 1 (THS>4.5 and <10 and fT4 normal)	1,178 (7.3)
	Subclinical hypothyroidism grade 2 (THS>10 and fT4 normal)	151 (0.9)
	Overt hypothyroidism with mildly raised TSH (4.5-10)	45 (0.3)
	Overt hypothyroidism (TSH>10)	123 (0.7)
Other	↓TSH, ↓fT4	13 (0.1)
	↑TSH, ↑fT4	54 (0.3)
	normal TSH,↓fT4	199 (1.2)
	normal TSH,↑fT4	721 (4.4)

Overall, the finding of overt TD was uncommon, however abnormal profiles were found among all categories of demographic, administrative and clinical characteristics of inpatients (Table 6-4). Among those specifically admitted for endocrine reasons, 31 patients (5.7%) presented overt thyrotoxicosis and 11 (2.0%) overt hypothyroidism. The smallest proportion of euthyroid results was found in patients admitted to ITU (60.5%) or treated with amiodarone (62.2%). In these two categories also the highest proportion of discordant results (11.4% and 14.0%, respectively) was found. In 3.6% of patients treated with amiodarone, biochemistry of overt thyroid dysfunction was noted.

Table 6-4: Patterns of thyroid panels found in inpatients with no history of TD; percent in brackets represents row value.

	TFT outcome (TSH+fT4)					
	Overt hyper-thyroidism (TSH<0.1)	Milder forms of hyperthroidism	Euthyroidism	Milder forms of hypothroidism	Overt hypo-thyroidism (TSH<0.1)	Other patterns of TFT
Sex: Male	60 (.8)	148 (1.9)	6,489 (83.6)	587 (7.6)	39 (.5)	435 (5.6)
Female	98 (1.2)	289 (3.4)	6,687 (78.7)	787 (9.3)	84 (1.0)	552 (6.5)
Age (y): < 30	14 (1.2)	24 (2.0)	965 (81.4)	103 (8.7)	6 (.5)	74 (6.2)
30 - 39	12 (1.1)	28 (2.6)	888 (82.5)	82 (7.6)	6 (.6)	61 (5.7)
40 - 49	21 (1.2)	47 (2.8)	1,404 (83.3)	118 (7.0)	8 (.5)	87 (5.2)
50 - 59	20 (.9)	57 (2.5)	1,824 (81.5)	201 (9.0)	10 (.4)	126 (5.6)
60 - 69	25 (.9)	62 (2.3)	2,248 (82.9)	212 (7.8)	28 (1.0)	136 (5.0)
70 - 79	30 (.9)	100 (3.0)	2,686 (81.2)	246 (7.4)	26 (.8)	218 (6.6)
80+	36 (.9)	119 (2.9)	3,161 (78.0)	412 (10.2)	39 (1.0)	285 (7.0)
Admission type:						
Elective	22 (.9)	68 (2.7)	2,054 (82.8)	181 (7.3)	17 (.7)	138 (5.6)
Emergency	136 (1.0)	369 (2.7)	11,122 (80.7)	1,193 (8.7)	106 (.8)	849 (6.2)
Specialty:						
General medicine	102 (1.0)	228 (2.2)	8,549 (82.9)	814 (7.9)	64 (.6)	551 (5.3)
Specialty medicine	30 (1.1)	67 (2.5)	2,094 (79.6)	242 (9.2)	24 (.9)	175 (6.6)
General surgery	9 (.9)	37 (3.5)	823 (77.9)	86 (8.1)	16 (1.5)	85 (8.0)
Specialty surgery	15 (.9)	66 (3.8)	1,402 (80.1)	138 (7.9)	11 (.6)	118 (6.7)
ICU	2 (.4)	39 (7.7)	308 (60.5)	94 (18.5)	8 (1.6)	58 (11.4)
Primary admission reason:						
Injuries and trauma	11 (.9)	48 (4.0)	910 (76.3)	124 (10.4)	19 (1.6)	80 (6.7)
CVD	44 (1.0)	73 (1.7)	3,593 (82.0)	418 (9.5)	20 (.5)	236 (5.4)
Digestive	17 (.8)	71 (3.3)	1,708 (80.4)	163 (7.7)	14 (.7)	152 (7.2)
Cancer	11 (1.0)	53 (4.9)	833 (76.5)	90 (8.3)	13 (1.2)	89 (8.2)
Respiratory	16 (1.1)	64 (4.3)	1,199 (80.1)	115 (7.7)	11 (.7)	91 (6.1)
Endocrine	31 (5.7)	20 (3.7)	395 (72.9)	46 (8.5)	11 (2.0)	39 (7.2)
Nervous or mental	8 (.4)	27 (1.5)	1,576 (86.5)	108 (5.9)	7 (.4)	97 (5.3)
Genitourinary	6 (.9)	13 (1.9)	546 (78.7)	70 (10.1)	9 (1.3)	50 (7.2)
Muscoskeletal	2 (.5)	14 (3.8)	296 (79.6)	29 (7.8)	2 (.5)	29 (7.8)
General malaise	5 (.4)	28 (2.0)	1,196 (84.9)	108 (7.7)	10 (.7)	61 (4.3)
Other	7 (.6)	26 (2.3)	924 (81.8)	103 (9.1)	7 (.6)	63 (5.6)
Severity of comorbidities (CCI score)						
Low	73 (1.1)	152 (2.3)	5,417 (83.3)	500 (7.7)	41 (.6)	323 (5.0)
Medium	59 (.9)	181 (2.7)	5,400 (80.1)	598 (8.9)	54 (.8)	448 (6.6)
High	26 (.9)	104 (3.5)	2,359 (78.4)	276 (9.2)	28 (.9)	216 (7.2)
Length of stay:						
1 day	21 (1.4)	28 (1.9)	1,263 (85.7)	113 (7.7)	2 (.1)	47 (3.2)
2-7 days	49 (.8)	133 (2.2)	5,152 (84.5)	442 (7.2)	27 (.4)	294 (4.8)
8-21 days	44 (.9)	152 (3.1)	3,915 (79.8)	416 (8.5)	41 (.8)	335 (6.8)
22+ days	44 (1.2)	124 (3.3)	2,846 (75.3)	403 (10.7)	53 (1.4)	311 (8.2)
Presence of:						
Dyslipidaemia	10 (.8)	32 (2.7)	977 (82.4)	95 (8.0)	8 (.7)	64 (5.4)
Diabetes mellitus	15 (.7)	49 (2.3)	1,758 (82.5)	165 (7.7)	12 (.6)	131 (6.2)
Atrial fibrillation	47 (1.6)	85 (2.8)	2,364 (78.1)	288 (9.5)	15 (.5)	226 (7.5)
Osteoporosis	0 (.0)	10 (3.2)	248 (78.7)	28 (8.9)	1 (.3)	28 (8.9)
Treated with:						
Amiodarone	13 (1.9)	22 (3.2)	434 (62.2)	119 (17.0)	12 (1.7)	98 (14.0)
Lithium	1 (1.5)	7 (10.6)	51 (77.3)	6 (9.1)	0 (.0)	1 (1.5)

6.3.2.4 *New overt thyroid dysfunction*

The baseline testing of 16,291 inpatients without a history of TD identified 129 subjects with overt hyperthyroidism and 114 with overt hypothyroidism. Additionally, 19 overtly hyperthyroid and nine hypothyroid cases were diagnosed during subsequent hospital admissions, giving a total of 281 (1.7% of those tested; 0.2% of the entire cohort) inpatients with newly diagnosed overt thyroid dysfunction.

Overt hyperthyroidism

There were 158 newly diagnosed cases of overt biochemical hyperthyroidism. Its prevalence increased with advancing age and the higher proportion was found in those aged 80 years and over (22.8%). The age distribution was negatively skewed with the median age of 63.5 years (IQR: 46-78). Two-thirds were women (N=98, 62.0%; Table 6-4, column 1). The majority were admitted as emergencies (N=136, 86.1%) and the most common primary reason for admission was either cardiac (27.8%, N=44; mainly AF) or endocrine (19.6%, N=31; mainly hyperthyroidism) which together accounted for nearly a half of all new hyperthyroid cases. The distribution of initial serum fT4 concentration was positively skewed with the median value of 31.0 pmol/L (IQR: 26.1-48.2). Twenty-one (14.2%) individuals were prescribed amiodarone and one was undergoing treatment with lithium, indicating potential iatrogenic pharmacological reasons for thyroid dysfunction.

Treatment with ATD was commenced in 77 (48.7%) newly diagnosed hyperthyroid inpatients and an additional 14 (9.6%) were referred to their general practitioners

for further management and/or the diagnosis was recorded in the hospital system. In 67 cases (42.4%), there was no record of any action taken upon overtly abnormal TFT results, which in eight (5.1%) of patients could have been explained by subsequent death during their hospital stay (i.e. possibly an active decision not to treat due to end of life care pathway).

Overt hypothyroidism

There were 123 new biochemical diagnoses of overt hypothyroidism. Finding new hypothyroidism among younger patients was uncommon whereas three-quarters (N=93, 75.6%) were older than 60 years; the median age was 68 years (IQR: 60-82). The distribution of initial serum TSH concentrations was positively skewed; the median value 31.76 mIU/L (IQR: 15.59-67.60). Notably, thyroid function testing was requested significantly later in those identified with hypothyroidism than in patients diagnosed with overt hyperthyroidism or in whom no overt thyroid dysfunction was diagnosed (Figure 6-3). There were higher proportions of diagnosis of overt hypothyroidism in patients in whom TFT was requested beyond the seventh day of stay, which was even more pronounced beyond the 21st day of hospital stay. New cases of overt hypothyroidism were found more common in women (N=84, 68.3%) and most (N=106, 86.1%) were admitted as emergencies. The most common primary reasons for admission were cardiovascular diseases (N=20, 16.3%), injuries and trauma (N=19, 15.4%), digestive diseases (N=14, 11.4%) and cancers (13, 10.6%), accounting together for over 50% of new hypothyroid admissions. 10% of patients with overt hypothyroidism (N=12) were concurrently receiving amiodarone treatment.

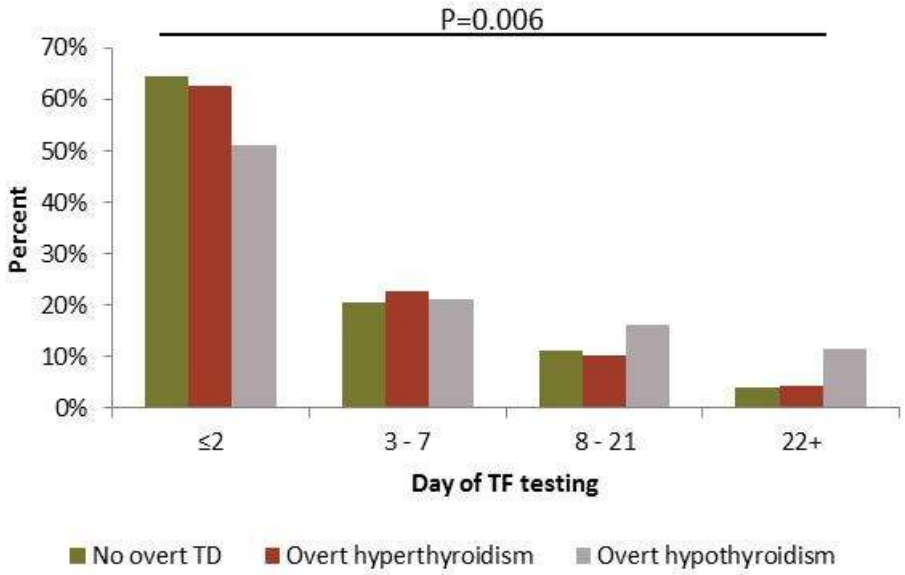

Figure 6-3: Day of hospital stay when the first TFT was requested in patients with overt hypothyroidism, with overt hyperthyroidism or with no overt thyroid dysfunction (TD)

Treatment with levothyroxine was commenced in 80 hypothyroid inpatients (65.0%); furthermore, in 11 (8.9%) cases there were notes relating to the diagnosis in the discharge letter. There was no action recorded for 32 (26.0%) individuals upon finding of overt hypothyroidism and five (4.1%) deaths were recorded amongst this patient group.

Altogether, in order to find one case of overt thyroid dysfunction, 75 thyroid function tests had to be obtained or 58 patients had to be tested. Assuming successful case finding as those in whom clinical intervention (either drug initiation or communication of findings in 91 hyper- and 91 hypothyroid diagnoses) was performed, these values increase to 118 tests obtained or 90 patients tested.

6.3.3 TFT monitoring in hyper- and hypothyroid inpatients

During the study period, there were 17,321 (6.4%) hospital admissions of 8,494 (5.7%) inpatients with a known history of thyroid disease. Contrary to previously analysed approach, which aimed to diagnose new cases of thyroid dysfunction, requests in these patients were likely to be intended to monitor adequacy of thyroid hormone replacement or to determine titration of antithyroid drugs. According to the study design, every admission which followed a diagnosis of TD identified by either ICD-10 code or use of thyroid medication was considered as a hospitalisation with history of thyroid dysfunction. Treatment was prescribed during 13,229 (76.4%) admissions (Figure 6-4) of which anti-thyroid medication for hyperthyroidism was prescribed during 481 admissions. 9,799 (56.6%) admissions were ICD-10 coded for thyroid dysfunction and included 792 coded for hyperthyroidism. 1,741 admissions of patients whose previous admissions were identified with TD had neither thyroid medication prescribed nor ICD-10 coding assigned.

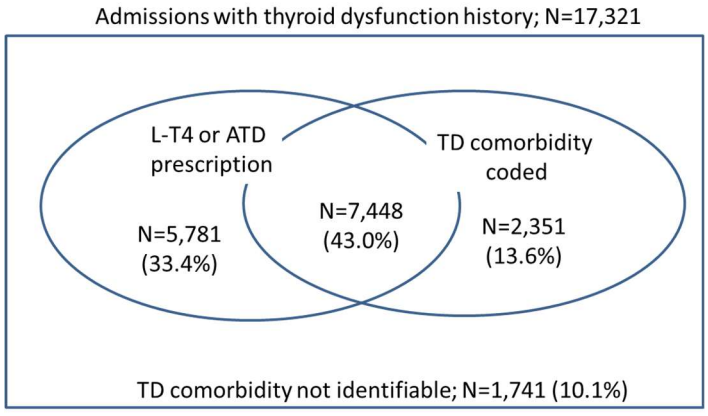

Figure 6-4: Venn diagram representing the distribution of identifiable attributes of thyroid dysfunction in admissions of patients with a history of TD.

6.3.3.1 *Characteristics of patients with history of thyroid dysfunction in hospital*

In the cohort of patients with pre-existing TD (Table 6-5), there were three times more women than men. The prevalence of TD increased with age and the median age was 68 years (IQR: 54-78). Patients with thyroid dysfunction were more likely to be found with medium or high comorbidity scores. The most common primary cause for hospital admission, accounting for almost a quarter of admissions, were cardiovascular reasons, which was significantly higher than in those with no history of TD. Dyslipidaemia, diabetes mellitus, AF and osteoporosis were all more prevalent in those with pre-existing TD, while the proportion of Down or Turner syndromes did not differ significantly between the cohorts. Treatment with amiodarone or lithium was more common among patients with TD. Inpatients with a history of TD were more likely to have higher numbers of hospital admissions and to be admitted as an emergency compared with subjects with no history of TD. Over 50% of subjects with TD spent more than 7 days in hospital during the study period, which was significantly higher than 37% of those with no history of TD.

Table 6-5: Baseline characteristics of patients with a pre-existing TD compared to inpatients with no history of TD

	Parameter	No history of TD N (%)	History of TD present N (%)	P value
Baseline admission	**Sex:** Male	77,257 (55.5)	2,121 (25.0)	<0.001
	Female	61,862 (44.5)	6,373 (75.0)	<0.001
	Age			
	16-29	26,275 (18.9)	300 (3.5)	<0.001
	30-39	17,181 (12.3)	435 (5.1)	<0.001
	40-49	20,029 (14.4)	811 (9.5)	<0.001
	50-59	20,247 (14.6)	1,240 (14.6)	0.9
	60-69	21,413 (15.4)	1,822 (21.5)	<0.001
	70-79	19,157 (13.8)	1,985 (23.4)	<0.001
	≥80	14,817 (10.7)	1,901 (22.4)	<0.001
	Severity of comorbidity (CCI score):			
	Low (0)	83,896 (60.3)	3,719 (43.8)	<0.001
	Medium (1-2)	42,694 (30.7)	3,529 (41.5)	<0.001
	High (≥3)	12,528 (9.0)	1,246 (14.7)	<0.001
	Primary reason for admission:			
	Injuries	24,935 (17.9)	786 (9.3)	<0.001
	Cardiac	26,572 (19.1)	1,978 (23.3)	<0.001
	Digestive	19,131 (13.8)	1,093 (12.9)	0.02
	Cancer	15,760 (11.3)	1,143 (13.5)	<0.001
	Respiratory	9,419 (6.8)	677 (8.0)	<0.001
	Endocrine	1,773 (1.3)	345 (4.1)	<0.001
	Nervous and Mental	6,758 (4.9)	457 (5.4)	0.03
	Genitourinary	8,730 (6.3)	494 (5.8)	0.09
	Muscosceletal	9,016 (6.5)	441 (5.2)	<0.001
	General malaise	4,989 (3.6)	378 (4.5)	<0.001
	Other	12,036 (8.7)	702 (8.3)	0.22
	Presence of:			
	Dyslipidaemia	9,622 (6.9)	861 (10.1)	<0.001
	Diabetes mellitus	10,103 (7.3)	1,129 (13.3)	<0.001
	Atrial Fibrillation	8,195 (5.9)	1,030 (12.1)	<0.001
	Osteoporosis	999 (.7)	167 (2.0)	<0.001
	Down or Turner Syndrome	18 (.0)	3 (.0)	0.9
	Treated with:			
	amiodarone	2,309 (1.7)	362 (4.3)	<0.001
	lithium	184 (.1)	66 (.8)	<0.001
During the study period	**Hospital admissions**:			
	1	93,431 (67.2)	4,566 (53.8)	<0.001
	2-4	37,641 (27.1)	3,043 (35.8)	<0.001
	≥5	8,047 (5.8)	885 (10.4)	<0.001
	Emergencies:			
	None	39,186 (28.2)	2,356 (27.7)	<0.001
	1	71,592 (51.5)	3,460 (40.7)	<0.001
	2-3	20,995 (15.1)	1,792 (21.1)	<0.001
	≥4	7,346 (5.3)	886 (10.4)	<0.001
	Cumulative length of stay (days):			
	1	19,389 (13.9)	432 (5.1)	<0.001
	2-7	67,295 (48.4)	3,393 (39.9)	<0.001
	8-21	30,371 (21.8)	2,336 (27.5)	<0.001
	≥22	22,064 (15.9)	2,333 (27.5)	<0.001

6.3.3.2 *Thyroid function testing in patients with a history of TD*

On average, one in four admissions (N=3,920; 22.6%) or one in three patients (N=2,901; 34.2%) were tested for thyroid dysfunction and 4,872 thyroid function tests were performed (18.5% of all hospital thyroid function testing). In those tested, the mean number TFT requested was 1.68 (±1.32 SD) per patient. 36.4% of tested patients had their TFTs measured more than once (N=1,055); tests were repeated during the same admissions in 617 (21.3%) inpatients. TFT were requested during 25% (N=3,212) of admissions associated with L-T4 prescription. During hospital admissions associated with ATD administration testing was undertaken in 49.1% (N=281).

Table 6-6 represents the baseline characteristics of inpatients with a history of TD stratified based on thyroid function testing status. 47.1% of hyperthyroid and 33.2% of hypothyroid inpatients had their thyroid status monitored while in hospital. TFT was requested irrespective of gender. Older patients' age were significantly associated with testing, older subjects having their TFT requested more often (P<0.001). Patients admitted to the hospital for symptoms of general malaise (AOR=3.24) or for reasons reflecting respiratory (AOR=1.65) or nervous and mental systems (AOR=2.46) were more likely to have thyroid function monitored when compared to those admitted for injuries or trauma.

The proportion of testing increased with higher Charlson comorbidity index categories - medium and high comorbidity burdens having the likelihood of testing increased by 35% and 74% when compared to those with low severity of comorbidity. Those tested were more often found with diabetes mellitus and AF while increased

comorbidity of osteoporosis was associated with a borderline significantly increased odds ratio. Presence of a diagnosis of dyslipidaemia resulted in less testing. There were only three inpatients with diagnosis either Down or Turner syndrome and they were excluded from further analysis. Treatment with amiodarone increased the likelihood of being tested while administration of lithium did not.

Subsequently, we analysed the cumulative number of hospital admissions, emergencies and LOS during the entire study period. We found that patients returning to hospital more often and those more commonly admitted as emergencies were more likely to have thyroid hormone profiling requested compared with elective admissions, as were patients with total stay longer than 7 days compared to those admitted only for one day during the study years.

Table 6-6: Odds Ratios for having TFT requested in patients with a pre-existing TD during any hospital stay.

	Patient characteristics	All; N=8,494	No TF tested, N=5,593 *(65.8%)*	TFT requested, N=2,901 *(34.2%)*	OR (95% CI)	P value
Baseline admission	**Baseline dysfunction:**					
	Hypothyroid	7,931 (93.4%)	5,295 *(66.8%)*	2,636 *(32.2%)*	1.00	
	Hyperthyroid	563 (6.6%)	298 *(52.9%)*	265 *(47.1%)*	1.79 (1.50-2.12)	<0.001
	Sex: Male	2,121 (25.0%)	1,430 (25.6%)	517 (23.3%)	1.00	
	Female	6,373 (75.0%)	4,163 (74.4%)	1,701 (76.7%)	1.01 (0.99-1.22)	NS
	Age, mean (SD)	65.4 (16.9)	63.7 (16.5)	68.8 (17.4)		
	median (IQR: 25-75%)	68 (54-78)	66 (53-76)	73 (58-82)		
	16-29 y.	300 (3.5%)	201 (3.6%)	99 (3.4%)	1.00	
	30-39 y.	435 (5.1%)	311 (5.6%)	124 (4.3%)	0.81 (0.59-1.11)	NS
	40-49 y.	811 (9.5%)	617 (11.0%)	194 (6.7%)	0.64 (0.48-0.85)	0.002
	50-59 y.	1,240 (14.6%)	884 (15.8%)	354 (12.3%)	0.82 (0.62-1.07)	NS
	60-69 y.	1,822 (21.5%)	1,295(23.2%)	527 (18.2%)	0.83 (0.64-1.07)	NS
	70-79 y.	1,985 (23.4%)	1,318(23.6%)	667 (23.0%)	1.03 (0.79-1.33)	NS
	≥80 y.	1,901 (22.4%)	967 (17.3%)	934 (32.2%)	1.96 (1.52-2.54)	<0.001
	Primary diagnosis:					
	Injuries	786 (9.3%)	526 (9.4%)	251 (8.7%)	1.00	
	Cardiac	1,978 (23.3%)	1,278 (22.8%)	694 (23.9%)	0.85 (0.69-1.36)	NS
	Digestive	1,093 (12.9%)	757 (13.5%)	306 (10.5%)	0.75 (0.65-0.87)	<0.001
	Cancer	1,143 (13.5%)	876 (15.7%)	268 (9.2%)	0.55 (0.47-0.63)	<0.001
	Respiratory	677 (8.0%)	378 (6.8%)	309 (10.7%)	1.65 (1.41-1.93)	<0.001
	Endocrine	345 (4.1%)	230 (4.1%)	135 (4.7%)	1.23 (0.95-1.60)	NS
	Nervous and Mental	457 (5.4%)	217 (3.9%)	262 (9.0%)	2.46 (2.04-2.96)	<0.001
	Genitourinary	494 (5.8%)	324 (5.8%)	159 (5.5%)	1.03 (0.81-1.31)	NS
	Muscosceletal	441 (5.2%)	354 (6.3%)	81 (2.8%)	0.43 (0.33-0.54)	<0.001
	General malaise	378 (4.5%)	152 (2.7%)	241 (8.3%)	3.24 (2.63-3.99)	<0.001
	Other	702 (8.3%)	501 (9.0%)	195 (6.7%)	0.73 (0.62-0.87)	<0.001
	Severity of comorbidity (original CCI score):					
	Low (0)	3,658 (43.1%)	2,579 (46.1%)	1,079 (37.2%)	1.00	
	Medium (1-2)	3,543 (41.7%)	2,265 (40.5%)	1,278 (44.1%)	1.35 (1.22-1.49)	<0.001
	High (≥3)	1,293 (15.2%)	749 (13.4%)	544 (18.8%)	1.74 (1.52-1.98)	<0.001
	Presence of:					
	Dyslipidaemia	867 (10.2%)	603 (10.8%)	264 (9.1%)	0.83 (0.71-0.97)	0.015
	Diabetes mellitus	1,140 (13.4%)	692 (12.4%)	448 (15.4%)	1.30 (1.14-1.49)	<0.001
	Atrial Fibrillation	1,083 (12.8%)	554 (9.9%)	529 (18.2%)	2.03 (1.79-2.31)	<0.001
	Osteoporosis	178 (2.1%)	105 (1.9%)	73 (2.5%)	1.35 (1.00-1.83)	0.052 (NS)
	Down or Turner Synd.	3 (0.0%)	3 (0.1%)	0 (0%)	NA	NA
	User of:					
	amiodarone	389 (4.6%)	215 (3.8%)	174 (6.0%)	1.60 (1.30-1.96)	<0.001
	lithium	64 (0.8%)	32 (0.6%)	32 (1.1%)	1.94 (1.19-3.17)	NS
During the study period	**Hospital admissions:**					
	1	5,091 (59.9%)	3,924 (70.2%)	1,167 (40.2%)	1.00	
	2-4	2,725 (32.1%)	1,489 (26.6%)	1,236 (42.6%)	2.79 (2.53-3.08)	<0.001
	≥5	678 (8.0%)	180 (3.2%)	498 (17.2%)	9.30 (7.75-11.17)	<0.001
	mean (SD)	2.0 (1.4)	1.6 (1.3)	2.9 (1.7)		
	Emergencies:					
	None	2,460 (29.0%)	2,159 (38.6%)	301 (10.4%)	1.00	
	1	3,728 (43.9%)	2,569 (45.9%)	1,159 (40.0%)	3.24 (2.82-3.72)	<0.001
	2-3	1,596 (18.8%)	697 (12.5%)	899 (31.0%)	9.25 (7.92-10.81)	<0.001
	≥4	710 (8.4%)	168 (3.0%)	542 (18.7%)	23.14 (18.74-28.58)	<0.001
	Cumulative length of stay (days):					
	1	484 (5.7%)	418 (7.5%)	66 (2.3%)	1.00	
	2-7	3,528 (41.5%)	2,938 (52.5%)	590 (20.3%)	1.27 (0.97-1.67)	NS (0.86)
	8-21	2,338 (27.5%)	1,535 (27.4%)	803 (27.7%)	3.31 (2.52-4.35)	<0.001
	≥22	2,144 (25.2%)	702 (12.6%)	1,442 (49.7%)	13.01 (9.88-17.12)	<0.001
	mean (SD)	19.0 (4.4)	10.5 (3.2)	35.5 (6.0)		

6.3.3.3 *Characteristics of TFT request in patients with pre-existing TD*

The previous analysis described the characteristics of the monitored cohort in general and stratified according to whether they were tested at the baseline admission. However, 46.2% patients with a history of TD were admitted to hospital more than once and admissions often had different characteristics. In order to find out who had thyroid function monitored and when this was undertaken, we modelled our data using the GEE utilising data from various admissions (Table 6-7).

Demographic factors such as age and gender did not significantly impact the decision for testing and neither did the severity of comorbidities. Hyperthyroid subjects were more likely (AOR=2.4) to have their thyroid function checked while in hospital than those with hypothyroidism. An increased likelihood of testing was also associated with increased odds of subsequent action by prescribing thyroid medication (AOR=2.2) or documenting the dysthyroid comorbidity with a suitable ICD-10 code (AOR=1.2) in those with thyroid dysfunction. Those admitted to hospital for longer periods (AOR= 1.5, 3.4, 8.8 for 2-7, 8-21, and 22+ days, respectively) as well as those undergoing emergency admission (AOR=1.8) were more likely to be tested. There was decreased thyroid function testing activity in admissions to Specialty medicine (AOR=0.5) or General and Specialty surgery (AOR=0.3 and 0.4) when compared to General medicine whereas the requesting frequency from ITU was not statistically different than that in General medicine.

Inpatients admitted with a primary diagnosis of nervous or mental health (AOR=2.1), endocrine (AOR=1.9), or cardiovascular (AOR=1.3) conditions, as well as those with symptoms and signs of general malaise (AOR=1.9), had increased odds of having

thyroid testing requested, while those admitted with musculoskeletal disorders (AOR=0.7) had lower odds compared with those admitted with injuries. The presence of AF (AOR=1.5) prompted thyroid function testing while a diagnosis of dyslipidaemia (AOR=0.8) or diabetes mellitus (AOR=0.9) decreased the odds for thyroid testing. The presence of osteoporosis was not significantly associated with thyroid function requesting patterns. Use of amiodarone (AOR=1.2) or lithium (AOR=1.6) increased the odds for testing. The details of the multilevel analysis of likelihood of thyroid function testing among inpatients with history of thyroid dysfunction are presented in Table 6-7.

Table 6-7: Factors significantly associated with TFT request in patients with a history of TD. The following factors were removed as not statistically significant: age, gender, CCI score and presence of osteoporosis

Parameter	AOR	95% CI for AOR	P -value
TD: Hypo-	1		
Hyperthyroidism	2.38	(1.97- 2.87)	<0.0001
Prescribed thyroid medication: No	1		
Yes	2.17	(1.90-2.47)	<0.0001
Length of stay: 1 day	1		
2-7 days	1.49	(1.26- 1.76)	<0.0001
8-21 days	3.41	(2.87- 4.07)	<0.0001
≥ 22 days	8.84	(7.30-10.70)	<0.0001
Specialty: General medicine	1		
Specialty medicine	0.52	(0.45- 0.59)	<0.0001
General surgery	0.31	(0.27- 0.36)	<0.0001
Specialty surgery	0.40	(0.40- 0.47)	<0.0001
ICU	0.79	(0.59- 1.05)	NS (0.1)
Adm. type: elective	1		
emergency	1.75	(1.53- 1.99)	<0.0001
Primary diagnosis: Injuries	1		
Cardiac	1.25	(1.05- 1.47)	0.01
Digestive	1.03	(0.86- 1.24)	NS (0.8)
Cancer	1.06	(0.87- 1.29)	NS (0.6)
Respiratory	0.86	(0.73- 1.04)	NS (0.1)
Endocrine	1.89	(1.47- 2.44)	<0.0001
Nervous and Mental	2.09	(1.68- 2.59)	<0.0001
Genitourinary	1.19	(0.95- 1.48)	NS (0.1)
Muscosceletal	0.74	(0.56- 0.99)	0.04
General malaise	1.93	(1.55- 2.41)	<0.0001
Other	1.15	(0.93- 1.42)	NS (0.2)
ICD-10 coded: No	1		
Yes	1.19	(1.10-1.30)	<0.0001
Presence of:			
Atrial Fibrillation	1.45	(1.28-1.63)	<0.0001
Dyslipidaemia	0.80	(0.70-0.92)	0.02
Diabetes mellitus	0.87	(0.78-0.97)	0.01
User of:			
amiodarone	1.22	(1.02- 1.48)	0.03
lithium	1.58	(1.10-2.26)	0.01

6.3.3.4 *Biochemical findings of TFT results in admissions of patients with TD history*

Thyroid function tests in patients with a history of thyroid dysfunction were often outside the normal range (abnormal TSH in 49.5% [N=1,939]; fT4 in 21.9% [N=859] and fT3 in 9.5% [N= 371]). Figure 6-5 presents the distribution of the first biochemical reading per admission in inpatients with previously diagnosed thyroid dysfunction. Light bars indicate results within the laboratory standardised 95% confidence intervals and black bars represent abnormal thyroid hormone concentrations.

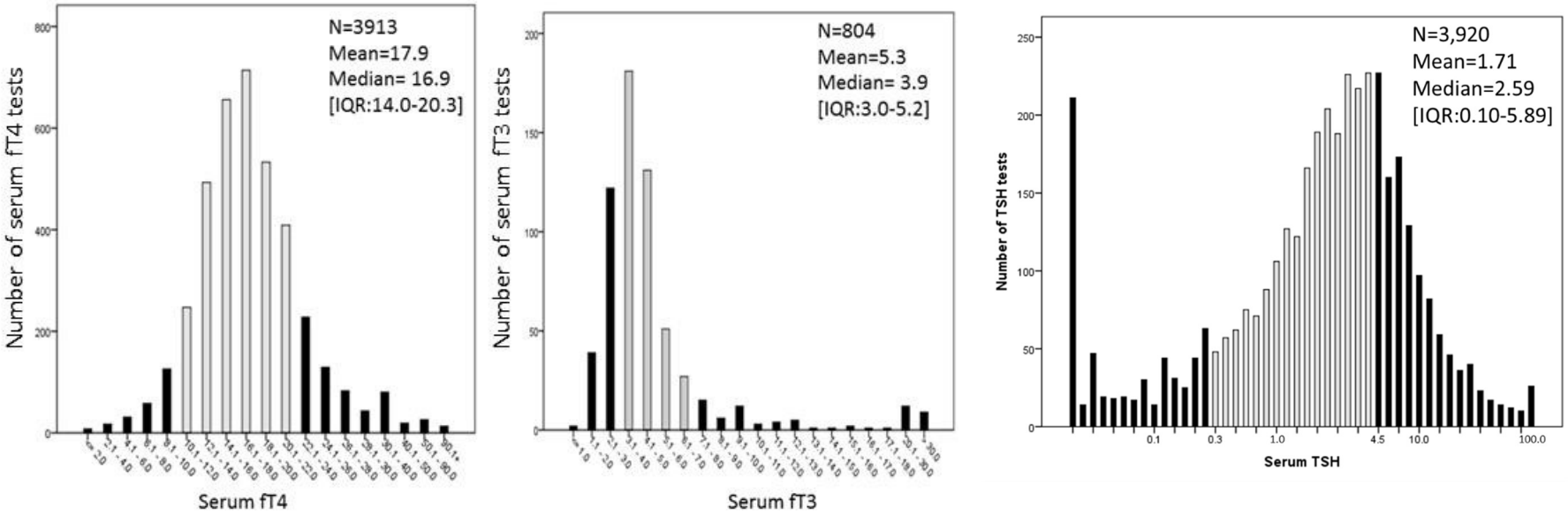

Figure 6-5: Distribution of biochemical thyroid function tests (light bars indicate concentrations within the standardised (95% CI) laboratory reference ranges. Serum fT4 and fT3 are presented on linear scale while serum TSH results are presented on a logarithmic scale.

Less than half of the admissions (41%) of monitored patients were associated with euthyroidism in combined analysis of serum fT4 and TSH (Table 6-8). Five percent of admissions were associated with overt hyperthyroidism (with TSH<0.1 and fT4 above normal) and when any degree of hyperthyroidism was considered this was found in more than 15% of admissions. Overt hypothyroidism was found in 2.6% and almost a third of all admissions were associated with varying degrees of hypothyroidism. Importantly, 10% of admissions during which testing was undertaken were associated with results not following typical HPT axis feedback responses. A pattern of increased fT4 with normal TSH was most commonly found.

Table 6-8: Distribution of the first TFT simultaneously measuring serum concentrations TSH and fT4 in patients with a history of TD

	TFT outcome	Baseline TFTs in patients N=2,901 (%)	TFTs during any TD admission			
			Total N=3,920 (%)	On L-T4 N=3,212 (%)	On ATD N=236 (%)	No treatment N=472 (%)
Hyperthyroid	Overt hyperthyroidism (TSH<0.1)	144 (5.0)	206 (5.3)	118 (3.7)	60 (25.4)	28 (5.9)
	Overt hyperthyroidism with detectable TSH (0.1-0.3)	63 (2.2)	85 (2.2)	59 (1.8)	13 (5.5)	13 (2.8)
	Subclinical hyperthyroidism grade 2 (TSH<0.1 and fT4 normal)	125 (4.3)	157 (4.0)	117 (3.6)	24 (10.2)	16 (3.4)
	Subclinical hyperthyroidism grade 1 (TSH 0.1-0.3 and fT4 normal)	109 (3.8)	145 (3.7)	115 (3.6)	8 (3.4)	22 (4.7)
Euthyroid		1,192 (41.1)	1,629 (41.6)	1,322 (41.2)	75 (31.8)	232 (49.2)
Hypothyroid	Subclinical hypothyroidism grade 1 (THS>4.5 and <10 and fT4 normal)	560 (19.3)	737 (18.8)	640 (19.9)	18 (7.6)	79 (16.7)
	Subclinical hypothyroidism grade 2 (THS>10 and fT4 normal)	312 (10.8)	394 (10.1)	353 (11.0)	9 (3.8)	32 (6.8)
	Overt hypothyroidism with mildly raised TSH (4.5-10)	40 (1.4)	45 (1.2)	38 (1.2)	4 (1.7)	3 (0.6)
	Overt hypothyroidism (TSH>10)	56 (1.9)	100 (2.6)	90 (2.8)	4 (1.7)	6 (1.3)
Other	↓TSH, ↓fT4	20 (1.4)	25 (0.6)	22 (0.7)	4 (1.7)	0 (0.0)
	↑TSH, ↑fT4	56 (1.9)	44 (1.1)	44 (1.4)	0 (0.0)	0 (0.0)
	normal TSH,↓fT4	52 (1.8)	61 (1.6)	53 (1.7)	2 (0.8)	6 (1.3)
	normal TSH,↑fT4	202 (7.0)	286 (7.3)	236 (7.3)	15 (6.4)	35 (7.4)

6.3.3.5 *Thyroid function in admissions with different concurrent treatment*

Levothyroxine

Among 3,207 thyroid function monitored admissions associated with L-T4 replacement (Table 6-8) 7% had undetectable serum TSH concentrations (N=335). Overall, various forms of hyperthyroidism while on levothyroxine replacement were found in 409 admissions (12.7%). A third of tested admissions associated with L-T4 prescription indicated varying degrees of hypothyroidism (N=1,121; 34.9%).

Adjustments to L-T4 doses following results of TFTs were identified during 356 (11%) admissions: in 32 cases of overt hyperthyroidism, in 36 overtly hypothyroid subjects and the remaining in milder degrees of thyroid dysfunction. Additionally, thyroid replacement was re-commenced during 16 admissions.

ATD

Treatment with ATD was recorded during 236 admissions (Table 6-8). The majority of those admissions were associated with either euthyroidism (31.8%) or overt hyperthyroidism (25.4%). 35 cases of hypothyroidism, 4 of which were overt (with TSH>10) were found among those prescribed ATD. The doses of ATD treatment were altered in 32 and thionamide treatment was re-instated in three admissions.

No treatment

Overt thyroid dysfunction was found during a small proportion of admissions with no record of any thyroid treatment being administered to patients. Overt hyperthyroidism was present in 5.9% (N=28) and overt hypothyroidism in 1.3% (N=6; Table 6-8) but no treatment was prescribed in hospital.

Overall, thyroid function testing in 3,914 hospital admissions of patients with previous TD history led to a change in thyroid treatment in 407 cases (10.4%) although thyroid function outside of normal range was found in 2,208 (56%).

6.4 Discussion

6.4.1 Cohort characteristics

Our study reveals a real-life analysis of the utilisation of thyroid function testing in a large hospital cohort and the outcomes of an applied testing strategy. It shows that thyroid hormone profiling is a high-volume test, requested by clinicians for patients hospitalised for a variety of reasons. Interestingly, contrary to the common belief of a constant "inflation" in the numbers of tests (Vaidya et al., 2013), we noted a significant decrease in annual numbers of thyroid test requests, which coincided with the economic recession.

We confirmed differences in clinical approaches to testing of thyroid function: patients with no previous history of TD, assumed to be tested for case finding, were significantly less often tested than those with pre-existing TD in whom, supposedly testing was aimed at monitoring of adequacy of thyroid treatment. The differences in testing frequencies were confirmed on both patient and admission levels. The cohorts differed in terms of frequency of testing and strategy of selection for TFT requests.

Based up on a *priori* assumption that thyroid function testing would be performed differently according to whether patients had a pre-existing TD or not, our study has confirmed differential testing strategies, which would support this assumption.

In a cohort of 140,174 inpatients with no previous thyroid dysfunction (95% of the study subjects), thyroid profiling aiming at case finding was done in 12% of patients, confirming a diagnosis of overt thyroid dysfunction in 0.2% of the cohort (overt hyperthyroidism in 158 and overt hypothyroidism in 123 inpatients during 5 years of study period). National (Association of Clinical Biochemistry, 2006) and international (Stockigt, 1996, Baloch et al., 2003, Ladenson et al., 2000) guidelines warn against routine thyroid function assessment in acutely hospitalised patients. In such patients, especially in the critically ill, non-thyroidal illness may result in significantly reduced specificity and sensitivity of the thyroid function tests. It is estimated that around 15% of hospital patients present with mild alterations in serum TSH concentrations due to effects of medication and/or non-thyroid related illness (Spencer et al., 1987). In intensive care units, thyroid function tests notoriously produce results wrongly indicating thyroid abnormalities

(Angelousi et al., 2011, Pimentel and Hansen, 2005). We demonstrated a high frequency and low efficiency of case finding, thus revealing a lack of compliance with guideline recommendations.

Patients with pre-existing thyroid dysfunction comprised 5% of study cohort (N=8,494), 93% of whom had a diagnosis of hypothyroidism. Such a big difference in prevalence of hypothyroidism versus hyperthyroidism, albeit not expected based on documented incidence rates (Leese et al., 2008, Vanderpump et al., 1995), is likely to be due to differences in duration of treatment. Hyperthyroidism often resolves after 18-24 months of medical therapy or following ablative treatment, whilst patients with hypothyroidism usually require life-long hormone replacement, determining an increased likelihood of being identified based on levothyroxine prescription. Although in cross-sectional studies such disproportion is considered a bias (Delgado-Rodriguez and Llorca, 2004), in our longitudinal study it reflects the real-life scenario in hospital wards.

The cohort of subjects with a history of thyroid dysfunction was older than inpatients with normal thyroid function with a higher prevalence of women, reflecting the epidemiology of TD in the community (Leese et al., 2008, Tunbridge et al., 1977, Vanderpump et al., 1995). Patients with TD had higher proportions of serious comorbidities, increased prevalence of dyslipidaemia, diabetes mellitus, AF and osteoporosis and were more often prescribed amiodarone or lithium when compared to those with no history of TD. Subjects with thyroid dysfunction were re-admitted to hospital more often, a higher proportion of those admissions

were emergencies and the total number of days spent in hospital during the study period was higher than in subjects with normal thyroid function. The differences between hyper-, hypo- and euthyroid inpatients are studied in greater detail in Chapter 7.

6.4.2 Thyroid function testing

Thyroid function testing was common, which may suggest a routine approach to requesting thyroid profiling. However, we were able to identify some systematic differences between tested and untested patients, representing factors modifying the decision to order TFTs. In the cohort of patients tested for case finding, the number of requests increased with age and was 30% higher in females, which does not reflect the female-to-male ratio of prevalence found in community studies. Inpatients were more likely to have thyroid function checked when they stayed longer in hospital or had more severe comorbidity index as measured using the CCI. Whether, in some cases, such delay reflected difficulties in diagnosing thyroid dysfunction based on clinical presentation remains unclear.

Although professional bodies and guidelines have not defined a clear testing strategy within the hospital setting, there are a number of recommendations for surveillance of patient groups at higher risk for thyroid dysfunction (Association of Clinical Biochemistry, 2006, Ladenson et al., 2000). We confirmed that hospitalised subjects prescribed lithium or those with co-morbidities of AF or osteoporosis were more often targeted for thyroid dysfunction case finding, in accord with such guidelines. However,

comorbidities of diabetes mellitus and dyslipidaemia did not trigger TFT requests. This is not in accord with guideline recommendations nor with a growing body of evidence indicating an increased prevalence of thyroid dysfunction in both conditions (Wang, 2013, Santini et al., 2014, Boelaert et al., 2010a). Additionally, serious health consequences such as significantly increased risk of sudden cardiac death have been associated with altered thyroid function in those undergoing hemodialysis for diabetes mellitus (Drechsler et al., 2014). Treatment with amiodarone was also not identified as an independent factor modifying testing behaviour, albeit patients on amiodarone were five times more likely to be tested when analysed using univariate methods. Such findings may suggest high collinearity with other factors. Indeed, 75% of amiodarone-treated subjects were admitted to hospital for cardiac reasons thus contributing greatly to the increase of case finding testing among this group of patients.

Monitoring thyroid function among those with a history of thyroid dysfunction was common and was requested in about a third of patients. Patients' gender and age or the severity of comorbidities did not affect thyroid function test requesting. Hyperthyroid patients had their thyroid function more closely monitored than subjects diagnosed with hypothyroidism, which was expected based on the need for more intensive monitoring in those with thyrotoxicosis (Jonklaas et al., 2014, Ross et al., 2016). Any acknowledgement of a co-existing history of TD, whether indicated by a prescription for thyroid treatment or by appropriate codes for TD as a comorbidity, independently increased the likelihood of testing. In our cohort,

only 57% of admissions had appropriate coding for the presence of thyroid dysfunction as a comorbidity. This is in accord with a study (Violan et al., 2013) comparing self-reported comorbidities with those recorded in the health care system. Regarding thyroid comorbidities, almost twice as many patients (1.8) reported their own chronic thyroid problems in a health survey than were coded in their electronic health record. Lack of accurate coding not only decreases the likelihood of having thyroid function monitored but also is associated with missing doses of levothyroxine, as shown in an internal audit from our department (data not published).

6.4.3 Biochemical findings in patients with no history of thyroid dysfunction

Thyroid function testing in both cohorts of inpatients described above indicated very different findings. Euthyroidism was confirmed in 81% of patients without a history of thyroid dysfunction. Such a high proportion of normal results casts significant doubts on whether patient selection for testing was based on strong clinical suspicion as recommended by the guidelines (Association of Clinical Biochemistry, 2006, Ladenson et al., 2000).

Abnormal thyroid function in hospitalised patients may be due to the effects of medication and/or non-thyroidal illness, which reverts to normal following recovery from the illness (Demers and Spencer, 2002). It could be expected that out of the 19% of patients with abnormal thyroid function (comprising various

degrees of hyper- and hypothyroidism as well as discordant results), a large proportion may have normalised spontaneously. Unfortunately, longitudinal data on TFTs outside the hospital admissions were not available. Hence, the distinction between transient and longer lasting thyroid dysfunction and an assessment of the prevalence of spontaneously reversible abnormalities proved impossible. Future linkage of hospital and GP data may shed further light on the correct interpretation of thyroid function in inpatients.

According to a previous review (Attia et al., 1999), 2–3% of hospitalised patients have abnormal serum TSH measurements, but after the treatment of their non-thyroidal diseases, less than half of these are confirmed to have underlying thyroid dysfunction. Among patients with no history of TD tested in our hospital, the proportion of those with abnormal TSH concentrations was much higher, accounting to almost 13%. Various degrees of hyper- and hypothyroidism and a small proportion of patients with discordant patterns of thyroid function tests were identified. Overt thyroid dysfunction requiring medical intervention was found in less than 2% of those tested, which was very similar to a study analysing 1,580 hospitalised patients of which 29 (1.8%) were found with overt thyroid dysfunction by biochemical and clinical examination (Spencer et al., 1987). In view of such a high proportion of abnormal TSH results which do not identify those in need of active intervention, we conclude that TSH testing alone, recommended by the national and international guidelines as a first line screening instrument (Association of Clinical Biochemistry, 2006, Baloch et al., 2003, Ross et al., 2016), is not sufficient in a hospital setting with additional measurement of serum

thyroid hormones being required. One possibility to overcome this hurdle is the application of a "cascading" approach, in which analysis of circulating thyroid hormones (fT4, fT3) is undertaken in the same sample used for TSH measurement and follows the finding of an abnormal TSH concetration. Such approach is economical and practical but is associated with a risk of missing rare diagnoses including TSH secreting pituitary adenomas in which concentrations of TSH may stay within the normal range.

The diagnosis of new cases of overt hyper- and hypothyroidism was rare (1.7% of those tested). Importantly, treatment was not always initiated, nor were the results communicated to the patient's GP, in all cases. In 42% of newly found hyperthyroidism and in 26% of hypothyroidism, there was no record of any action being taken upon finding of overtly abnormal thyroid function in the discharge notes, which is required by the discharge standards (NHS England Patient Safety Domain, 2016). This might have resulted in delayed diagnosis of true overt thyroid dysfunction. Further investigation is needed to determine if the lack of recording of action resulting from finding overtly abnormal thyroid profiles was caused by clinical difficulties in interpretation of the results or by administrative system imperfections.

Excessive inpatient laboratory testing has been associated with additional health care cost, unnecessary blood sampling, false-positive results, and even hospital-acquired anaemia (Koch et al., 2013, Salisbury et al., 2011). Altogether, in our hospital, 58 patients had to be tested to find one with overt thyroid dysfunction or 90 if initiation of any clinical intervention (treatment or GP recommendation) was analysed.

The values increased to 75 and 118, respectively, if the number of tests and not the number of patients was calculated. These numbers suggest a degree of wasting of laboratory resources and are much higher than those found in another study of hospital-wide testing behaviour where only two redundant tests were done for every one influencing a clinical decision (Miyakis et al., 2006). We conclude that our study reveals a significant issue with over-testing in a case-finding strategy in patients with no history of thyroid dysfunction and demonstrates the need for clear guidance to optimise the criteria to warrant thyroid function testing in inpatients.

6.4.4 Biochemical findings in patients with pre-existing thyroid dysfunction

We demonstrated high levels of aberrant thyroid function in patients with pre-existing TD. Abnormal TFT results in patients with previously diagnosed thyroid dysfunction were common, found during nearly 60% of admissions in which thyroid function was monitored. Both, insufficient and excessive administration of thyroid-related medication in those with thyroid dysfunction may lead to serious consequences. Thus timely diagnosis, institution of treatment and appropriate monitoring of thyroid function needs to be undertaken in both hospitalised and ambulatory patients (Laurberg et al., 2005). In our cohort of patients with pre-existing TD, levothyroxine was prescribed during 82% of admissions with thyroid function requested (3,212/3,920; Table 6-8). Serum TSH concentrations above 10 mIU/L were found in 14% of those admissions suggesting insufficient hormone replacement dosage.

Additionally, in 4% of admissions during which L-T4 was prescribed, testing revealed a picture of biochemical overt hyperthyroidism suggesting overtreatment.

Thyroid function alterations in hospitalised patients with pre-existing thyroid dysfunction may be caused by factors relating to the treatment of the dysfunction itself e.g. omission of doses of thyroid medication, inadequate drug doses or concurrent administration of medications that interfere with the absorption of thyroid medication (Somwaru et al., 2009, Liwanpo and Hershman, 2009, Schiff et al., 2005). In these cases adequate clinical action needs to be taken. Sometimes, however, similarly to findings in patients with no previous thyroid dysfunction, medication or non-thyroidal illness may affect HTP axis homeostasis mechanisms, which may be reversed once the illness is cured. In these patients thyroid medication should not be altered while in hospital (Jonklaas et al., 2014). In our study, 11% of subjects prescribed thyroxine had the dose of levothyroxine adjusted whilst in hospital.

It has to be noted that patients with previous thyroid dysfunction were older, had more severe comorbidities, returned to hospital more often and had longer hospital stays. It remains unclear if the presence of uncontrolled thyroid dysfunction caused an additional health burden thereby resulting in the above-mentioned factors or, if the weaker health state of these patients is reflected in the observed aberrations in thyroid function.

The scope and strategy of monitoring thyroid function in hospitalised patients with pre-existing thyroid dysfunction is not a well-investigated. Although ATA

guidelines on the management of hypothyroidism or national guidelines on thyroid function testing (Jonklaas et al., 2014, Association of Clinical Biochemistry, 2006) dedicate whole sections to monitoring and treatment of thyroid dysfunction in hospital, the recommendations are based on low quality evidence due to a lack of studies of the area. Importantly, recommendations have been made for further studies on the subject. Our study provides important insights into of the processes and consequences of thyroid function tests monitoring in those with pre-existing thyroid dysfunction.

6.4.5 Study limitation

Our study audits thyroid testing behaviours in a single secondary/tertiary hospital and it may be difficult to extrapolate our findings to other settings. The Queen Elizabeth Hospital serves as a national centre for liver, heart and lung transplant as well as for cancer studies, thus the frequency of the most challenging cases in these areas may be increased. Moreover, this is a regional centre for trauma and burns and serves as a Royal Centre for Defense Medicine treating military personnel with life-threatening injuries from conflict zones. As a rule, patients with obstetric and gynaecological disorders are treated in the neighbouring Women's Hospital, however intensive care for these specialties is provided by the Queen Elizabeth Hospital. Consequently, our cohort may include a high number of acute cases and overrepresentation of intensive care patients. Comparison to national data of hospitalised patients is needed to clarify the influences of the hospital profile.

6.4.6 Conclusions

Our study revealed high volume of thyroid function testing among hospitalised patients. We found that TFT was common (11%) in patients with no history of TD, while the finding of overt thyroid dysfunction was very rare (2% of the tested; 0.2% of the entire cohort). The testing volume increased with advancing age and the number of new diagnoses of overt dysfunction was higher in older subjects. Thyroid function testing was even more frequent in hospitalised patients with pre-existing TD. We established that a third of patients had their treatment monitored while in hospital in whom a high prevalence of thyroid function outside the reference range was detected. The finding of overtly abnormal thyroid function results did not always trigger adjustment of medication dosage. Similarly, the diagnosis of new thyroid dysfunction was not always followed by initiation of treatment or communication of the finding with patient's GP. Although, a low threshold of testing may be justified, especially in the elderly, the high proportion of results not requiring medical intervention suggest that more economical approaches to TFT requesting are required.

Chapter 7. ALL-CAUSE MORTALITY AND HEALTH SYSTEM UTILISATION IN HYPERTHYROID INPATIENTS

7.1 Introduction

In the latest strategic planning, NHS England has declared its dedication to improve numerous patient outcomes including reduction in mortality and morbidity of various mental and physical health conditions and reduction in avoidable hospital admissions and bed days (NHS England, 2013). In order to achieve these goals effectively, information is needed on mortality and bed utilisation in particular diagnostic groups. For some conditions, like diabetes mellitus, such data are accumulating rapidly, while with others such as thyroid dysfunction (even despite its high prevalence) there is much less information available.

Thyroid dysfunction (TD) is very common. In England, hyperthyroidism affects 3% of women and 0.3% of men (Tunbridge et al., 1977). Hypothyroidism is diagnosed in over 3% of population (Health and Social Care Information Centre, 2014) and is the seventh most common long-term condition in adults (Department of Health, 2012). Both, hyperthyroidism and hypothyroidism have been linked to many other

serious conditions such as AF, heart failure, stroke, pulmonary embolism and coagulation disorders, all of which contribute to increased mortality (Biondi, 2012, Parmar, 2005, Osman et al., 2002). The majority of studies, as well as the results of a metaanalysis (Brandt et al., 2011), confirm increased mortality in hyperthyroid individuals. Additionally, there are already established risks of long-term sickness absence, lower rate of return to work, and higher risk of unemployment and disability pensioning (Nexo et al., 2014). Importantly, thyroid dysfunction is often autoimmune in nature and is therefore associated with the increased morbidity and mortality of other co-existing autoimmune conditions (Boelaert et al., 2010a).

Despite the frequency of thyroid dysfunction and its association with serious consequences, healthcare utilisation of patients with TD has not been studied thoroughly. Besides a few reports on thyroid emergencies, such as myxoedema coma and thyroid storm (Kofinas et al., 2015, Angell et al., 2015), the epidemiology of inpatients with TD and management of co-existing morbidities remains uncharted. In present times of growing pressures on the efficiency of hospital bed utilisation, the issue of appropriate risk estimates is of paramount importance.

In this chapter, we set out to compare mortality rates in patients with a history of hyperthyroidism to those with hypothyroidism, as well as those with no history of TD. Next, the differences in hospital utilisation between the groups were assessed and we investigated whether diagnosed and treated TD is associated with an additional risk of being admitted to hospital due to cardiovascular, respiratory, digestive or mental and behavioural conditions.

7.2 Methods

Based on the previously studied cohort, a nested matched case-control study was designed to compare the outcomes in inpatients with hyperthyroidism (cases) to those with hypothyroidism (controls) and to those with no history of TD (controls). The project was revised, approved and registered with the University Hospitals Birmingham NHS Foundation Trust (CARMS-12123).

7.2.1 Study dataset and data linkage

The study was conducted using a cohort of patients admitted to the University Hospitals Birmingham NHS FT from 1st January 2007 to 31st December 2011. The analysis of inpatient hospital activity was limited to "ordinary admissions" by excluding emergency department attendances without further in-hospital admissions, transfers, military check-ups and admissions of minors (<16 years).

Data retrieved from the hospital Patient Administration System (PAS) was linked by the unique patient identifier (Hospital Number) with PICS and Telepath laboratory systems. Inpatients were divided according to their underlying TD as described in the section 7.2.2. Hyperthyroid subject were then matched with hypo- and euthyroid controls (section 7.2.3) in a 1 to 4 ratio.

Inpatients included into the nested study were further followed up until the 31st December 2015. Previously extracted data were updated. Information

on the events of death was obtained from linkage of the dataset with the Personal Demographic Service section of the national Spine database, maintained by the Health and Social Care Information Centre. The linking process was done by the NHS Trust Informatics Department based on the individual NHS number. The received dataset was cleaned to solve inconsistencies or to remove invalid data.

7.2.2 Identification of underlying thyroid dysfunction

Hospital admissions within the cohort were categorised as hyperthyroid or hypothyroid based on the presence of a thyroid dysfunction ICD-10 code in either the admission or discharge fields (E05 for hyper-; E02-03 for hypothyroid) and/or prescription of the respective thyroid treatment. Hospital stays with carbimazole (CMZ) or propylthiouracil (PTU) treatment were classed as hyperthyroid admission and those on levothyroxine (L-T4) without concurrent antithyroid drug (ATD) treatment as hypothyroid. In addition, admissions associated with abnormal thyroid function test results were categorised into hyperthyroid if TSH was <0.1 mIU/L and fT4 was >22 pmol/L and hypothyroid if TSH was >10 mIU/L and fT4 was <10 pmol/L. A number of inconsistencies were identified including admissions coded for hypothyroidism and during which treatment for hyperthyroidism was administered or vice versa. These discrepancies were resolved assuming superiority of the treatment decision over the administrative coding and the category was assigned in line with the medication prescribed.

Next, inpatients were stratified into the appropriate categories based on the first diagnosis of TD. Allocation to the category was not flexible and potential changes in diagnosis during the subsequent hospital stays did not affect the stratification. Admissions not identified as being associated with TD were assigned to a euthyroid category. Inpatients with no thyroid dysfunction during any of the admissions formed the euthyroid control pool.

7.2.3 Matching process

The process of matching was conducted with IBM SPSS statistical package version 22 using function Fuzzy with priority given to exact matches. The matching variables included age (in a one year banding), gender and a calendar year of admission. Originally, the study aimed to match exactly with a 1 to 4 ratio with no replacement. However, applying these tight constrains left 47 cases with no matches and an additional 28 cases with just one match. The decision was made to relax the age limits by one year increments repeating the process. Eventually the matching was conducted allowing relaxation of 4 years of age and priority given to exact matches, however this resulted in 18 cases having 2 hypothyroid controls and 23 cases matched in a 1-to-3 ratio in the hypothyroid arm.

7.2.4 Study outcomes

All-cause mortality was the primary outcome of the study defined as death during the study period. Dates of deaths were acquired from the national database, irrespective of the place of death.

Secondary outcomes included estimates of differences between hyper-, hypo- and euthyroid inpatients in hospital use. This was assessed as total number of hospitalisations, mean length of stay (LOS), proportions of patients being admitted as emergency or being treated at intensive therapy units (ITU) and proportions of patients ever admitted with primary cardiovascular (CVD), respiratory, digestive or mental health conditions during the study period.

7.2.5 Variable definitions

The dataset was stratified and categorised into factors representing demographic, clinical and administrative characteristics. The age of inpatients was calculated at baseline and was analysed as a continuous variable with one year increments.

ICD-10 codes recorded at each admission and discharge were used twice: (1) to classify primary reason for admission and (2) to calculate a Charlson Comorbidity Index (CCI) score. ICD-10 codes for primary reason of admission were extracted and then grouped into ICD-10 chapters (WHO, 2010). Primary admissions for CVD (codes starting with the letter I), respiratory (the letter J) and mental health reasons (the letter F) were studied due to the previously established links with hyperthyroidism (Brandt et

al., 2014, Nyirenda et al., 2005, Brandt et al., 2013b). In addition, admissions with primary diagnoses of digestive disorders (ICD-10 codes starting with the letter K) were also analysed due to frequent gastrointestinal (GI) symptomatology at TD presentation and physiological as well as pathophysiological links with both hyper- and hypothyroidism. While the proportions reflect the distribution of the specific conditions prevalent within the cohort of studied patients, they do not give any indication as to the relationship between the conditions. That is, a single individual can have multiple conditions recorded across multiple hospital admissions.

ICD-10 classification was further used to calculate the CCI scores as described in section 6.2.2.1. CCI index was analysed as an interval variable with an increment of one score.

Survival time was calculated assuming the date of the first hospital admission as the time zero; date of event was defined as date of death and the completion of the follow-up (31st of December 2015) as the date of censoring. Length of stay (LOS) was calculated as each calendar day during which the patient remained in hospital. Mean LOS was calculated for each subject individually. It was converted into count data by truncation of the decimal places and analysed as one day increment. ITU admissions were aggregated into binary response based on whether a patient was ever treated in the ITU setting during the study period. For each patient, the calendar year of the first hospital admission was extracted and this was used as an exact matching factor in the selection process and then as a variable to correct the estimates of studied effects.

7.2.6 Statistical analysis

Kaplan-Meier curves were plotted to illustrated the survival of the hyper-,hypo- and euthyroid patients. Mortality data was tested for validity of proportional hazard assumption by including the time dependent covariate in the model. Time-dependent covariate was calculated as a product of the time and each variable entered into the model separately. Since the assumption was violated when all three arms were analysed, we limited the survival dataset only to hyperthyroid and euthyroid patients were the hazard rates were confirmed proportional (P>0.05). Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazard models stratified into matched sets to reflect similarities between cases and their matched controls. Additional variables used to build the models were gender, age at baseline, calendar year of first hospital admission and CCI scores.

Moreover, a sensitivity analysis was conducted comparing mortality in hyperthyroid subjects and euthyroid controls without any significant comorbidity. That was defined by the CCI score of zero and alive status within the first 12 months. A multivariable analysis to determine all-cause mortality for these inpatients was conducted as above with no CCI variable entered into the model.

In view of the matched design a General Estimating Equation (GEE) was used to model the secondary outcomes. 95% CI, the unadjusted (OR) and adjusted odds ratios (AOR) were calculated. Data on ITU admissions and primary reasons for admission was modelled with binary logistical analysis. Variables of counts (number of hospital

admissions, emergency admissions and mean LOS) approximately followed the Poisson distribution and thus were analysed with log-linear methods. Unadjusted and multivariable-adjusted (age, sex, year of the first hospital admission and CCI) models were used to estimate the association between euthyroid patients and the hyper- and hypothyroid groups. Proportions were compared with Chi-square test. Statistical significance level was set at 5% for all analyses. All data was analysed with IBM SPSS Statistics version 22.

7.3 Results

7.3.1 Identification of hyper- hypo- and euthyroid inpatients

The process of identification of cases and two pools of controls is illustrated in Figure 7-1. Altogether, 671 hyperthyroid inpatients were identified and matched with hypo- and euthyroid controls and then followed up for up to 9 years, providing 44,745 person-years of follow-up (mean FU: 7.48 y. ±2.46 SD). Overall, there were 17,955 hospital admissions analysed in 5,980 inpatients.

During the study period 20 patients from the euthyroid control group (0.7%) and 32 (4.8%) from hyperthyroid cases developed hypothyroidism and were treated with levothyroxine. Three euthyroid subjects (0.1%) developed hyperthyroidism and were treated with ATD.

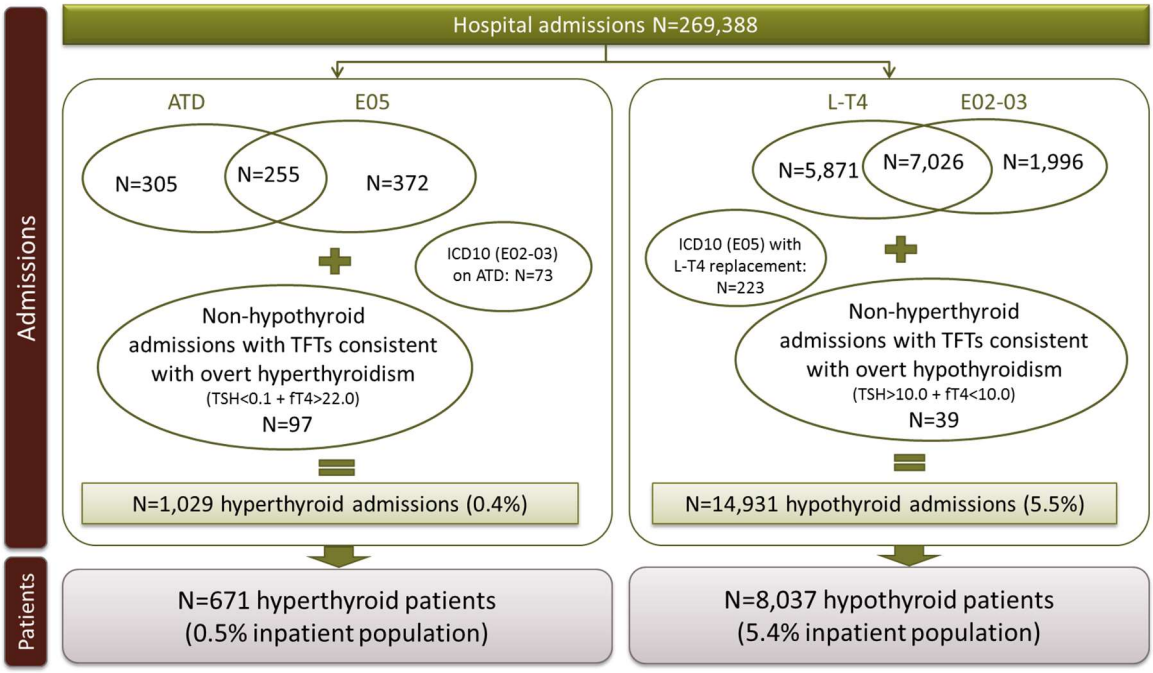

Figure 7-1: Process of identification of hyper- and hypothyroid admissions, which were next combined into the corresponding inpatients categories; E05: ICD-10 code for hyperthyroidism, E02-03: codes for hypothyroidism.

7.3.2 Baseline characteristics

Due to matching applied in the study design, the distribution of age, gender and calendar year of first admission was balanced between hyper-, hypo- and euthyroid subjects. There were over twice as many women it the study as men (Table 7-1). The distribution of age was right-skewed with a mean of 61 (±19.9) and a median 64 years (IQR: 46-79).

Table 7-1: Baseline characteristics of inpatients stratified based on TD diagnosis; matched controls are presented alongside the available pool of controls of hypo- and euthyroid patients.

	Hypothyroid		Hyper-thyroid N=671	Euthyroid	
	Matched N=2,625 (32.8%)	All N=7,994		Matched N=2,684 (1.9%)	All N=138,948
Age, year					
mean (±SD)	**61 (±19.5)**	66 (±16.6)	**61 (±20.2)**	**61 (±20.2)**	52 (±20.7)
16-29, n (%)	**197 (7.5)**	251 (3.1)	**65 (9.7)**	**252 (9.4)**	26,289 (18.9)
30-39, n (%)	**222 (8.5)**	393 (4.9)	**55 (8.2)**	**220 (8.2)**	17,181 (12.4)
40-49, n (%)	**332 (12.6)**	747 (9.3)	**84 (12.5)**	**336 (12.5)**	20,042 (14.4)
50-59, n (%)	**329 (12.5)**	1,188 (14.9)	**81 (12.1)**	**324 (12.1)**	20,264 (14.6)
60-69, n (%)	**483 (18.4)**	1,734 (21.7)	**123 (18.3)**	**484 (18.0)**	21,418 (15.4)
70-79, n (%)	**460 (17.5)**	1,910 (23.9)	**117 (17.4)**	**452 (16.8)**	19,157 (13.8)
≥80, n (%)	**602 (22.9**)	1,771 (22.2)	**146 (21.8)**	**615 (23.0)**	14,597 (10.5)
Male, n (%)	**767 (29.2)**	1,977 (24.7)	**201 (30.0)**	**805 (30.0)**	77,200 (55.6)
Female, n (%)	**1,858 (70.8)**	6,017 (75.3)	**470 (70.0)**	**1,880 (70.0)**	61,748 (44.4)
CCI score					
Mean (±SD)	**1.07 (±1.03)**	1.10 (±1.05)	**1.05 (±1.02)**	**0.95 (±0.97)**	0.78 (±0.88)
Median (IQR)	**1 (0-2)**	1 (0-2)	**1 (0-2)**	**0 (0-1)**	0 (0-1)
TFT measured, n (%)	**221 (32.8)**	2,832 (35.2)	**416 (61.8)**	**131 (19.5)**	15,799 (11.4)
Reason for admission:					
Cardiac, n (%)	**538 (20.5)**	1,864 (23.3)	**182 (27.1)**	**528 (19.7)**	26,538 (19.1)
Digestive, n (%)	**344 (13.1)**	1,053 (13.2)	**78 (11.6)**	**406 (15.1)**	19,108 (13.8)
Respiratory, n (%)	**199 (7.6)**	613 (7.7)	**60 (8.9)**	**206 (7.7)**	9,406 (6.8)
Mental, n (%)	**16 (0.7)**	35 (0.4)	**5 (0.7)**	**18 (0.7)**	34 (0.02)
LoS, day					
Mean (±SD)	**9.0 (3.0)**	9.2 (3.0)	**9.4 (3.1)**	**7.7 (2.8)**	6.9 (2.6)
Median (IQR)	**4 (2-10)**	4 (2-10)	**4 (2-10)**	**4 (2-10)**	3 (2-7)

There was a significant difference in distribution of CCI among the cases and matched controls (Figure 7-2). Euthyroid subjects were significantly more likely to have a CCI score of 0 and less likely to have a CCI score of 1 compared with those with any TD. No significant differences were found at higher CCI scores.

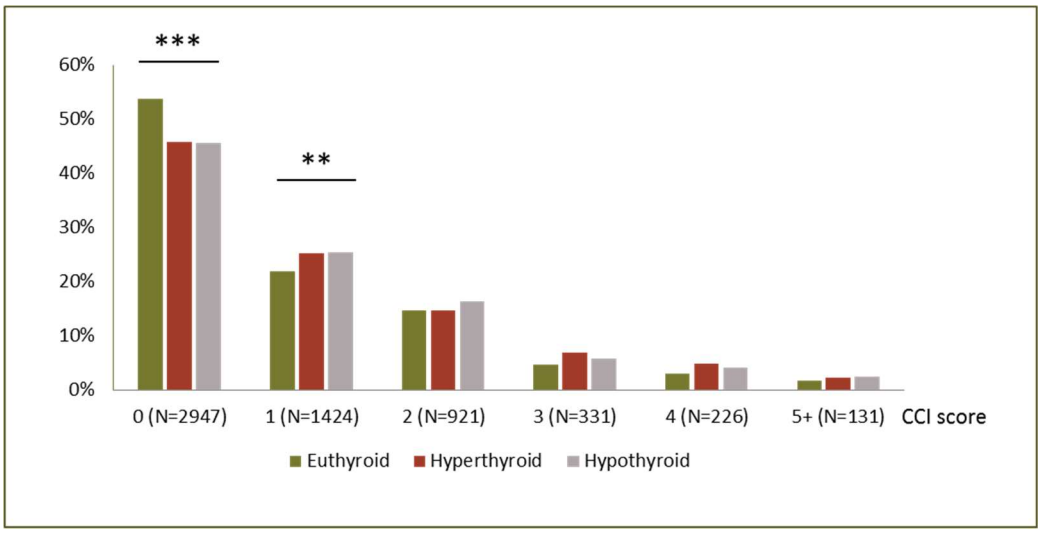

Figure 7-2: Distribution of CCI scores in hyper-, hypo- and euthyroid inpatients (* P<0.001; ** P≥0.001 and P<0.01; * P ≥ 0.01 and P<0.05)**

There was no significant difference in the proportion of patients admitted to ITU during the baseline hospital stay between hyperthyroid and matched euthyroid and hypothyroid patients.

7.3.3 All-cause mortality

During the follow-up period, 2,162 (36%) patients in the study cohort died. The proportion of death in those with hyperthyroidism was 40.4% (N=271), with hypothyroidism 37.6% (N=986) and 33.7% (N=905) in those with no TD (P=0.001). Mortality was found to be significantly higher in individuals with hyperthyroidism (Figure 7-3).

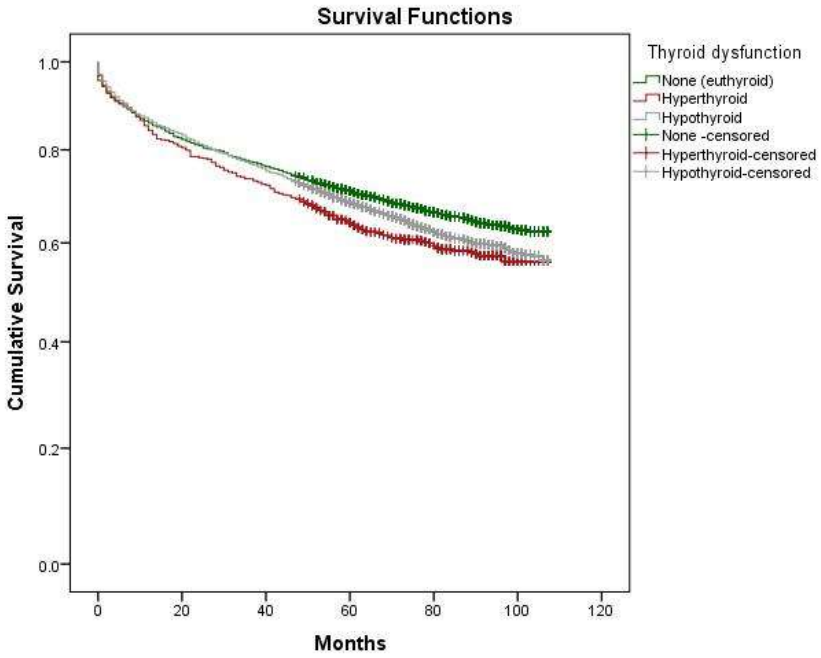

Figure 7-3: Kaplan-Meier graph of mortality in hyper-, hypo- and euthyroid inpatients during nine years (108 months) of follow-up.

Hyperthyroid inpatients had an increased unadjusted hazard risk of death compared with euthyroid matches (1.29 [95%CI: 1.12-1.50; P=0.001]). A significantly increased mortality risk of 20% remained in hyperthyroid patients after the correction for other clinical and demographic variables (Table 7-2). Comorbidity was another factor independently predicting the mortality in the study cohort.

Table 7-2: Multivariable Cox regression analysis of hazard of risk; AHR – adjusted hazard risk, CI –confidence interval.

	AHR	95% CI for AHR		Sig.
		Lower	Upper	
Euthyroid	1.00			
Hyperthyroid	**1.22**	**1.05**	**1.42**	**0.012**
CCI	**1.55**	**1.47**	**1.64**	**<0.001**
Age	1.00	0.90	1.11	0.97 (NS)
Admission year	0.96	0.96	1.06	0.44 (NS)
Female	1.21	0.15	9.64	0.85 (NS)

7.3.3.1 *Sensitivity analysis excluding hyperthyroid patients becoming hypothyroid and their matches*

We identified 32 subjects who were initially hyperthyroid but then became hypothyroid requiring treatment with L-T4. Exclusion of these cases and their matches did not affect the results of the mortality analysis. Hazard risk of mortality for hyperthyroid patients remained increased by 20% (P=0.02).

7.3.3.2 *Sensitivity analysis comparing mortality in hyperthyroid cases and euthyroid controls with no serious comorbidity*

Out of a total number of 307 hyperthyroid subjects with no serious comorbidities, 291 cases had at least one corresponding euthyroid control. The ratio of matching was variable: one-to-one in 59; one-to-two in 72; one-to-three in 95; and one-to-four in 65 cases.

There were 6,518 persons-years at risk within this selected cohort. The details of the basic characteristics are presented in Table 7-3. The cohort with no serious comorbidities was younger than the original nested cohort but the proportions between genders remained the same.

Table 7-3: Basic characteristics of sub-group of hyperthyroid cases and euthyroid controls without any serious comorbidity (N=1,039).

	Hyperthyroid N=291	Euthyroid N=748
Age, years		
mean (SD)	52.6 (±20.7)	47.9 (±20.3)
16-29, n (%)	49 (16.8)	165 (22.1)
30-39, n (%)	43 (14.8)	146 (19.5)
40-49, n (%)	45 (15.5)	125 (16.7)
50-59, n (%)	43 (14.8)	104 (13.9)
60-69, n (%)	42 (14.4)	77 (10.3)
70-79, n (%)	30 (10.3)	55 (7.4)
≥80, n (%)	39 (13.4)	76 (10.2)
Male, n (%)	83 (28.5)	210 (28.1)
Female, n (%)	208 (71.5)	538 (71.9)
Year of first admission:		
2007, n (%)	94 (32.3)	227 (30.3)
2008, n (%)	60 (20.6)	161 (21.5)
2009, n (%)	58 (19.9%)	145 (19.4)
2010, n (%)	43 (14.8)	120 (16.0)
2011, n (%)	36 (12.4)	95 (12.7)
CCI score (%)	0 (100)	0 (100)
Reason for admission:		
Cardiac, n (%)	78 (26.8)	98 (13.1)
Digestive, n (%)	56 (19.2)	139 (18.6)
Respiratory, n (%)	28 (9.6)	62 (8.3)
Mental, n (%)	5 (1.7)	14 (1.9)
LoS, days		
Mean (SD)	5.4 (2.3)	5.0 (2.8)
Median (IQR)	3 (2-6)	3 (2-5)

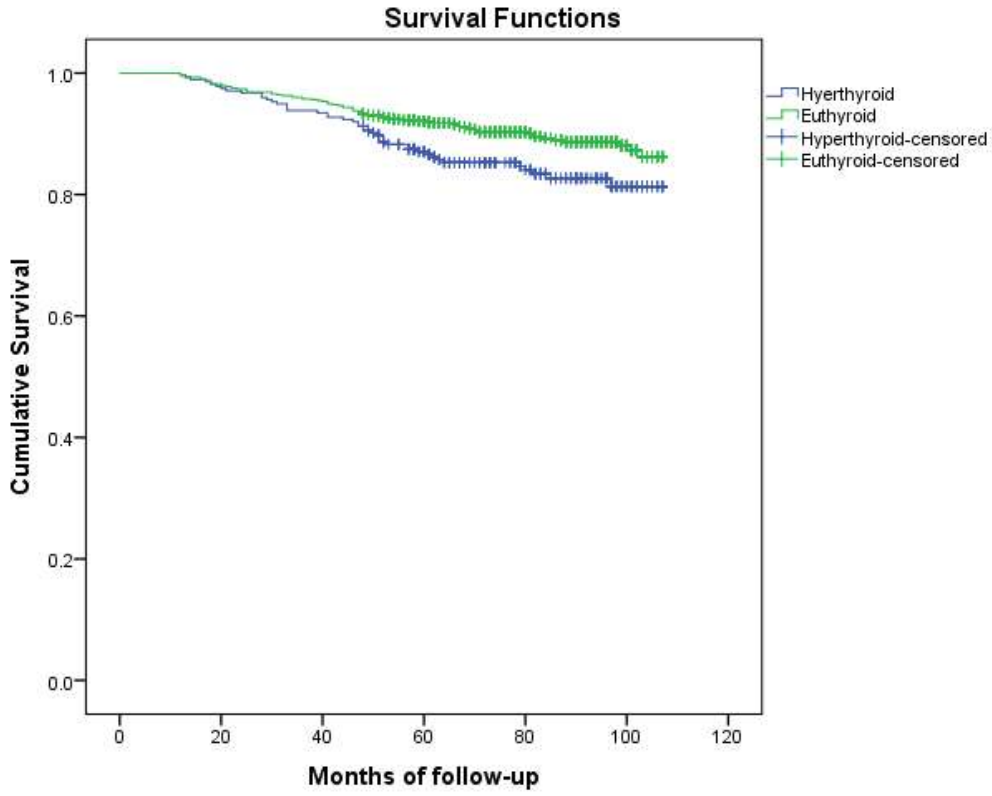

Figure 7-4: Kaplan-Meier survival curves in hyperthyroid and euthyroid subjects with no serious comorbidities at baseline. The hazard function (HR=1.6) was borderline significant (P=0.05)

Out of the total number of 1,039 inpatients included in the analysis, 157 (15.1%) died before the census date. There were 60 deaths among hyperthyroid subjects which is 16 more than the expected number (P=0.002). In hyperthyroid patients with no relevant comorbidities, the mortality hazard ratio (Figure 7-4) was significantly increased (HR=1.56 [1.08-2.27], P=0.019).

7.3.4 Hospital use

7.3.4.1 *Frequency of hospital admissions*

There were a total of 17,955 hospital admissions during the nine year study period. Over half of the patients were admitted multiple times (N=3,256; 54.4%), with 5% of patients admitted more than 10 times. The mean was 3.0 times per person (±0.05 SE, [95%CI: 2.9-3.1]). Patients with hyperthyroidism were more often admitted to hospital (mean 4.1 ±0.25; [3.6-4.6]) than euthyroid (mean 2.5 ±0.06, [2.4-2.6], P<0.001) and hypothyroid controls (mean 3.3±0.09, [3.1-3.5], P<0.001). The odds of each additional hospital admission were significantly increased for individuals with thyroid dysfunction; they were raised by 60% for hyperthyroid and by 30% for hypothyroid inpatients whether unadjusted (OR=1.64 [1.45-1.86], P<0.001 and OR=1.33 [1.24-1.42], P<0.001, respectively) or adjusted (Table 7-4).

Table 7-4: Likelihood of subsequent admission to hospital. Presence of TD, calendar year of first admission and CCI score were independent predictors of the model.

	AOR	95% CI for AOR		Sig.
		Lower	Upper	
Euthyroid	**1.00**			
Hyperthyroid	**1.61**	**1.42**	**1.82**	**<0.001**
Hypothyroid	**1.31**	**1.22**	**1.40**	**<0.001**
CCI	**1.08**	**1.06**	**1.11**	**<0.001**
Admission year	**0.86**	**0.84**	**0.88**	**<0.001**
Age	1.00	1.00	1.00	0.56 (NS)
Female	0.96	0.89	1.04	0.32 (NS)

Three-quarters of all admissions (N=13,109; 73.0%) were emergencies. The proportion of emergencies among hyperthyroid inpatients was significantly higher (77.4%, N=2,101; P<0.001) than in euthyroid and hypothyroid controls (72.2%, N=4,774 and 72.3%, N=6,234 respectively). There was a significant difference (P<0.001) in the mean number of emergency admissions (±SE) for hyper-, hypo- and euthyroid subjects which were: 3.2 (±0.07), 2.4 (±0.03), 1.8 (±0.03) respectively over the study period. Figure 7-5 represents the clustered distribution of number of the emergencies by thyroid status.

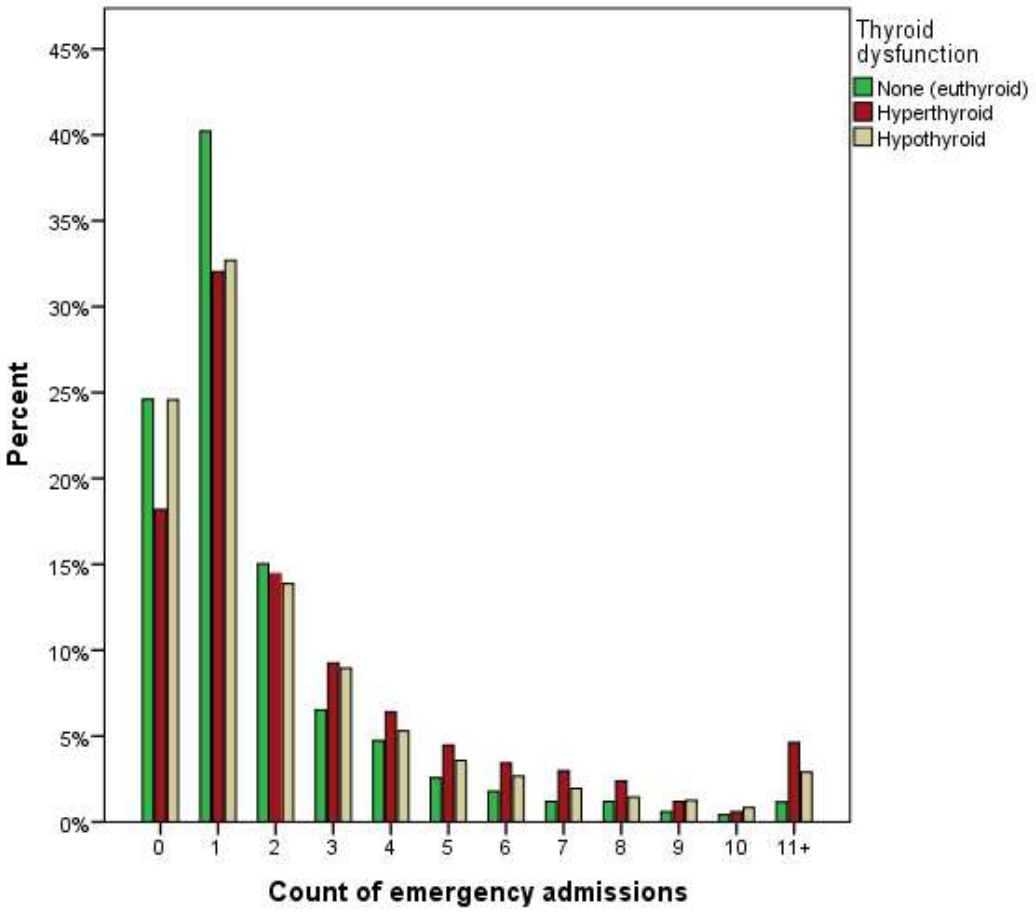

Figure 7-5: Distribution of emergency admissions within each thyroid dysfunction category.

Thyroid dysfunction was associated with significant increase in likelihood of more frequent emergency admissions. The odds of each additional emergency admission in hyperthyroid individuals were increased by 80% (OR=1.8, [1.5-2.1]) and in hypothyroid by 30% (OR=1.8, [1.5-2.1]) when compared to euthyroid controls. Again, the significant difference among the groups remained after adjustment for other clinical and demographic factors (Table 7-5).

Table 7-5: GEE log-linear regression model of likelihood of emergency admissions

	AOR	95% CI for AOR		Sig.
		Lower	Upper	
Euthyroid	**1.00**			
Hyperthyroid	**1.74**	**1.50**	**2.02**	**<0.001**
Hypothyroid	**1.31**	**1.20**	**1.43**	**<0.001**
CCI	**1.06**	**1.03**	**1.10**	**<0.001**
Age	**1.00**	**1.00**	**1.01**	**0.003**
Admission year	**0.84**	**0.81**	**0.86**	**<0.001**
Female	1.05	0.94	1.16	0.4 (NS)

7.3.4.2 *Length of hospital stay*

The mean length of stay (LOS) in the entire study cohort was 8.8±0.04 days and the median 5 days (IQR: 2-10). Similarly to length of baseline admissions, the mean LOS was higher in patients with TD (hyper- 9.6 ±0.12 SE; hypo- 9.4 ±0.06; euthyroid 8.0 ±0.05 days per hospital admission); the medians and IQR were respectively: 6 (3-11), 5 (3-11), 4 (2-9) days per hospital admission; see Figure 7-6.

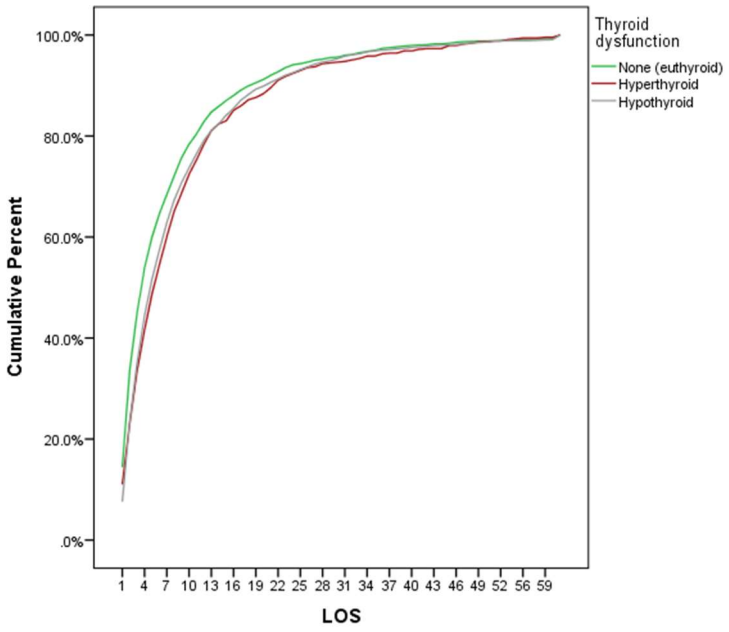

Figure 7-6: Cumulative distribution of mean length of hospital stay (LOS).

Following log-linear regression analysis of LOS, patients with hyper- and hypothyroidism were more likely to have a longer hospital stay (Table 7-6).

Table 7-6: Likelihood of longer hospital stay: hyper- and hypothyroidism, CCI score and age were found to be independent predictors in log-linear GEE analysis

	AOR	95% CI for AOR		Sig.
		Lower	Upper	
Euthyroid	**1.00**			
Hyperthyroid	**3.45**	**1.53**	**7.82**	**0.001**
Hypothyroid	**2.74**	**1.54**	**4.90**	**0.003**
CCI	**2.88**	**2.28**	**3.64**	**<0.001**
Age	**1.15**	**1.13**	**1.16**	**<0.001**
Admission year	0.81	0.66	1.00	0.05
Female	0.80	0.43	1.49	0.5 (NS)

7.3.4.3 *ITU admissions*

Seven hundred and fifty patients (12.5%) were admitted to intensive care during 1143 (6.4%) admissions. The most common reasons for hospital admission requiring ITU treatment were CVD (N_{adm}=300), cancer (N_{adm}=165) and respiratory system (N_{adm}=135), which together accounted for over half of ITU admissions.

The likelihood of ITU admission was higher among hyper- and hypothyroid inpatients (AOR: 1.4 [1.1-1.8], P=0.01 and 1.3 [1.1-1.6], P<0.001 respectively). Higher CCI score (AOR: 1.3 [1.3-1.4], P<0.001) was associated with increased likelihood of ITU care while female gender (AOR: 0.6 [0.5-0.7], P<0.001) and older age (AOR: 0.99 [0.99-1.00], P=0.009) were predictors of reduced odds of admission to ITU. The model was corrected for the calendar year of the first admission to hospital during the study period (AOR: 0.90 [0.85-0.96], P=0.002).

7.3.4.4 *Primary reasons for admission*

Study subjects were frequently admitted to hospital due to certain signs and symptoms or abnormal laboratory results (N=3,244; 18.1%) rather than following diagnoses of specific conditions (codes from ICD-10 chapter R were used). Cardiovascular, respiratory and digestive system conditions were other common reasons for hospitalisation (Table 7-7).

Table 7-7: Primary reasons for hospital admissions in study patients over 9 years of follow-up.

Primary reason for admission:	Thyroid dysfunction					
	None (euthyroid)		Hyperthyroid		Hypothyroid	
	Admissions N=6,616 (%)	Patients N=2,684 (%)	Admissions N=2,716 (%)	Patients N=671 (%)	Admissions N=8,623 (%)	Patients N=2,625 (%)
Cardiovascular	889 (13.4)	603 (22.4)	520 (19.1)	230 (34.3)	1,214 (14.1)	711 (27.1)
Respiratory	624 (9.4)	357 (13.3)	265 (9.8)	119 (17.7)	670 (7.8)	406 (15.5)
Digestive	717 (10.8)	487 (18.1)	220 (8.1)	135 (20.1)	857 (9.9)	509 (19.4)
Mental and behavioural	55 (0.8)	136 (5.1)	44 (1.6)	44 (6.6)	55 (0.6)	152 (5.8)

Endocrine reasons for admissions accounted for 3.6% of all admission (N=645) in 430 inpatients (7.2%). Admissions due to TD were rare: 111 (0.6%) hyperthyroid admissions in 101 (1.7%) patients and 14 (0.08%) hypothyroid admissions in 14 (0.2%) patients. There was only one thyroid emergency during the total period of follow up and a principal diagnosis of thyroid storm [E055] was made, whereas there were no admissions for myxoedema coma [E035].

7.3.4.4.1 Patients admitted due to cardiovascular reasons

Hospital stays for cardiovascular causes were the second biggest group of admissions; altogether 1,544 (25.8%) study patients were admitted for primary CVD causes in 2,623 (14.6%) admissions. Hyperthyroidism (OR=1.86, [1.56-2.20], P<0.001) and hypothyroidism (OR=1.33, [1.17-1.50], P<0.001) were associated with significantly increased likelihood of admission for CVD causes. In particular (Figure 7-7), admissions of dysrhythmias, heart failure, cardiomyopathy, hypertensive

and arterial diseases were significantly different among the patients of various thyroid status. The estimates of admission due to particular CVD diagnoses in comparison to euthyroid inpatients are presented in Table 7-8.

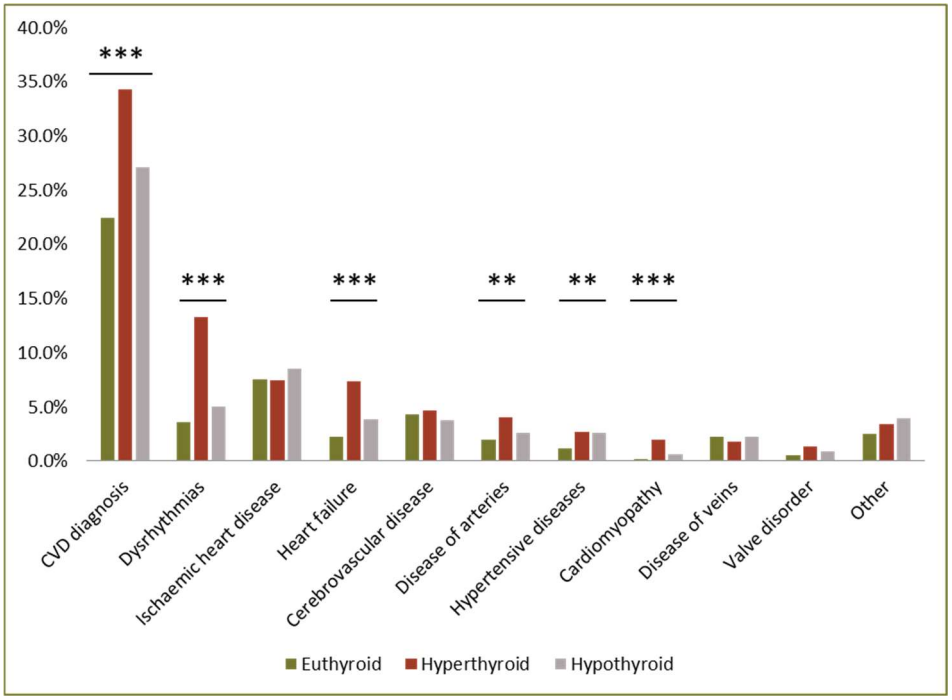

Figure 7-7: Distribution of CVD diagnoses in hyperthyroid controls and matched hypothyroid and euthyroid inpatients (* P<0.001; ** P≥0.001 and P<0.01; * P ≥ 0.01 and P<0.05)**

Table 7-8: Likelihood of admission due to particular CVD diagnosis compared to euthyroid subjects (HD- heart disease).

Primary CVD reason for admission:	Euthyroid	Hyperthyroid			Hypothyroid		
	N (%)	N (%)	OR (95% CI)	P value	N (%)	OR (95% CI)	P value
Dysrhythmias	97 (3.6)	**89 (13.3)**	**4.08 (3.01-5.53)**	**<0.001**	**131 (5.0)**	**1.40 (1.06-1.84)**	**0.02**
Ischaemic HD	202 (7.5)	50 (7.5)	0.99 (0.72-1.39)	NS	224 (8.5)	1.47 (0.95-1.39)	NS
Heart failure	61 (2.3)	**49 (7.3)**	**3.39 (2.31-4.97)**	**<0.001**	**101 (3.8)**	**1.72 (1.24-2.39)**	**0.001**
Diseases of arteries	53 (2.0)	**27 (4.0)**	**2.08 (1.27-3.41)**	**0.004**	67 (2.6)	1.30 (0.89-1.90)	NS
Cerebrovascular dis.	115 (4.3)	31 (4.6)	1.08 (0.72-1.62)	NS	99 (3.8)	0.88 (0.66-1.56)	NS
Hypertensive dis.	32 (1.2)	**18 (2.7)**	**2.28 (1.30-4.02)**	**0.004**	**67 (2.6)**	**2.17 (1.41-3.35)**	**<0.001**
Cardiomyopathy	5 (0.2)	**13 (1.9)**	**10.59 (3.98-28.17)**	**<0.001**	**16 (0.6)**	**3.29 (1.20-8.99)**	**0.02**
Diseases of veins	59 (2.2)	12 (1.8)	0.81 (0.43-1.52)	NS	58 (2.2)	0.98 (0.70-1.44)	NS
Valve disorders	15 (0.6)	**9 (1.3)**	**2.42 (1.09-5.38)**	**0.03**	22 (0.8)	2.42 (0.78-2.91)	NS
Other	66 (2.5)	23 (3.4)	1.41 (0.88-2.27)	NS	**103 (3.9)**	**1.62 (1.17-2.25)**	**0.004**

One-third of studied men (N=571, 32%) and a quarter of studied women (N=1059, 25%; P<0.001) presented with CVD. When gender was analysed separately (Table 7-9), there was a significantly higher proportion of hyperthyroid (in men OR=2.51, [1.88-3.34], P<0.001; in women OR=1.61, [1.30-2.00], P<0.001) and hypothyroid inpatients (men OR=1.41, [1.18-1.77], P<0.001; women OR=1.30, [1.12-1.50], P<0.001) when compared to euthyroid subjects of the same gender.

Table 7-9: Admissions for primary CVD stratified by gender

	Thyroid dysfunction			P-value
	None (euthyroid)	Hyperthyroid	Hypothyroid	
Males	215 (26.7%)	96 (47.8%)	260 (33.9%)	<0.001
Females	414 (22.0%)	147 (31.3%)	498 (26.8%)	<0.001

The higher likelihood of CVD in the entire cohort was age-dependent, with each year of life raising the chances of CVD episodes by 3% across the cohort

(OR=1.027 [1.024-1.031], P<0.001). Thyroid dysfunction was associated with increased risk of CVD in younger but not in older subjects (Figure 7-8).

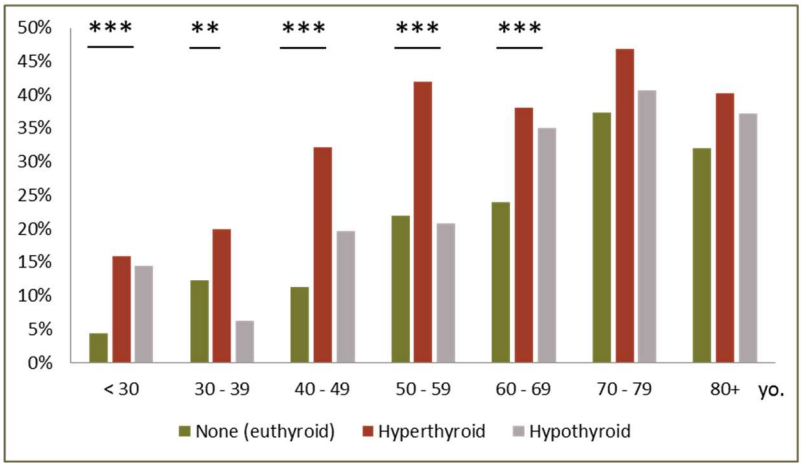

Figure 7-8: Proportions of inpatients admitted for primary cardiovascular reason stratified by age at baseline. (* P<0.001; ** P≥0.001 and P<0.01; * P ≥ 0.01 and P<0.05)**

Admissions for CVD causes were more likely in patients with higher CCI scores across the entire cohort (P<0.001). Patients with hyperthyroidism and low CCI scores were more likely to be admitted for CVD reasons (Figure 7-9).

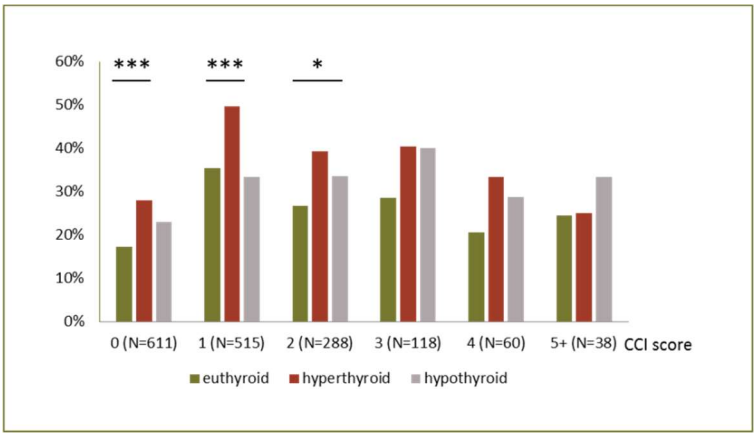

Figure 7-9: Proportions of CVD patients within thyroid status groups stratified by the CCI score (* P<0.001; ** P≥0.001 and P<0.01; * P ≥ 0.01 and P<0.05)**

When all factors were analysed simultaneously (Table 7-10), underlying TD, gender and age were significantly associated with likelihood of CVD morbidity; the model was corrected for year of first admission which had a negative effect. CCI was not independently associated with likelihood of admission for cardiovascular causes.

Table 7-10: Factors associated with likelihood of CVD admission

		95% Confidence Interval		P-value
Parameter	**AOR**	Lower	Upper	
Euthyroid	**1**			
Hyperthyroid	**1.93**	**1.60**	**2.32**	**<0.001**
Hypothyroid	**1.32**	**1.16**	**1.51**	**<0.001**
Female	**0.62**	**0.54**	**0.72**	**<0.001**
Age (per year)	**1.30**	**1.025**	**1.032**	**<0.001**
Year of admission (per year)	**.85**	**.81**	**.89**	**<0.001**
CCI score (per score)	1.036	.990	1.084	0.13 (NS)

7.3.4.4.2 Respiratory disorders

Respiratory causes represented another important diagnostic group accounting for 1,558 (8.7%) hospital admissions in 889 (14.9%) study subjects. The proportions of subjects with respiratory admissions were significantly different between the groups (euthyroid 13.4%, N=360; hyperthyroid 17.9%, N=120; hypothyroid 15.6%, N=409; P=0.003). The likelihood of a patient with hyperthyroidism being admitted for respiratory reasons was increased by 40% (AOR: 1.41 [1.13-1.75], P=0.002) and of a hypothyroid subject by 20% (AOR: 1.19 [1.03-1.38], P=0.02) when compared to euthyroid inpatients.

The most common reasons for respiratory admissions (Figure 7-10) were acute lower respiratory infections including pneumonia (J13-J18, J20-J22; N_{adm}=745; N_{pts}=549), chronic obstructive pulmonary disease (COPD; J44; N_{adm}=370; N_{pts}=218) and asthma (J45; N_{adm}=112; N_{pts}=81). Hyperthyroid subjects were significantly more likely to be admitted for lower respiratory infections (OR=1.48, [1.14-1.91], P=0.003) or for COPD (OR=1.76, [1.14-2.73], P=0.01) when compared to euthyroid inpatients. The proportions of hypothyroid individuals were no different from euthyroid controls in any of the studied respiratory reasons for admission.

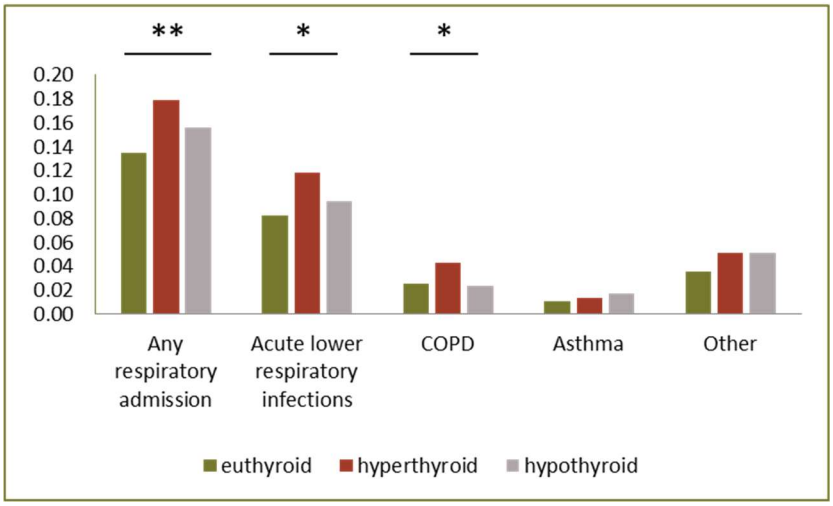

Figure 7-10: Proportions of patients admitted due to most common pulmonary causes.

Two hundred and twenty-five men (12.7% of men) and 664 women (15.8% of women) were admitted for respiratory causes While there was no association of TD with respiratory admissions in women, significant differences were seen in men; the likelihood of respiratory admissions doubled in hyperthyroid

(OR=1.96 [1.31-2.93], P=0.001) and increased by 40% in hypothyroid men (OR=1.38 [1.01-1.88], P=0.04) compared to med with no TD.

Age was a significant covariate when analysed in the entire cohort, increasing the likelihood of hospitalisation for respiratory diseases by 2% per year of life (AOR=1.020 [1.016-1.25]; P<0.001). When stratified for thyroid status, there was no effect of age on the probability of respiratory admission in different groups. Each additional point of the CCI score increased the likelihood of hospitalisation for respiratory diseases by 18% (OR=1.18 [1.13-1.24]) which was similar across the different thyroid status groups. In multivariate analysis (Table 7-11), the presence of hyperthyroidism but not hypothyroidism independently predicted respiratory hospitalisation, in addition to female gender, older age and more severe comorbidity status.

Table 7-11: Multivariate analysis of likelihood of hospitalisation with primary admission reason from respiratory disorders.

Parameter	AOR	95% Confidence Interval		P-value
		Lower	Upper	
Euthyroid	1			
Hyperthyroid	1.38	1.11	1.73	**0.005**
Hypothyroid	1.16	0.997	1.34	0.06
Female	1.25	1.05	1.48	**0.01**
Age (per year)	1.02	1.01	1.02	**<0.001**
CCI score (per score)	1.12	1.07	1.18	**<0.001**
Year of admission (per year)	0.83	0.78	0.88	**<0.001**

7.3.4.4.3 Mental health and behavioural disorders

Hospitalisation for mental health disorders was not very common, being found in only 2.4% of studied patients (N=144). The two main reasons for hospitalisation were delirium (F05; N_{pts}=48, N_{adm} =80) and disorders due to use of alcohol (F10; N_{pts}=21, N_{adm}=84), followed by dementia (F03; N_{pts}=16, N_{adm}=18).

In univariate analysis, the likelihood of mental health disorder related admissions was significantly raised in hyperthyroid patients (OR=1.87 [1.13-3.14], P=0.016). In hypothyroid patients, the increase was of borderline significance (OR=1.46 [0.999-2.15], P=0.051). When corrected for other factors in multivariable analysis (Table 7-12), the effect of hyperthyroidism was slightly stronger. Older age was another factor positively influencing likelihood of admissions for mental and behavioural disorders while increasing severity of co-morbidity was less likely to be associated with admissions for mental health disorders.

Table 7-12: GEE multivariable analysis of likelihood of hospital admissions due to mental health and behavioural disorders

Parameter	AOR	95% Wald Confidence		P-value
		Lower	Upper	
Euthyroid	1			
Hyperthyroid	**1.93**	**1.15**	**3.22**	**0.012**
Hypothyroid	1.47	0.99	2.16	0.053
Age (per year)	**1.03**	**1.02**	**1.04**	**<0.001**
CCI score (per score)	**0.87**	**0.77**	**1.00**	**0.047**
Female	1.06	0.72	1.56	0.76
Year of admission (per year)	1.05	0.93	1.17	0.43

7.3.4.4.4 Inpatients hospitalised due to digestive reasons

One in five patients (N=1,135, 19.0%) was admitted to hospital for gastrointestinal (GI) causes during 1,794 admissions. The most common reasons were various non-infective conditions of intestines and peritoneum (K50-K67; N_{pts}= 461 (7.7%), N_{adm}=658 (3.7%)) and disorders of gallbladder, biliary tract and pancreas (K80-K87) found in 245 (4.1%) subjects (N_{adm}=379, 2.1%).

There was no significant difference in hospitalisation rates due to combined morbidity from the digestive system in patients with and without TD. However, after division of the diagnoses into particular organ systems (Figure 7-11), an association of admission for conditions of the intestines and peritoneum with TD became apparent (P=0.002).

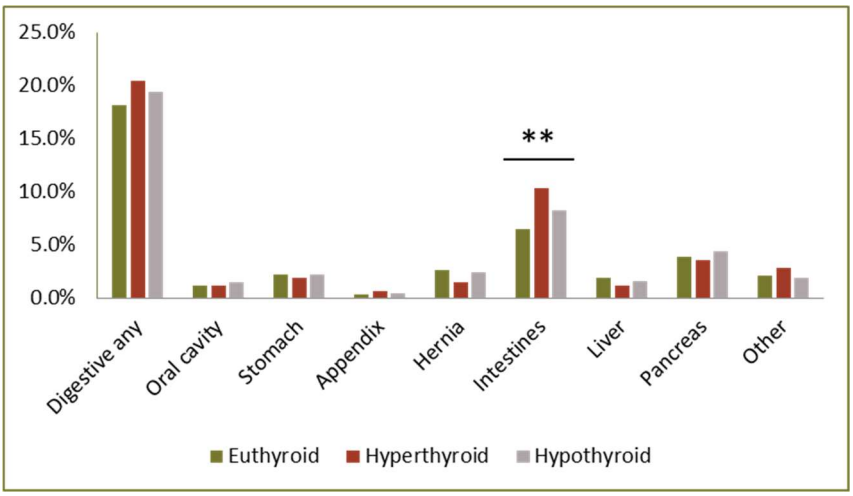

Figure 7-11: Primary digestive diagnoses in euthyroid, hyper- and hypothyroid inpatients. (* P<0.001; ** P≥0.001 and P<0.01; * P ≥ 0.01 and P<0.05)**

Hyperthyroid (OR=1.64 [1.22-2.21], P=0.001) and hypothyroid patients (OR=1.29 [1.04-1.60], P=0.02) were more likely to be admitted to hospital with non-infectious disorders of intestines and peritoneum than euthyroid controls. This association remained significant after adjustment for clinical and demographic factors (Table 7-13).

Table 7-13: Factors predicting the likelihood of hospital admission due to intestine or peritoneum disorders.

Parameter	AOR	95% Wald Confidence		P-value
		Lower	Upper	
Euthyroid	1			
Hyperthyroid	**1.67**	**1.24**	**2.25**	**0.001**
Hypothyroid	**1.30**	**1.04**	**1.61**	**0.02**
Age (per year)	**1.01**	**1.01**	**1.02**	**<0.001**
Female	**1.31**	**1.05**	**1.63**	**0.02**
Year of admission (per year)	**0.85**	**0.79**	**0.92**	**<0.001**
CCI score (per score)	0.93	0.85	1.01	0.07

7.4 Discussion

7.4.1 Characteristics of the study cohort

The study cohort under investigation comprised adult inpatients admitted to a single tertiary care centre. Hyperthyroid cases were matched with euthyroid and hypothyroid controls derived from the same population. Many studies on thyroid dysfunction state that subjects studied were recruited from the hospital setting (Franklyn et al., 1998, Metso et al., 2007, Nyirenda et al., 2005, Osman et al., 2007), however, such a definition applies to the broad range of services and subjects are most often seen in outpatient clinics and not during hospitalisation. The present study

is the first to address the mortality risk and the hospital use of inpatients with and without a history of thyroid dysfunction.

Almost 6,000 patients were followed up for up to 9 years. Subjects were admitted to hospital for a variety of reasons. Due to the matching design, the selection of subjects mimicked the hyperthyroid cases in terms of age, gender and year of the first admission. In practice, it meant that the hypothyroid study cohort was on average 5 years younger and the euthyroid 9 years older than their total pools. The proportion of gender distribution was also altered from an overall female proportion just below 46% to 70%, representative to hyperthyroid patients.

Moreover, matching also indirectly influenced other variables, making them more similar to those of hyperthyroid patients. As expected, after reducing the proportions of younger inpatients, comorbidity scores and LoS increased in the study cohort as compared to all patients. By matching based on the year of admission, any potential bias introduced by procedural changes or coding imperfections should be similarly distributed between groups.

The presence of thyroid dysfunction was not always recorded in the administrative system and administration of the medication and, to lesser extent, biochemical results had to be used in order to correctly identify the patients (Schiff et al., 2005).

7.4.2 Mortality of hyperthyroid inpatients compared with controls

We found increased mortality from all causes in the cohort of hyperthyroid inpatients compared to both hypo- and euthyroid subjects. These findings are in agreement with the final conclusion of metaanalysis aggregating data from eight studies (Brandt et al., 2011). There was large variation among the published studies in terms of treatment modalities, causes, populations and methods of risk estimation. The present study addressed the inpatient population only and all cases and all controls were derived from patients admitted to a single hospital.

Intuitively, hospital patients are expected to be burdened with higher comorbidity, which may additionally influence their risk of mortality. When serious illness strongly associated with high mortality is present, other contributing factors may easily be overlooked, especially those with long-term effects. In multivariable Cox regression analysis we demonstrated that hyperthyroidism, but not hypothyroidism, is associated with risk of death independent of the severity of comorbidity expressed using the CCI score. Our reported increase in mortality risk of almost 20% is similar in its magnitude to previous studies from varied settings (Laulund et al., 2014, Brandt et al., 2012, Brandt et al., 2011, Franklyn et al., 1998, Metso et al., 2007, Osman et al., 2007). Additionally, we also confirmed the independence of these two factors in a sub-analysis in which only euthyroid and hyperthyroid subjects with no serious comorbidity were compared. A number of serious diseases, which have already been associated with thyroid dysfunction (acute myocardial infarction, congestive heart

failure, cerebral vascular disease or cancers) as well as conditions associated with long-term consequences (diabetes mellitus and its complications) were excluded. The results demonstrate that underlying hyperthyroidism on its own may possibly affect the development of pathologies leading to increased mortality.

When adjusted for comorbidity, hypothyroidism was not associated with excess mortality when compared to euthyroid subjects, which is in line with other large epidemiological studies (Flynn et al., 2004, Laulund et al., 2014). This observation may support the recommendation for definitive treatment for thyrotoxicosis with radioiodine, which is likely to result in hypothyroidism.

Our group has previously shown increased all-cause and cardiovascular mortality in patients with hyperthyroidism (Franklyn et al., 1998, Franklyn et al., 2005). We confirmed that in a further study, which I co-authored (Boelaert et al., 2013). Importantly, in that study, increased all-cause mortality risk was no longer present in patients rendered hypothyroid following radioiodine treatment.

In the current study, the categorisation of patients was not dynamic, hence, during follow-up the group of hyperthyroidism became "contaminated" with those who developed hypothyroidism. The proportion of patients affected in this way was, nevertheless, small and did not influence the final results. The effect of "hypothyroid contamination" due to lack of dynamic categorisation may potentially, however, explain the lack of increased mortality in mortality studies where analyses

were not corrected for the consequence of definite treatment (Ryodi et al., 2014, Flynn et al., 2006, Nyirenda et al., 2005).

Despite many studies demonstrating links between hyperthyroidism and increased risk of mortality, the problem may not be appreciated by those considering public health in part due to underreporting in death certificates. Between 2001 and 2010, hyperthyroidism was recorded as the underlying cause of death in 629 and as contributing factor in 2,021 cases in England (Goldacre and Duncan, 2013). At the same time there were more than 5 million certificates issued (Office for National Statistics, 2014). Since the prevalence of thyrotoxicosis is 1-2% and increases with age (Tunbridge et al., 1977), one could expect a much higher proportion of statements of hyperthyroidism on death certificates than the reported 0.05% especially among older patients. The small number of death certificates acknowledging the contributing effect of thyrotoxicosis suggests a lack of awareness of long-term consequences of hyperthyroidism among clinicians, in spite of a growing body of evidence to the contrary. The lack of such awareness may result in under-diagnosis and inadequate treatment of hyperthyroidism which may have important long-term consequences.

We conclude that inpatients with a history of hyperthyroidism, but not those with hypothyroidism, have an increased likelihood of death.. Whether early and efficient treatment may prevent further development of pathophysiological changes leading to excess of deaths needs further study.

7.4.3 Hospital admission characteristics

Thyroid dysfunction in hospitalised inpatients was associated with worse hospital outcomes. Hyperthyroid and, to a lesser but still significant extent, hypothyroid subjects differed from euthyroid controls with regard to frequency of hospital admission, rate of emergency admissions, length of hospital stay and the likelihood of requiring intensive care. Interestingly, the association of thyroid dysfunction with any of the aforementioned hospital outcomes was independent of the initial burden of comorbidity.

Hospitalisation rates among patients with thyroid dysfunction are not well described in the literature. In fact, although some publications address the problem of CVD admissions while documenting cardiovascular comorbidity (Flynn et al., 2006, Nyirenda et al., 2005, Ryodi et al., 2014), our study presents the first comparison of bed use of patients with and without thyroid dysfunction.

A consistent increase in many measures of hospital utilisation suggests that thyroid dysfunction in general but especially hyperthyroidism, is associated with long-term and not easily reversible pathophysiological changes which hinder the process of recuperation. Our study was not designed to investigate causal relationships therefore our data do not allow us to conclude whether hyperthyroidism triggers, or is merely associated with, other clinical pathologies.

7.4.4 Increase in cardiovascular admissions among TD patients

In our study we demonstrated a significant association of treated overt thyroid dysfunction with increased risk of hospital stay due to cardiovascular reasons. When particular causes for admissions were analysed, hyperthyroidism was linked to a significantly raised likelihood of admission in patients with cardiomyopathy, dysrhythmias, heart failure, hypertensive diseases and valve or arterial disorders. Effects of comorbid hypothyroidism were less pronounced but were still significant in inpatients with hypertensive disorders, heart failure, dysrhythmias, cardiomyopathy and collectively identified other CVD. The findings are in line with our understanding of the effect of thyroid hormone on the cardiovascular system derived from numerous clinical studies (Biondi, 2012, Grais and Sowers, 2014, Klein and Danzi, 2007).

Arrhythmia is a major cause for morbidity and mortality in thyroid dysfunction. According to a recent systematic review, patients with untreated overt clinical or subclinical thyroid dysfunction are at increased risk of arrhythmia: atrial dysrhythmias in hyperthyroidism and ventricular in hypothyroidism (Marrakchi et al., 2015). It is controversial as to whether these cardiovascular alterations in TD are purely functional or as a consequence of structural damage.

Without differentiating arrhythmia into particular subtypes, we demonstrated that treated hyperthyroid patients are four times more likely to be admitted for arrhythmia, while in treated hypothyroid patients the odds of hospital admission

were increased by 40% when compared to those without thyroid dysfunction. To correctly interpret the results, the two way relation between thyroid dysfunction and arrhythmia needs to be highlighted: TD may have causal effects on arrhythmia but also a commonly prescribed antiarrhythmic medication (amiodarone) may result in overt thyroid dysfunction due to its high iodine load. We did not study the mechnisms underlying the relationship between arrhythmias and TD.

Complications of AF include heart failure and stroke. We were able to confirm a significant association of treated TD with heart failure but did not identify an association with cerebrovascular diseases. Both outcomes have been studied in overt and subclinical TD populations. While more studies predominantly indicate a positive association between thyroid disorders and an increased risk of heart failure (Gerdes and Iervasi, 2010, Triggiani and Iacoviello, 2013, Mitchell et al., 2013, Biondi, 2012, von Scheidt et al., 2014), the evidence of the association between thyroid disorders and incidence of cerebrovascular disease remains inconclusive (Friberg et al., 2012, Flynn et al., 2006, Franklyn et al., 1998, la Cour et al., 2015, Six-Merker et al., 2016).

Cardiomyopathy was not a common reason for hospitalisation but its relationship with thyroid dysfunction was pronounced (OR=10.6 for hyper- and OR=3.3 for hypothyroidism). Cardiomyopathies represent a heterogeneous group of diseases that often lead to progressive heart failure with significant morbidity and mortality. The most common form, dilated cardiomyopathy, affecting five in 100,000 adults, is the third leading cause of heart failure worldwide (Rakar et al., 1997).

There is a growing body of evidence of an association between cardiomyopathy and thyroid dysfunction (Aggarwal et al., 2015, Wang et al., 2015, Azemi et al., 2013, Goland et al., 1999). Cardiomyopathy has been linked to administration of levothyroxine and to subclinical or overt hypothyroidism (Wang et al., 2015). Significant changes to myocardial function have also been observed in hyperthyroidism. In general, complete or near complete recovery of cardiac function is expected after treatment though it is dependent on the duration of thyrotoxicosis prior to treatment initiation and beta-blocker administration (Oliveros-Ruiz et al., 2013). However, there are reports of irreversible cardiomyopathy in hyperthyroid patients as long as 15 years after successful treatment (Ebisawa et al., 1994). Despite the importance of the condition, the links between cardiomyopathy and thyroid dysfunction have not been extensively studied. We believe our findings add to the existing body of literature and warrant further investigation.

7.4.5 Association of TD with respiratory admissions

We demonstrated significant relationships between the presence of thyroid dysfunction and increase in hospital admissions caused by respiratory disorders. Unlike cardiovascular risks, the mechanisms of association of thyroid dysfunction with pulmonary diseases have not been studied extensively and the results of some previously published small studies do not thoroughly explain the effects of thyroid dysfunction on respiratory function.

In thyrotoxicosis, a hypermetabolic state induces an increase in basal metabolic rate, oxygen consumption and carbon dioxide (CO_2) production. Patients are often dyspnoeic, have lower resting arterial partial pressure of CO_2 (pCO_2), tidal volume with increased ventilator responses to CO_2 and hypoxia (Pino-Garcia et al., 1998). The changes are even more pronounced during exercise and are considered to be secondary to an altered central respiratory drive, possibly due to increased adrenergic stimulation (Small et al., 1992). In the hypothyroid hypometabolic state, pCO_2 is increased and maximal inspiratory pressure and minimal expiratory pressure decreased (Terzano et al., 2014).

Abnormalities in lung function have been associated with development of myopathy also affecting respiratory muscles both in hyper- and hypothyroid states. A linear relationship between thyroid hormone levels and respiratory forces had been demonstrated (Siafakas et al., 1992, Terzano et al., 2014). Importantly, most of the changes are believed to be reversible with treatment (Kendrick et al., 1988).

Our findings confirmed those from another big population study from Denmark analysing various comorbidities before and after the diagnosis of hyperthyroidism (Brandt et al., 2013b). The authors showed a significant 50% increase in risk of developing lung disease before, and 30% after, diagnosis of hyperthyroidism. However, the authors limited their lung disease definition only to chronic forms, while we found associations within respiratory diseases in general, for example in chronic COPD as well as in acute lower pulmonary infections.

Thyroid dysfunction has also been linked with mortality from pulmonary causes. When analysing contributing causes of deaths in those with acquired TD as the underlying cause of death (Goldacre and Duncan, 2013), pneumonia was listed as the first most commonly contributing cause of death in both types of thyroid dysfunction, with COPD as the fourth main underlying cause of death in those with contributing TD. In addition, likelihood of death from lung diseases in Graves' disease patients, but not those with toxic nodular goitre, was found to be significantly increased (Brandt et al., 2013a). These findings support potential links of TD with respiratory diseases.

However, as the mechanisms explaining the associations of thyroid disease with respiratory episodes are not fully understood, the results have to be interpreted with caution. A statistical phenomenon known as Berkson fallacy – proving that multiple diagnoses may be overrepresented in hospital studies – has to be considered (Berkson, 1946). However, this theory does not affect the analysis in which the disease of interest is not the reason for admission. In our study, thyroid dysfunction was the main reason for admission in only less than 0.7% of hospital admissions which potentially had very little (if any) effect on calculated odds ratio (Snoep et al., 2014).

The Berkson theory was further developed by studying possible causal effects of an exposure on disease occurrence called often the "indirect" Berkson fallacy (Flanders et al., 1989). This may also affect the results of our study. Hyperthyroidism has previously been associated with cigarette smoking which can also be a factor indirectly increasing occurrence of respiratory diseases: if in hyperthyroid subjects

the proportion of smokers is higher than in controls and smoking is associated with increased risk of pulmonary diseases, so one can expect a higher proportion of lung diseases in hyperthyroid patients. Unfortunately, we do not have data on smoking, or in fact any other unknown potential common exposure factor, therefore the influence of indirect Berkson's fallacy on the results of our analysis remains unknown.

Further studies, both clinical and laboratory, are needed to understand the mechanisms of the identified associations between thyroid dysfunction and respiratory conditions.

7.4.6 TD patients with admissions caused by mental and behavioural disorders

We have demonstrated that hospitalisation due to mental health issues was significantly increased in hyperthyroid subjects by 40%. We also noted a 16% rise in admissions in hypothyroid patients, but the significance of this association was borderline. Our findings are supported by other studies linking hyperthyroidism (Brandt et al., 2014) or hypothyroidism (Thvilum et al., 2014) and thyroid dysfunction in general (Radhakrishnan et al., 2013, Carta et al., 2004) with an increase in psychiatric morbidity. Recently, Delitala et al. (2016) have established the U-shaped relation of more extreme values of fT4 associated with more depressive symptoms. Autoimmunity has also been associated with a range of mental and behavioural disorders (van de Ven et al., 2012, Engum et al., 2005, Carta et al., 2004).

The finding of a borderline significant association between hypothyroidism and hospitalisation for mental health issues may in part be explained by action of levothyroxine replacement reversing the adverse effects of hypothyroidism on mood. According to Lin (2016), LT4 reduces the incident rate of depression in Hashimoto's thyroiditis after one year of treatment to the level comparable to the general population.

The general low number of primary mental health admissions within our study cohort reflects the NHS policy (and local policy) to provide help in specialised psychiatric facilities. It could be construed that the psychiatric admissions constitute biased cohort of patients with difficult or regular cases underrepresented in the study cohort as compared to community or specialised psychiatric hospitals. For that reason, division into further mental health diagnostic groups was not undertaken.

7.4.7 Principal admissions from digestive system and TD

Thyroid diseases often present with gastrointestinal symptomatology mainly as a result of motility disturbances. In hypothyroidism the most common GI complaints include constipation, anorexia, nausea or vomiting and abdominal pain, while in hyperthyroidism – diarrhoea, abdominal pain, vomiting and weight loss or in some cases weight gain (Kyriacou et al., 2015, Ebert, 2010b). The majority of symptoms are easily reversible with treatment of underlying thyroid dysfunction as they are caused by the hyper- or hypometabolic state and altered intestinal motility. Others, like GI bacterial overgrowth are found in over a half of hypothyroid patients,

and remain despite the return to euthyroidism (Lauritano et al., 2007). Autoimmune diseases of thyroid (Hashimoto's hypothyroidism and Graves' hyperthyroidism) have been associated with inflammatory bowel disease, primary biliary cirrhosis, coeliac disease and ulcerative colitis (Ebert, 2010b, Kyriacou et al., 2015).

The single most affected GI organ in TD is the liver: thyroid hormone metabolism is dependent on hepatic function and thyroid hormones are needed for normal liver functioning. In fact, hepatic dysfunction caused by thyrotoxicosis is relatively common with both hepatic and cholestatic liver injuries reported (Malik and Hodgson, 2002). In addition, therapy for hyperthyroidism itself can cause hepatic consequences. Altered liver function and hepatitis can occur in about 30% of patients treated with PTU (Williams et al., 1997) which in most cases returns to normal following withdrawal of treatment. CMZ may also have a similar effect although its prevalence is less common.

In spite of a variety of interacting conditions, epidemiological research in the area of GI and thyroid dysfunction has not been thoroughly explored. To the best of our knowledge, our study demonstrates for the first time that patients with thyroid dysfunction are more likely to be hospitalised due to intestinal or peritoneal conditions compared to those without thyroid dysfunction. These findings are supported by case series and smaller studies finding associations between a variety of non-infectious intestinal conditions with TD (West et al., 2004, Sategna-Guidetti et al., 1998, Topal et al., 2011, Singh et al., 2016, Laterza et al., 2016). We did not find any statistically

significant associations between any other GI tract organ and thyroid dysfunction including liver complications.

7.4.8 Strengths and limitations

The strengths of our study are the relatively long follow-up of a large cohort of subjects representing hyperthyroid inpatients admitted to a multidisciplinary, tertiary hospital over a prolonged period of time and their matches selected from hypothyroid and euthyroid populations admitted to the same centre at the same time. Due to the requirements of the information system used in the hospital, all admissions were uniformly coded with the ICD-10 classification system and there was no missing data in principal admissions codes. This made it possible to conduct an analysis correcting for baseline comorbidity burden as defined by CCI.

However, there were a number of limitations to this study. The data are derived from one hospital only and all analyses assume that the cohort was approximately closed i.e. patients did not leave the area and returned to the same hospital for both continuation and a new treatment. Such an assumption was made given that in the West Midlands region, outflow migration is relatively low (1.7%) (Census 2011). Furthermore, patients with significant illness are less likely to move out of the area (Brown and Leyland, 2009), therefore it is likely that they returned to our hospital. Whilst this represents a potential bias in some population based studies, in our cohort, which consists of older and more ill subjects than the rest of the local residents, it provides additional confidence that our assumption of a closed cohort is correct.

Owing to the nature of the study it was not possible to discriminate between the aetiologies of the hyperthyroidism or to adjust for risk factors including smoking and alcohol consumption, which are common for thyroid dysfunction and studied comorbidities. Data regarding the date of diagnosis, underlying aetiology, disease severity and treatment administered were not available for the majority of patients.

7.4.9 Conclusions

We demonstrated increased all-cause mortality in inpatients with a history of hyperthyroidism compared to those with pre-existing hypothyroidism and subjects with no history of thyroid dysfunction. Importantly, this increase was independent from the severity of comorbidities present during the baseline admission. Furthermore, hyperthyroidism was found to be associated with a significant additional health burden through a higher frequency of hospital admissions, longer hospital stays and increased likelihood of intensive care treatment. The likelihood of hospital admission for cardiovascular respiratory, digestive and mental health reasons was also increased in patients with hyperthyroidism compared to those with pre-existing hypothyroidism and to those with no thyroid dysfunction. Further studies are needed to identify ways to alleviate these long-term adverse effects of hyperthyroidism in the hospital setting.

Chapter 8. SUMMARY OF FINDINGS AND FUTURE STUDIES

The work in this thesis has explored some of the challenges in the diagnosis and treatment of hyperthyroidism in real world outpatient and inpatient settings. We also investigated the long-term consequences associated with hyperthyroidism, including effects on weight gain as well as the morbidity and mortality relating to inpatients with thyrotoxicosis. The main findings from this thesis can be summarised into three areas:

8.1.1 Diagnosis of hyperthyroidism

The thesis demonstrates that classical symptoms and signs of hyperthyroidism are significantly less prevalent in older patients presenting to the specialist outpatient clinic. Entirely or nearly asymptomatic (≤2 of classical symptoms) presentations were found in over a half of the elderly patients aged 60 years and over. More severe hyperthyroidism at presentation and being a current cigarette smoker were associated with a greater number of symptoms and signs.

Due to unspecific symptomatology of hyperthyroidism, thyroid function testing (TFT) is essential for accurate diagnosis. Our studies revealed a high volume of TFT among

hospitalised patients. Assuming that patients with no history of thyroid dysfunction (TD) were tested for identification of new cases, we determined that TFT was common (11%) in this group of patients. Analysis of thyroid function tests results indicated that the finding of overt thyroid dysfunction was very rare (2% of those tested; 0.2% of the entire cohort). The volume of tests increased with advancing age, and the number of new diagnoses of both overt hyper- and hypothyroidism was higher in older subjects.

Although, a low threshold for thyroid function testing may be justified, especially in the elderly, the very high proportion of patients with results that did not indicate the need for medical intervention suggest that more economical approaches to TFT requesting are required. As a follow-on project, I propose to use a Bayesian statistical approach to analyse the likelihood of hospitalised patients requiring intervention for thyroid dysfunction contingent upon the characteristics of the tested cohort of subjects. The results of this analysis will form the basis to develop a decision support application, which could be built into the hospital-wide PICS information system to ensure that appropriate testing strategies can be employed that are efficient and economical. The results of this proposed informatics intervention may then be assessed following implementation in a 'before- and-after' analysis with the data collected for this thesis representing the 'before' phase.

Interestingly, in 612 patients admitted to hospital with hyperthyroidism, only one case of thyroid storm was found. There are no data assessing the prevalence of thyroid storm in the UK, while in Japan the diagnosis was made in 5.4% of thyrotoxic patients

admitted to hospital (Akamizu et al., 2012). In future studies, I would like to re-address the data to verify notes of inpatients with hyperthyroidism and grade them according to Burch-Warofsky and/or JTA scales to re-assess the presence of thyroid storm and to investigate the treatments used.

8.1.2 Treatment for hyperthyroidism

This thesis provides further insights into some aspects of the treatment for hyperthyroidism and in particular the longitudinal effects of thionamide therapy. First, we established the characteristics of patients selected for first-line treatment with a course of antithyroid drugs, which comprised more than a half of the studied cohort. We noted that most factors previously identified as those affecting outcomes of ATD treatment significantly influenced the therapy selection for patients in our clinic. We confirmed high rates of unsuccessful treatment either due to inability to restore euthyroidism or secondary to short periods of remission following discontinuation of antithyroid medication. However, the proportion of patients treated successfully was higher when compared to a previous study from our centre (Allahabadia et al., 2000), which may in part be attributed to the practical application of findings from earlier studies. We demonstrated that the previously identified factors associated with failure of treatment with thionamides such as male gender, large goitres and more severe presentation of thyrotoxicosis were significantly affecting the choice of therapy. Patients presenting with such characteristics were more readily given the definitive treatment.

We investigated excess weight gain during the treatment for hyperthyroidism as an adverse effect depending of the type of therapy used. We demonstrated that administration of radioiodine was associated with a small but significant excess increase in weight compared to treatment with a course of thionamides. Additionally, the induction of hypothyroidism, commonly associated with I-131 treatment, resulted in a further small but significant weight increase. Importantly, we observed significant associations between serial serum concentrations of TSH as well as fT4 outside the reference range with differences in weight change during follow-up.

When evaluating thyroid function testing in hospitalised patients with pre-existing thyroid dysfunction, we established that a third of patients had their treatment monitored while in hospital. A high prevalence of thyroid function tests outside the reference range was detected, whereas the finding of overtly abnormal thyroid function results did not always trigger the adjustment of medication dosage. Similarly, the diagnosis of new cases of thyroid dysfunction did not consistently result in the initiation of treatment or communication of the finding with patient's GP.

Together with the Trust IT Department, I would like to develop a decision support application prompting appropriate action to be undertaken upon finding of abnormal thyroid function tests. This intervention would be assessed in future studies, using our present results as comparison.

8.1.3 Long-term consequences of hyperthyroidism

In this thesis, we demonstrated increased all-cause mortality in inpatients with a history of hyperthyroidism compared to those with hypothyroidism as well as those with no history of thyroid dysfunction. Importantly, this increase was independent from the severity of comorbidities present during the baseline admission.

Moreover, hyperthyroidism as comorbidity in hospitalised subjects was associated with a significant additional health burden through a higher frequency of hospital admissions, longer hospital stays and increased likelihood of intensive care treatment. The likelihood of being admitted for cardiovascular reasons was also increased in patients with hyperthyroidism compared to those with hypothyroidism and to those with no thyroid dysfunction. Similar results were found investigating admissions for respiratory, digestive and mental health reasons. Our findings are of particular importance to hospital clinicians dealing with serious illnesses with well-established short-term mortality who may easily overlook non-acute underlying diseases with significant adverse long-term consequences.

In order to further analyse the long-term consequences of hyperthyroidism, I propose to link the vast amount of clinical and biochemical data, collected for decades in the Thyroid Clinic with routinely collected hospital data on diagnoses and procedures. These combined new datasets, will allow me to investigate the prevalence of long term health conditions associated with hyperthyroidism including those relating to the cardiovascular system, musculoskeletal system

and neurocognitive functioning. These studies may focus in particular on patients with toxic nodular hyperthyroidism who have more indolent disease and are usually older. While many studies analyse outcomes separately in subclinical and overt hyperthyroidism, I would like to take a longitudinal approach observing associations between health outcomes and development of toxic nodular disease from the euthyroid nodular stage through subclinical to overt dysfunction. Additionally, I propose to investigate whether radioiodine treatment affects outcomes relating to osteoporosis and fracture risk as has been reported previously (Vestergaard et al., 2000).

Through the detailed analysis of existing data sources, this thesis provides crucial insights into the diagnosis, treatment and long-term consequences of hyperthyroidism. We demonstrate that accurate diagnosis and successful treatment may be challenging, and that patients and clinicians may benefit from additional tools to correctly evaluate and select therapeutic options in order to minimise the adverse long-term consequences associated with this common endocrine disorder.

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APPENDICES

1. Categorisation of ICD-10 coding system

2. List of ICD-10 (WHO 2010) codes used to identify conditions scored in Charlson Comorbidity Index

Table Appendix-1: Categorisation of ICD-10 coding system (WHO, 2010) for purpose of data analysis on thyroid function testing in hospitalised patients. Chapter of codes P00*-P99* on conditions originating in the perinatal period has not been used.
* represents truncation of any symbol.

Category	ICD-10 codes
Injuries	S00*-T98*, V01*-Y98*
Cardiac	I00*-I99*, R00*-R03*
Digestive	K00*-K93*, R1*
Cancer	C00*-D48*
Respiratory	J00*-J99*, R04*-R09*
Endocrine	E00*-E90*
Nervous and Mental health	F00*-F99*, R40*-R46*
Genitourinary	N00*-N99*, R3*
Musculoskeletal	M00*-M99*
General malaise	R50*-R69*
Other	A00*-B99*, D50*-D89*, O00*-O99*, Q00*-99*, R47*-R49*, R70*-R99*

Table Appendix-2: List of ICD-10 (WHO 2010) codes used to identify conditions scored in Charlson Comorbidity Index, * represents truncation of any symbol.

Condition	ICD-10 code
1. Acute Myocardial Infarction	I21*, I22*, I252
2. Congestive Heart Failure	I43*, I50* I099, I110, I130, I132, I255, I420, I425-I429, P290
3. Peripheral Vascular Disease	I70*, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
4. Cerebrovascular Disease	G45*, G46*, I60* - I62*, I63, I64* - I68*, I69, H340
5. Dementia	F00* - F03*, G30, F051*, G311*
6. Chronic Pulmonary Disease	J40* - J46*, J47, J60* - J66*, J67, I278, I279, J684, J701, J703
7. Rheumatologic Disease (Connective Tissue Disease)	M05*, M32* - M34*, M06, M315, M351*, M353*, M360*
8. Peptic Ulcer Disease	K25* - K28*
9. Mild Liver Disease	B18, K73, K74, K700* - K703*, K709*, K713* - K715*, K717, K760*, K762* - K764*, K768*, K769*, Z944*
10. Diabetes without complications	E100*, E101*, E106*, E108*, E109, E110*, E111*, E116*, E118* - E121*, E126*, E128, E129*, E130*, E131*, E136*, E138* - E140*, E141, E146*, E148*, E149*
11. Diabetes with chronic complications	E102*, E103*, E104*, E105*, E107*, E112, E113, E114*, E115*, E117*, E122*, E123*, E124*, E125, E127*, E132*, E133*, E134*, E135*, E137*, E142, E143*, E144*, E145*, E147*
12. Hemiplegia, Paraplegia	G81*, G82, G041*, G114*, G801*, G802*, G830*, G831*, G832*, G833*, G834, G839*
13. Renal Disease	N18*, N19, N052*, N053*, N054*, N055*, N056*, N057*, N250, I120*, I131*, N032*, N033*, N034*, N035*, N036*, N037, Z490*, Z491*, Z492*, Z940*, Z992*
14. Cancer	C00* - C06*, C07, C08* - C13*, C14, C15* - C18*, C19, C20*-C25*, C26 C30* - C34*, C37*, C38*, C39, C40*, C41*, C43*, C45 - C49*, C50, C51 - C58*, C60, C61* - C68*, C69, C70* - C75*, C76, C81* - C85*, C88, C90* - C93*, C94* - C97*
15. Moderate, Severe Liver Disease	K704*, K711*, K721*, K729*, K765*, K766*, K767, I850*, I859*, I864*, I982*
16. Metastatic Carcinoma	C77* - C80*
17. AIDS/HIV	B20* - B22*, B24*