CLINICAL EXPRESSION, PATHOPHYSIOLOGICAL CONSEQUENCES AND GENERAL HEALTH STATUS IN ELDERLY INDIVIDUALS WITH SUBCLINICAL THYROID DYSFUNCTION

by
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ABSTRACT

Subclinical thyroid dysfunction (SCTD), characterised by abnormal serum thyrotrophin concentrations (TSH) with normal free thyroxine (FT_4), is regularly encountered in primary care. The clinical manifestations of SCTD are not well established, particularly in older individuals in whom SCTD, co-morbid conditions and symptoms frequently occur.

This thesis clarifies the clinical expression and pathophysiological consequences of SCTD in the elderly with reference to existing evidence and a cross-sectional study evaluating thyroid function (TF), health status and specific symptoms in community dwelling individuals aged 65 years and above.

TF for 2870 participants was categorised, 2703 (94%) euthyroid, 138 (4.8%) subclinical hypothyroidism and 29 (1%) subclinical hyperthyroidism. No significant differences in the prevalence of individual symptoms, pairs of symptoms or multiple symptoms were observed between TF groups. In the presence of individual or multiple symptoms, health status scores were significantly lower.

In conclusion, symptoms and impaired health status were not associated with SCTD in this study. Results suggest that assessment of symptoms and health status does not aid clinical decision making with respect to management of SCTD in the elderly. Coupled with weak evidence demonstrating pathophysiological consequences in SCTD, overall findings suggest this population is unlikely to benefit from treatment for SCTD.

DEDICATION

This thesis is dedicated to John and Sylvia McCahon

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
ATPO	Anti Thyroid Peroxidase
BETS	Birmingham Elderly Thyroid Study
BMD	Bone Mineral Density
CDMI	Colour Doppler Myocardial Imaging
CI	Chief Investigator
CRF	Case Report Form
DEXA	Dual Energy X-ray Absorptiometry
DHEAS	Dehydroepiandosterone
Dpd	Deoxypyridinoline
ECG	Electrocardiogram
Endo Schyper	Endogenous subclinial hyperthyroidism
Exo Schyper	Exogenous subclinial hyperthyroidism
FT3	Free Triiodothyronine
FT4	Free thyroxine
GP	General Practitioner
IBS	Integrated back scatter
IL-6	Interleukin 6
LREC	Local Research Ethics Committee
MREC	Multi-centre Research Ethics Committee
NCCLS	National Committee for Clinical Laboratory Standards
OHyper	Overt Hyperthyroidism
OHypo	Overt Hypothyroidism
ONS	Office of National Statistics
PC-CRTU	Primary Care Clinical Research and Trials Unit
PI	Principal Investigator
PWTDI	Pulse Wave Tissue Doppler Imaging
QUS	Quantitative Ultrasonography
R&D	Research and Development
SCTD	Subclinical Thyroid Dysfunction
Schyper	Subclinical hyperthyroidism
Schypo	Subclinical hypothyroidism
TFT	Thyroid Function Test
TNF-α	Tumour Necrosis Factor alpha
TSH	Thyrotrophin [thyroid stimulating hormone]
TD	Thyroid dysfunction

INTRODUCTION

Thyroid dysfunction is common in older age and often encountered in primary care. Elderly individuals frequently consult general practitioners (GPs) regarding symptoms such as dry skin, frequent palpitation, poor memory, weak muscles and lethargy which are traditionally associated with overt thyroid dysfunction. When elderly individuals present with these symptoms, GPs generally request thyroid function tests (TFT) which measure serum concentrations of thyrotrophin (also known as thyroid stimulating hormone [TSH]) and free thyroxine (FT4). Normal or euthyroid function is defined by serum concentrations of thyrotrophin and free thyroxine within their respective local laboratory reference criteria. In contrast overt thyroid dysfunction is diagnosed when the serum concentrations of both thyrotrophin and FT4 are outside of their respective reference range. In older individuals TFT results more frequently reveal subclinical thyroid dysfunction, defined by serum thyrotrophin concentration outside of the local laboratory reference range accompanied by FT4 concentration within the reference range.

On receipt of TFT results indicating subclinical thyroid dysfunction in an elderly individual with symptoms, a GP has to decide to either closely monitor thyroid function via repeated TFT or to commence treatment aimed at restoring normal thyroid function.

Whilst the signs and symptoms of overt thyroid dysfunction are well established and adverse clinical consequences are widely documented, data related to the pathophysiological consequences of subclinical thyroid dysfunction are inconsistent. Consequentially there is no consensus with respect to recommendations for screening, management and treatment for subclinical thyroid dysfunction. Essentially subclinical thyroid dysfunction, as the name suggests is a biochemical diagnosis.

Nonetheless given the biochemical profile it is reasonable to assume that subclinical thyroid dysfunction is a mild form of overt thyroid function and as such is associated with a similar albeit less severe adverse clinical consequences. Furthermore a greater prevalence of symptoms and moderate benefits of treatment in terms of decreasing symptom severity have been described in younger adults with subclinical thyroid dysfunction compared with euthyroid individuals. In older individuals however the relationship between symptoms and subclinical thyroid dysfunction remains ambiguous. This is predominantly because the symptoms traditionally associated with overt thyroid dysfunction also accompany normal healthy ageing. Similarly the benefits of treating elderly individuals are uncertain with polypharmacy being an additional burden in this population.

To further inform the debate with regard to screening, monitoring and treatment it is therefore necessary to establish the pathophysiological consequences of subclinical thyroid dysfunction in individuals' age 65 years or more. Furthermore it is necessary to confirm whether symptoms in this population are pathophysiological or physiological in origin. Clarification of the pathophysiological consequences and characterisation of symptoms associated with subclinical thyroid dysfunction in this population will further support GP decision making when ordering TFTs and commencing treatment. Furthermore these data will enable development of recommendations for GP management of subclinical thyroid dysfunction in older individuals and thereby reduce unnecessary investigation and treatment in this population based upon presentation of symptoms.

The questions which remain unanswered are;

i) Are symptoms usually associated with overt thyroid dysfunction prevalent in elderly individuals with subclinical thyroid dysfunction?

ii) Is subclinical thyroid dysfunction in elderly individuals associated with similar adverse pathophysiological consequences as overt thyroid dysfunction?

This thesis therefore explores the pathophysiological manifestations of subclinical thyroid dysfunction in the elderly with reference to i) the large body of existing evidence pertaining to the clinical expression and pathophysiological consequences of subclinical thyroid dysfunction and ii) the results of a cross-sectional study evaluating thyroid function and the presence, severity and change in expression of symptoms suggestive of overt thyroid dysfunction and perceived health status in a large UK based community dwelling population aged 65 years and above.

Following the introduction and presentation of the aims and objectives of this thesis, chapter 1 provides a broad overview of the function of the thyroid gland and describes the relationships between biochemical parameters of thyroid function. Subsequently the clinical presentation and pathophysiological consequences of overt thyroid dysfunction are described before subclinical thyroid dysfunction is introduced and defined in chapter 2. Chapter 2 further describes the prevalence and aetiology of subclinical thyroid dysfunction and reports current expert opinion and recommendations for management of subclinical thyroid dysfunction. Chapters 3-6 summarise the large body of literature surrounding the clinical presentation and pathophysiological consequences of subclinical thyroid dysfunction. The pathophysiological consequences and physical signs of subclinical hypothyroidism and subclinical hyperthyroidism are described respectively in chapters 3 and 4. In chapters 5 and 6 the evidence related to expression of symptoms in individuals with and with out subclinical hypothyroidism and subclinical hyperthyroidism is presented

and examined. Evidence reported in these four chapters is then summarised before the rationale for the cross sectional study exploring symptoms and perceived health status in elderly individuals with and without subclinical thyroid dysfunction is further clarified. The methodology and results of a cross sectional study are then reported in Chapters 8-15. The findings of the literature review and cross sectional study are further examined with reference to existing literature and strengths and limitations of the thesis are discussed. Chapter 17 concludes that the evidence demonstrating pathophysiological consequences of subclinical thyroid dysfunction in the over 65s is insufficient to justify treatment and recommends a degree of caution with respect to repeat testing and initiation of treatment based upon impaired health status and presentation of symptoms in this population.

AIM

The aim of this thesis is to determine the association between symptoms suggestive of overt thyroid dysfunction and subclinical thyroid dysfunction and further clarify the pathophysiological consequences of subclinical hypothyroidism and subclinical hyperthyroidism in the elderly community dwelling population.

OBJECTIVES

To fulfil the aim of this thesis, there were four objectives;

1. **To clarify the importance of subclinical hypothyroidism and subclinical hyperthyroidism with reference to existing evidence pertaining to the clinical presentation and pathophysiological consequences of subclinical thyroid dysfunction.**

This objective was addressed by means of a systematic literature review which collates, interprets and summarises current evidence related to the pathophysiological consequences of subclinical thyroid dysfunction.

2. **To characterise individual symptoms and combinations of symptoms associated with subclinical hypothyroidism and subclinical hyperthyroidism in an elderly UK based community dwelling population.**

This objective was addressed using a cross-sectional study design to evaluate thyroid function and self-reported symptoms suggestive of overt thyroid dysfunction in a large cohort (n= 5881) of community dwelling elderly individuals. Concurrent thyroid function testing enabled biochemical classification of thyroid function as euthyroid, subclinical hypothyroidism or subclinical hyperthyroidism. The prevalence of individual symptoms, combinations of symptoms and total number of symptoms reported were compared between the euthyroidism group and the groups with subclinical hypothyroidism and subclinical hyperthyroidism.

3. **To evaluate the relationship between health status and subclinical thyroid dysfunction and explore the impact of individual symptoms on perceived health status in an elderly community dwelling cohort.**

To fulfil this objective data related to perceived health status was collected alongside data relating to symptoms. Exploratory analysis is undertaken to investigate the impact of both subclinical thyroid dysfunction and the presence of individual symptoms on health status and the impact of individual and total number of symptoms on health status. Findings provide an improved understanding of the relationship between subclinical thyroid dysfunction and health status and enable determination of whether health status is independently associated with symptoms or with subclinical thyroid dysfunction.

4. **To establish the relationship between serum concentrations of the thyroid parameters thyrotrophin and free thyroxine and expression of individual symptoms and combinations of symptoms in an elderly community dwelling cohort.**

In fulfilment of this aim, the distribution of serum concentrations of thyrotrophin and free thyroxine are compared between groups reporting presence and absence of individual symptoms and combinations of symptoms.

CHAPTER 1 THYROID FUNCTION

Overview of chapter 1

This chapter sets the background for this body of work by presenting a brief overview of the anatomy and normal function of the thyroid gland. In addition, the relationship between the hormone that regulates thyroid function and the hormones synthesised and secreted by the thyroid gland will be presented. Knowledge of normal thyroid function and the relationship between these thyroid parameters is essential for understanding of the physiological effects and clinical manifestations of thyroid dysfunction. This is followed by a description of the abnormal biochemical profile observed in overt hypothyroidism and overt hypothyroidism and the adverse clinical consequences associated with overt thyroid dysfunction.

1.1 Thyroid anatomy and location

The thyroid is a bi-lobed gland situated at the upper end of the trachea. The lateral lobes are approximately 4 cm in length and 2 cm in thickness, and are connected by a thin band of tissue called the isthmus. Each lobe receives a rich and rapid (4-6ml/min/g of tissue) supply of blood from two sources; the superior thyroid artery (a branch of the external carotid artery) and the interior thyroid artery (a branch of the subclavian artery). Thyroid tissue comprises numerous follicles, each of which has a central colloid filled cavity lined with follicular cells.

1.2 Function of the thyroid gland

The function of the thyroid gland is the synthesis, storage and secretion of the thyroid hormones, tertraiodothyronine, (otherwise known as thyroxine [T4]) and triiodothyronine (T3). These thyroid hormones are responsible for control and regulation of basal metabolic rate (BMR, the minimum amount of energy expended to maintain vital processes) and have an essential role in the metabolism of carbohydrates, fats and proteins and in the development and maintenance of both mental and physical function. These hormones are involved in almost every organ system of the body, therefore dysfunctions of the thyroid gland exhibit a broad spectrum of clinical effects.

1.3 Regulation of thyroid hormones

Since the hypothalamus and anterior pituitary gland coordinate the endocrine system, synthesis and secretion of the thyroid hormones is ultimately under their control. With the anterior pituitary gland acting as a sensor of circulating thyroid

hormone concentration, this coordination is directed through the hormone thyrotrophin (otherwise known as thyroid stimulating hormone [TSH]) via a negative feed-back regulatory mechanism. Thyrotrophin is synthesised and secreted by the anterior pituitary gland in response to a decline in circulating thyroid hormone concentration, accompanied by secretion of thyrotrophin releasing hormone by the hypothalamus. Thyrotrophin continues to stimulate thyroid gland activity until sufficient concentrations of circulating thyroid hormone are detected by the anterior pituitary gland. Restoration of normal concentrations of thyroid hormones leads to down regulation of thyrotrophin production and subsequent reduction in thyroid gland activity. The inverse log-linear relationship between serum thyrotrophin and free thyroxine means that a small decrease in free thyroxine concentration is associated with exponential increases in serum thyrotrophin concentration.

Thyrotrophin acts upon the thyroid gland to encourage an increased uptake of iodide ions thereby intensifying protein synthesis and cellular metabolism. [1] These activities are accompanied by an increase in the overall size, vasculature, intracellular volume and colloid storage capacity of the gland, allowing additional synthesis and storage of thyroid hormones. Meanwhile, thyroid hormones are secreted into the general circulation. In the blood, thyroid hormones are transported almost entirely bound to the plasma proteins; thyroxine binding globulin (TBG), pre-albumin and albumin. Howver, a small proportion remains unbound and it is this free fraction of thyroid hormone (free thyroxine [FT4] and free triiodothyronine [FT3]) that is biologically active and available to act on the tissues to promote energy production, growth and development. Since FT4 is converted to the more active FT3 in the tissues, both of the thyroid hormones have the same metabolic and physiological effects. [2]

1.4 Nomenclature

Thyroid gland dysfunction is commonly described as under- or over-active based upon the concentrations of thyroid hormone being produced. The term overt thyroid dysfunction is the generic term used to describe conditions that arise as a result of consistently altered thyroid function with excess or insufficient concentrations of thyroid hormone. More specifically, the condition resulting from thyroid hormone excess accompanied by suppressed serum thyrotrophin concentration is known as overt hyperthyroidism and insufficient thyroid hormone in combination with surplus serum thyrotrophin concentration is described as overt hypothyroidism.

1.5 Physiological effects of overt hyperthyroidism

Excessive concentrations of the thyroid hormones lead to an increase in basal metabolic rate with an associated increase in oxygen consumption and heat production (thermogenesis). [3] This general increase in cellular metabolic activity also results in an increased rate of carbohydrate metabolism, leading to greater absorption of glucose and enhanced glycolysis (conversion of glucose to lactic acid), glycogenolysis (catabolism of glycogen stores to produce glucose) and gluconeogeneisis (catabolism of non–carbohydrate sources) if carbohydrate is in short supply. Metabolism of fat is similarly stimulated by increased concentrations of thyroid hormones resulting in an increase in synthesis, mobilisation and degradation of lipids. When the gland is functioning normally, these effects are necessary to maintain basal metabolic rate and as such are relatively short lived. In altered thyroid function, however, these effects persist and can lead to significant morbidity and mortality. [1]

1.6 Morbidity associated with overt hyperthyroidism

A persistent excess of thyroid hormone confers high basal metabolic rate and increased metabolism leading to heat intolerance and weight loss. With respect to enhancement of the protein metabolism, protein degradation dominates which, if persistent, leads to a decrease in muscle mass and muscle weakness. Other common musculoskeletal complaints are muscle cramping, stiffness, paraesthesia (sensation of pins and needles), joint swelling, and carpal tunnel syndrome. Likewise, excess thyroid hormones enhance bone metabolism with bone resorption being affected to a greater extent than synthesis. This results in net loss of bone and reduced bone mineral density, accompanied by increased urinary excretion of calcium and phosphate. These effects can lead to hypercalcaemia and an increased risk of osteoporosis and fracture. [4-6] The cardiovascular system is also a major target of thyroid hormone action. [7] The indirect effects of raised metabolic rate due to increased demand for oxygen and heat dissipation to peripheral vessels are increased cardiac output and blood flow. Thyroid hormones also directly act on the heart to increase cardiac contractility and heart rate. Sinus tachycardia is the most common cardiac disturbance of overt hyperthyroidism. Atrial fibrillation (AF), a risk factor for embolism, is however a more clinically significant cardiac condition associated with overt hyperthyroidism. [8,9] AF occurs in up to 15% of patients with overt hyperthyroidism compared with just 4% of the general population and incidence increases with age. [10] Thyroid hormones also influence vascular smooth muscle cells to promote relaxation and reduce systemic vascular resistance. This in turn improves diastolic relaxation leading to more efficient use of energy and nutrients by the cardiomyocytes. [7,11] The increase in peripheral metabolism leads to

an increased demand on cardiac output. The mechanism by which increased cardiac output is achieved is thought to be activated by a decrease in vascular resistance and an increase in blood volume. Cardiac preload augments stroke volume in response to increased venous return and overall cardiac output is amplified in response to a raised stroke volume and increased heart rate. [12]

An association between overt hyperthyroidism and anxiety, depression and changes in mood and cognitive functions has been widely reported, however, the exact mechanisms for these relationships remain largely unknown. Additionally, perceived quality of life and health status has been shown to be significantly impaired in individuals with overt hyperthyroidism. [13,14,15]

The symptoms of excess thyroid hormone reflect hypersensitivity and include intolerance to heat, breathlessness, palpitation, diarrhoea due to intestinal hypermotility, excessive perspiration, tremor, weak muscles, weight loss, irritability, short attention span and fatigue. [16,17] Physical signs include rapid pulse, fine tremor and atrial fibrillation. [3] In the longer term, thyroid hormone excess is associated with significant morbidity in the form of osteoporosis, heart failure and AF. [18] Overt hyperthyroidism is also associated with an increased mortality risk particularly from cardiovascular and cerebrovascular causes. [19]

1.7 Thyroid hormone deficiency: overt hypothyroidism

The pathophysiological effects of thyroid hormone deficiency are diametrically opposed to those described for overt hyperthyroidism. Diminished metabolic rate and thermogenesis are associated with reduced heat production, decreased oxygen demand and blood flow to the tissues. Since overall energy production and expenditure is reduced, degradation of carbohydrate and fat is diminished, leading to

storage of glycogen with weight gain and a rise in the concentration of plasma lipids which confer an increased risk for atherosclerosis. Cholesterol levels are further affected due to a reduction in action of thyroid hormones on production of low density lipoprotein cholesterol receptors by the liver and a reduction in the removal of low density lipoprotein cholesterol from the circulation.

The accompanying effects of overt hypothyroidism manifest as intolerance to cold, constipation, weight gain, hoarse voice, puffy eyes, dry skin, muscle cramps, poor memory and delayed reflex relaxation time. Hypertension may manifest due to the direct effect of thyroid hormone increasing vascular resistance to prevent heat loss, increased arterial stiffness and/or alterations to endothelial function. [20,21,22] Furthermore, atherosclerotic narrowing of the arteries potentiated by serum lipid anomalies may contribute to hypertension associated with overt hypothyroidism.
Skeletal muscle is also a known target organ for thyroid hormones with a wide range of alterations in neuromuscular and neuropsychiatry function being well established in overt hypothyroidism. [21] Alterations in muscle structure and function can manifest as painful paraesthesia (partial numbness, tingling, buzzing and vibration, pins and needles sensations) and cramping of the hands and feet. The deficiency in thyroid hormones affects metabolism of the myocytes, causing a reduction in speed of muscle contraction and relaxation. Cell wall integrity is also adversely affected leading to muscle necrosis. Proximal weakness and slow reflexes are therefore well established findings in individuals with overt hypothyroidism. [23] Like overt hyperthyroidism, hypothyroidism has also been shown to impact on aspects of cognitive function and mood, and patients frequently have neuropsychiatric complaints. Most studies suggest an association between hypothyroidism and

depression. Overt hypothyroidism has also been associated with impaired quality of life. [24] However this relationship is complicated, and it is unclear whether reduced quality of life associated with overt hypothyroidism is a cause or a consequence of depression. Additionally, dementia has been widely linked to overt hypothyroidism. [25] Despite increased bone quantity, overt hypothyroidism has also been associated with increased fracture risk, both before and after diagnosis. [26] In the longer term, overt hypothyroidism is associated with adverse cardiac consequences and events such as atherosclerosis, coronary heart disease, myocardial infarction; angina and increased cardiovascular mortality risk. [27]

1.8 Prevalence

Overt thyroid dysfunction is one of the most common chronic endocrine disorders in the general population. In 2006, 3% of the UK population were prescribed thyroxine replacement therapy for treatment of overt hypothyroidism. [28] Data derived from a cross-sectional study of a representative sample of the UK population suggested a higher prevalence of overt hypothyroidism in women than in men (1.4% versus 0.1%, respectively) and with advancing age. [29] This study reported an overall prevalence of overt hyperthyroidism of 2.0% in women and around 0.2% in men. Outside of the UK, prevalence rates have been shown to vary considerably in accordance with ethnicity, age and frequency of anti-thyroid antibody status of the population studied. [30,31,32,33] An additional explanation for the discrepancies in prevalence data from around the world is the difference in iodine sufficiency between geographical locations. However prevalence data derived in areas of iodine deficiency and sufficiency consistently demonstrate a higher prevalence of both hyper- and hypothyroidism in older age groups compared with those younger than 60 years of

age. Less generalisable and rigorous estimates of prevalence have been reported due to research methods being highly selective with respect to the populations being studied. Additionally, in some studies prevalence may be overestimated due to misclassification of thyroid function in individuals receiving drugs that interfere with thyroid function tests or with concomitant or acute illnesses that impact upon serum thyrotrophin independently of thyroid disease. Despite the discrepancies between smaller studies, epidemiological data from large cross-sectional and longitudinal screening studies demonstrates that overt thyroid dysfunction is a common and clinically significant disorder.

1.9 Aetiology

The predominant cause of spontaneous overt hypothyroidism is autoimmune infiltration and destruction of the thyroid gland due to Hashimotos thyroiditis or primary atrophic hypothyroidism. Alternatively, destructive treatment for overt hyperthyroidism in the form of total or partial thyroidectomy and/or radioiodine therapy can often prompt under activity of the thyroid gland and lead to reduced thyroid hormone synthesis.

Similarly, overt hyperthyroidism can be of autoimmune or iatrogenic origin. Graves' disease is an autoimmune disease of unknown cause. In Graves' disease, auto antibodies of the immunoglobulin G subclass mimic thyrotrophin by binding to thyrotrophin receptors on the thyroid cell membranes and stimulate thyroid function. Development of autonomously functioning follicular adenomas within the gland also leads to overt hyperthyroidism. These benign thyroid nodules known as "hot nodules" cause the thyroid gland to become unresponsive to the normal secretary

control mechanisms and continually secrete thyroid hormone into the circulation. This condition is known as either solitary toxic nodule or toxic multinodular goitre depending upon the number of nodules. Intentional or unintentional excessive thyroid hormone replacement therapy can also be responsible for overt hyperthyroidism.

Since iodine is essential for thyroid hormone production, another major cause of overt hypothyroidism worldwide is iodine deficiency. Insufficient dietary intake is the main cause of iodine deficiency with dietary sources containing varying degrees dependant upon the amount available in the soil and/or in animal feed. The recommended daily intake of iodine is 150μg with population based iodine intake programmes achieving adequate intake through iodisation of salt.

Excess dietary iodine intake or iodine-containing medication or drugs that mimic iodine action can be responsible for overt hypothyroidism (via iodine induced inhibition of thyroid hormone production) or overt hyperthyroidism (through surplus production of thyroid hormone). The drug amiodarone, which is frequently prescribed for cardiac arrhythmias, is iodine rich and may be responsible for either hyperthyroidism or hypothyroidism in up to 18% of patients with apparently normal thyroid function or pre-existing disease. [34] Likewise, lithium therapy for psychotic disorders has been shown to induce hypothyroidism or hyperthyroidism in 10% of patients, particularly in the presence of thyroid auto antibodies.

Altered concentrations of serum thyrotrophin and thyroid hormones are not exclusive to overt thyroid dysfunction, however, and may also be identified in hospitalised individuals, patients with transient thyroid dysfunction due to viral infection, or during

recovery from other non thyroidal illnesses. Transient increases in serum thyrotrophin concentration due to non thyroidal illnesses continue for approximately seven-ten days. In contrast, persistent alterations in serum thyrotrophin concentration will stabilise to a new baseline in six to eight weeks and are indicative of more permanent alterations in thyroid function.

1.10 Clinical expression of overt thyroid dysfunction

Almost all cases of overt thyroid dysfunction encountered in general practice are caused by primary disease of the thyroid. Biochemical measurement of thyroid function is required to exclude or confirm diagnosis of overt thyroid dysfunction. The majority of studies suggest that consideration of physical symptoms in isolation is associated with very poor diagnostic accuracy for overt thyroid dysfunction. [35,36] Whilst endocrinology text books describe classical signs and symptoms of overt hypothyroidism and hyperthyroidism, in routine primary care practice many of these manifestations are rarely apparent. The clinical presentation of individuals with overt hypothyroidism and overt hyperthyroidism varies widely. [35,36] Additionally, many of the classical signs and symptoms are non-specific and as such frequently present in euthyroid individuals. [37,38] A number of validated instruments are available for evaluation of the signs and symptoms of overt hypothyroidism and overt hyperthyroidism. [39,40,41,42] Some of these tools are intended to aid diagnosis and assessment of severity of thyroid dysfunction, whereas others are designed for monitoring the response to treatment. In terms of diagnosis, arguably the availability of relatively low cost assays leads to thyroid function testing without the use of such instruments in the majority of cases. [43]

Nevertheless, several investigators support the use of multiple symptoms as a diagnostic tool for identification of individuals in whom subsequent testing would be appropriate. [38,44,45] Simple scoring systems have been shown to increase the pre-test probability of overt thyroid dysfunction by 15-19%. [38] In general, however, high frequencies of false positive results have been associated with these clinical scoring systems. A recent study to assess the significance of the clinical versus biochemical diagnosis of overt hypothyroidism reported correct classification of only 21% according to the Billewicz score. [39] Almost half of the 388 individuals with primary hypothyroidism were classified as euthyroid and the remaining 29% fell into the inconclusive category. In another recent study in which the Billewicz questionnaire was administered to individuals with overt hypothyroidism and age matched controls, the classical symptoms were described much less frequently than in the earlier literature. [37] There is, however, evidence to suggest that the clinical picture of overt thyroid dysfunction has changed over time. Classical signs and symptoms of thyroid dysfunction are now observed much less frequently than in earlier studies. [37] The most plausible explanation for this is earlier diagnosis of overt thyroid dysfunction due to the wide availability of more sensitive and cost-effective assays for measurement of serum thyrotrophin and FT4 concentrations. [46,47] Previously, the diagnosis may have been made based upon the clinical manifestations of more severe or longstanding thyroid dysfunction. Older scoring systems developed before the 1970s when assays for measurement of serum thyrotrophin and FT4 were not available may now be less sensitive and of limited use for identification of signs and symptoms of relatively early thyroid dysfunction. [39,40,41] The diagnosis of overt thyroid dysfunction can be particularly challenging in older individuals, not least because the signs and symptoms of this dysfunction also accompany normal healthy ageing.

Signs and symptoms in older people may also be masked by coexisting disease and concomitant medication. Several authors have documented a decrease in the number and severity of symptoms of overt thyroid dysfunction with increasing age. [11,49] There are also data supporting age related alterations in the clinical manifestation of overt thyroid dysfunction with a different constellation of signs and symptoms being expressed in older individuals compared with younger people. One study evaluating 24 clinical signs reported a significantly lower mean number of signs in 67 individuals aged 70 years or more with overt hypothyroidism (mean age 79.3 years, range 70-98 years) compared with 54 younger individuals (mean age 40.8 years, range 23-55 years) with overt hypothyroidism (6.6 ± 4 versus 9.3 ±4.7 respectively, p <0.01). [50] Furthermore, four signs were observed significantly less frequently in elderly individuals compared with younger subjects; sensitivity to cold temperatures (34.9% versus 64.8 %, p<0.002), paraesthesia (17.9% versus 61.1%, p<0.001), weight gain (23.7% versus 58.5%, p<0.001) and muscle cramps (20.3% versus 54.7%, p<0.001). Similarly, in a study comparing presence of 19 classic signs of hyperthyroidism in older (≥70 years, mean age 80.2 years) and younger (≤50 years; mean age 37.4 years) patients with overt hyperthyroidism, the mean number of signs observed was significantly lower in older than younger individuals (6.0 ± 3.5 versus 10.8 ± 3.1 respectively, p<0.001). [51] Seven of the 19 signs (hyperactive reflexes, excessive sweating, heat intolerance, tremor, nervousness, polydipsia, and increased appetite) were observed significantly less frequently in older subjects than in younger individuals. However anorexia was significantly more prevalent in older individuals than in younger individuals with overt hyperthyroidism (32% versus 4%, p <0.001). This study also recruited a third group which comprised 68 older (≥70 years, men age 81.3 years) euthyroid controls matched to older individuals with overt

hyperthyroidism by gender, age and co-morbidity. Comparison between the older groups with and without overt hyperthyroidism identified three signs, namely apathy (Odds Ratio, OR 14.8, 95% CI 3.8-57.5, p<0.001), weight loss (OR 8.7, 95% CI 3.1-24.4, p<0.001) and tachycardia (OR 11.2, 95% CI 4.3-29.4, p<0.001) significantly associated with overt hyperthyroidism. [51] Another study described a gradual decrease in the total number and frequency of signs and symptoms beyond the age of 50 years, [49] with little change in clinical presentation observed, until the age of 50 years. It seems therefore, that diagnosis becomes more difficult as age progresses. More recently, a cross-sectional study of 3049 patients with overt hyperthyroidism demonstrated that the majority of individuals aged 61 years or older reported a maximum of two symptoms (54%) compared with 36% in those aged 16-32 years, 32% in those aged 33-44 years and 30% in 45-60 year groups. [52] Equally, the group aged 61 years or more was less likely to report five or more symptoms than the younger age groups. These results support and further extend the findings of earlier smaller studies by demonstrating an association between advancing age and number of symptoms that is independent of severity and aetiology of overt hyperthyroidism.

Summary of chapter 1

This chapter described the clinical manifestations and pathophysiological consequences of overt hypothyroidism and overt hyperthyroidism. Overt thyroid dysfunction in the form of overt hyperthyroidism and overt hypothyroidism are common endocrine disorders resulting from an insufficient or excess amount of circulating thyroid hormones accompanied by altered serum thyrotrophin concentrations. Overt hyperthyroidism is associated with significant short term morbidity and longer term morbidity and mortality. Similarly, overt hypothyroidism is associated with considerable morbidity. Diagnosis of overt thyroid dysfunction depends first on adequate suspicion supported by clinical features, then upon demonstration of abnormal serum concentrations of thyrotrophin and free thyroxine. Clinical parameters alone fare poorly in establishing an unequivocal diagnosis of overt thyroid dysfunction. Age modifies the prevalence of overt thyroid dysfunction as well as the classic profile of signs and symptoms meaning that this disorder is more prevalent in older individuals but also more difficult to identify based upon clinical presentation.

In the next chapter, subclinical hypothyroidism and subclinical hyperthyroidism are introduced and the distinction between subclinical and overt thyroid dysfunction is defined.

CHAPTER 2 BIOCHEMICAL DIAGNOSIS OF THYROID DYSFUNCTION

Overview of chapter 2

In this chapter the biochemical tests routinely used to confirm or refute thyroid dysfunction and the reference criteria upon which the diagnosis of subclinical and overt hyper and hypothyroidism is based are described. Subsequently, an overview of the aetiology and prevalence of subclinical hyperthyroidism and subclinical hypothyroidism is presented. Finally, statements of expert opinion and recommendations with regard to testing, management and treatment of subclinical thyroid dysfunction are presented.

2.1 Definition of subclinical thyroid dysfunction

Subclinical hypothyroidism and subclinical hyperthyroidism were identified as clinical entities during development of the 2nd and 3rd generation serum thyrotrophin assays, and as such, the diagnoses are essentially biochemical. The term 'subclinical thyroid dysfunction' is used when abnormal concentrations of serum thyrotrophin and normal concentrations of circulating thyroxine (FT4) are observed. [53] The distinction between overt and subclinical thyroid dysfunction disease therefore is based purely upon biochemical criteria with subclinical hyperthyroidism being defined by a reduction in concentration of serum thyrotrophin accompanied by concentrations of the thyroid hormone FT4 within the standard reference range. [54] In contrast, subclinical hypothyroidism is characterised by a raised serum thyrotrophin concentration in conjunction with a serum FT4 concentration which is within the standard reference range. [54] Subclinical hypothyroidism is often subdivided

according to the degree of elevation in serum thyrotrophin concentration. A thyrotrophin concentration of between 4.5-10mIU/L (detected in around 75% of cases) is generally regarded as being indicative of less severe thyroid failure than a thyrotrophin concentration greater than 10mIU/L. [55,56,57] Similarly, subclinical hyperthyroidism is often subdivided based the upon degree of thyrotrophin suppression, with concentrations of less than 0.01mIU/L representative of more severe thyroid dysfunction than concentrations of between 0.1-0.4mIU/L. [58] This stratification of serum thyrotrophin concentration is frequently used to define subgroups for analysis in research and is utilised in guideline documents of expert opinion in relation to testing, management and treatment of subclinical thyroid dysfunction. Subclinical thyroid dysfunction is considered by some to be essentially a biomedical diagnosis characterised by abnormal serum thyrotrophin (TSH) in association with normal serum thyroid hormone. [54] Others, however, have designated subclinical thyroid dysfunction, a mild form of overt thyroid dysfunction and have demonstrated presence of symptoms suggestive of overt thyroid dysfunction. [59]

2.2 Prevalence of subclinical thyroid dysfunction

Worldwide prevalence figures for subclinical hypothyroidism and subclinical hyperthyroidism are variable. The use of different assays for measurement of serum thyrotrophin concentration, differing reference criteria for definition of subclinical thyroid dysfunction and inclusion of some individuals receiving treatment for thyroid dysfunction are the most likely reasons for the diverse prevalence estimates reported. Older studies of UK-based populations report a prevalence of subclinical hypothyroidism of around 5-6% [60,61] and subclinical hyperthyroidism of approximately 1-2%. [62] These studies also suggest that the prevalence of subclinical hypothyroidism and subclinical hyperthyroidism is higher in older individuals and in women. Our own recent local study in which approximately 5800 community dwelling individuals aged 65 years or more were screened reported an overall prevalence of subclinical hypothyroidism of 2.9% and subclinical hyperthyroidism of 2.1%. [63] Like the overt forms of this dysfunction, prevalence figures vary considerably with ethnicity, dietary iodine intake and frequency of anti-thyroid antibodies of the populations studied. [64] As is the case with overt thyroid dysfunction, the prevalence of subclinical hypothyroidism is greater in areas of iodine sufficiency and subclinical hyperthyroidism is more common in areas that are iodine deficient. [65] Data derived from populations located in iodine sufficient and iodine deficient areas consistently demonstrate an increased prevalence of subclinical thyroid dysfunction in females and older individuals.

2.3 Aetiology of subclinical thyroid dysfunction

Subclinical hyperthyroidism and subclinical hypothyroidism have similar causes to the overt forms of these disorders. Subclinical hypothyroidism has two main causes in the UK, namely autoimmunity and overzealous treatment for overt hyperthyroidism. The aetiology of subclinical hyperthyroidism can be divided into two categories: exogenous and endogenous. These terms are used to define the origins of the disease with endogenous being indicative of spontaneous disease (endo denotes from within) and exogenous disease defining disease of external origin (exo denoting external). Exogenous subclinical hyperthyroidism can be intentionally induced, for example as in patients with differentiated thyroid carcinoma (DTC) receiving thyrotrophin-suppressive thyroxine therapy, or unintentionally due to over aggressive anti thyroid therapy. The most common cause of exogenous subclinical hyperthyroidism is therefore the use of unintentional or intentional excessive suppressive doses of thyroid hormone. The endogenous form is usually related to autonomous thyroid dysfunction. It remains to be seen whether endogenous and exogenous subclinical hyperthyroidism are comparable conditions that exert equivalent effects.

2.4 Statistical nature of defining a reference range

Reference intervals are widely used medical decision making tools and aid the clinician in differentiating between healthy and ‘unhealthy’ patients. In general, these are population, assay and statistical methodology dependent. The National Committee for Clinical Laboratory Standards (NCCLS) suggest that calculation of reference criteria is based upon measurement of at least 120 ‘normal’ healthy

samples. The reference range is calculated from the sample mean and two standard deviations of the data set. The value corresponding to the 2.5th percentile defines the lower limit of the reference range and the value corresponding with the 97.5th percentile indicates the upper limit of the reference range. The most sensitive indicator of thyroid dysfunction is serum thyrotrophin concentration, however there are no universal reference criteria or reference material for definition of normal serum thyrotrophin concentration, therefore reference ranges vary from one endocrine laboratory to the next. Reference criteria for serum thyrotrophin concentration are derived from screened samples of healthy volunteers with no known or apparent thyroid dysfunction or medication known to affect thyroid function. However there has been much debate about this derivation method particularly in relation to defining the upper limit of normal. [66,67,68] Over the last 20 years the upper limit has been reduced from 10mIU/L to around 4mIU/L and some authors suggest further reductions are necessary. [69] These suggestions are based upon data derived from exclusion of individuals with thyroid auto antibodies, goitre or a strong family history of thyroid disease from the reference population. In such thyroid disease and risk factor free populations the upper limit decreases to between 2.5mIU/L to 3.0 mIU/L. [66] Some argue that the refined reference range is better than the standardised population–based reference range particularly because elevated thyrotrophin values may predict future hypothyroidism. [66, 70] Additionally, current assays for detection of anti thyroid antibody are not sufficiently sensitive to identify all individuals with low grade thyroid autoimmunity. [71] Furthermore, an increased risk of overt hypothyroidism has been demonstrated in antibody negative individuals. This decreased upper limit of normal would however increase the sensitivity of the diagnosis and decrease specificity resulting in a greater number of individuals being

given a false positive diagnosis. Furthermore, lowering the upper limit of the reference range would have a large impact upon the prevalence figures for the older age groups and would lead to reclassification of one in five euthyroid individuals to subclinically hypothyroid. One recent study demonstrated a modified serum thyrotrophin distribution in older individuals and suggested that serum thyrotrophin progressively moves towards higher concentrations with advancing age. [72] Re-analysis of data from the NHANES study demonstrated that the upper limit of normal at the 97.5th percentile was 3.56mIU/L for the 20-29 age group, 4.5mIU/L in individuals aged 50-59 years and 7.5mIU/L in individuals older than 80 years. Seventy percent of older patients with a serum thyrotrophin concentration greater than 4.5mI/L were therefore within their age-specific reference range. It is possible that current statistically defined laboratory reference criteria for serum thyrotrophin concentration are neither adequately sensitive nor specific for identification of abnormal concentrations of serum thyrotrophin in older age groups and as such current prevalence rates for subclinical hypothyroidism in the older individuals may be substantially over estimated. However, in a further study, the geometric mean serum thyrotrophin concentration and the 95% confidence intervals for older individuals (1.45mIU/L; 95% CI 0.54-3.9) did not differ significantly from that in middle aged individuals (1.24mIU/L; 95% CI 0.29-5.4). The investigators therefore concluded that one reference range is appropriate for all age groups. [73] The development of age-specific reference ranges would cause additional problems, with screening of more individuals being required in order to obtain a suitable reference sample. Equally, extrapolation of data from such a selected population may also be inappropriate. [74,75]

2.5 Diagnosis of subclinical thyroid dysfunction in primary care

The definitive diagnosis of subclinical thyroid dysfunction is based upon the relationship between serum thyrotrophin and serum free thyroxine. Expert opinion and guidance recommends routine front line measurement of both serum thyrotrophin and free thyroxine concentration for patients without a previous thyroid function test on record and on all specimens where the request for thyroid function testing is not accompanied by any additional clinical details. [43] Estimation of FT3 is generally recommended when serum thyrotrophin concentration is below the lower threshold of the laboratory reference criteria and FT4 is greater than the higher threshold; however protocols for measurement of FT3 are laboratory specific and vary accordingly.

The annual cost of thyroid function testing in the UK is approximately £30 million. [76] Estimates suggest that one in four people in the UK have a thyroid function test annually with the majority of requests for thyroid function testing coming from primary care. Measurement of serum thyrotrophin concentration is reported to be one of the most frequently requested test by primary care physicians and repeat tests are frequent despite normal initial findings. [77,78] In view of the high prevalence of thyroid dysfunction in the general population and the wide availability of cost-effective and sensitive assays for measurement of thyroid dysfunction this level of testing may seem justified. There have however been suggestions that the associated diagnostic yield is low. Meyerovitch et al examined data from a large health care database in order to determine the use of routine tests of serum thyrotrophin concentration by primary care physicians over a period of five years. Findings demonstrated an increased rate of testing with advancing age and an average frequency of three repeat requests for measurement of serum thyrotrophin per person during the five

year period. [79] Furthermore, 95% of the initial tests were within the reference range and remained so throughout the five year study period. More recently, a small retrospective observational study and survey of general practitioners in the UK reported variability across 19 primary care practices with respect to testing and treatment of subclinical thyroid dysfunction. This study suggested that thyroid function testing is being requested frequently and repeatedly for elderly individuals based upon presentation with a variety of non specific symptoms. [80] Equally, administration of thyroxine therapy was described in elderly individuals presenting with and without symptoms after one thyroid function test result. [80] Similarly, a survey assessing the procedural options most frequently followed and the difficulties encountered by GPs suggested that development of standardised protocols is necessary to aid GP testing and management of subclinical thyroid dysfunction. [81]

2.6 Current management strategies

In terms of frequency of thyroid function testing, expert opinion from the UK Association for Biochemistry (ACB), the British Thyroid Association (BTA) and the British Thyroid Foundation (BTF) suggest repeat testing to confirm subclinical hyperthyroidism if initial serum thyrotrophin is below 0.1mIU/L and after exclusion of interference from concomitant non thyroidal illness or medication. Monitoring on a 6-12 monthly basis is also advocated. [71] Repeated thyroid function testing should, however be requested based upon the clinical presentation with earlier repeat testing being conducted in elderly individuals and subjects with vascular disease.

Successful treatment of overt thyroid dysfunction requires normalisation of thyroid hormone concentration in peripheral tissues. In overt hypothyroidism this is achieved through administration of thyroxine replacement therapy. Similarly, overt

hyperthyroidism is readily treated with anti thyroid therapy often in combination with thyroidectomy or radioiodine therapy. [82,83] Whilst treatment of abnormal thyroid hormone levels in overt thyroid dysfunction is generally accepted, the threshold and indications for treatment of subclinical dysfunction is an unresolved issue due to a lack of evidence pertaining to the clinical impact of these disorders and the benefits associated with treatment. [68,76,84] This is particularly so in the elderly in whom the burden of other existing chronic disease and polypharmacy is common. [85,86] In terms of treatment of subclinical hypothyroidism, expert opinion recommends treatment of individuals with a serum thyrotrophin concentration >10mIU/L. [87] Treatment for milder subclinical hypothyroidism (4.5-10mIU/L) remains controversial with frequent monitoring being preferential. Similarly, the benefits of treating subclinical hyperthyroidism particularly in older individuals are uncertain.[88] Recent recommendations from a panel of experts suggest treatment of endogenous subclinical hyperthyroidism in the presence of serum thyrotrophin concentration of <0.1 mIU/L, [71] particularly, in individuals aged 60 years of age or more with clinical symptoms or at increased risk for heart disease and osteoporosis. The panel did not however recommend routine treatment in individuals with serum thyrotrophin concentration of between 0.1–0.45mIU/L regardless of expression of symptoms.

Another controversial aspect of subclinical thyroid dysfunction is with regard to routine screening. In view of the high prevalence of subclinical thyroid dysfunction in the general population some advocate routine screening. [55,89] Others argue however that screening programmes cannot be justified because the associated clinical burden of subclinical thyroid dysfunction is unknown and there is no robust evidence to demonstrate that early diagnosis and treatment in the subclinical phase improves clinical outcomes. [67,90] The American Thyroid Association (ATA) has recommended

initial screening of men and women at 35 years of age and every five years there after. In contrast, the America Association of Clinical Endocrinology (AACE) supported only screening of elderly women. [87] A more recent joint statement from a conference between the various US based professional organisations agreed that current data are insufficient to advocate population based screening due to the uncertainty with regard to the benefits of early treatment, although aggressive case finding in those aged 60 years or more is promoted. [87]

Summary of chapter 2

The current chapter introduced and clarified the biochemical distinction between overt and subclinical thyroid dysfunction and provided an overview of the aetiology and prevalence of subclinical hyperthyroidism and subclinical hypothyroidism. Subclinical thyroid dysfunction is a common disorder frequently encountered in primary care. It seems that despite numerous guidelines and position papers, testing, treatment and management of subclinical thyroid dysfunction remains largely intuitive and non evidence based. This is mainly due to a lack of consensus with regard to the clinical burden and importance of these conditions in individuals with subclinical thyroid dysfunction. For some authors, subclinical thyroid dysfunction represents a well characterised condition which requires treatment. For others, it is essentially a laboratory diagnosis. It seems reasonable to propose that as the degree of thyroid dysfunction increases, the clinical expression and pathophysiological consequences become more prominent. It is therefore equally reasonable to assume that milder symptoms and less severe adverse health consequences are evident in individuals with subclinical thyroid dysfunction compared with individuals with overt thyroid dysfunction. Primary care clinicians would benefit from further clarification and guidance in relation to these issues. The aim of the next four chapters is to clarify further the pathophysiological consequences and clinical presentation of subclinical hypothyroidism and subclinical hyperthyroidism with reference to current evidence.

Overview of chapters 3-6

The aim of the next four chapters is to clarify the clinical importance and relevance of subclinical thyroid dysfunction with reference to the current evidence base drawing on the range of published literature within the field. The results of the literature searches will be divided into four subject areas and summarised in the following four chapters.

In chapter 3 and 4, data related to the clinical signs and pathophysiological consequences of subclinical hypothyroidism and subclinical hyperthyroidism respectively are presented and summarised. Chapters 5 and 6 present and summarise data pertaining to expression of symptoms in subclinical hypothyroidism (chapter 5) and subclinical hyperthyroidism (chapter 6) respectively. For the purposes of this thesis, clinical signs are defined as clinical anomalies that are evident on physical examination or assessment by a clinician and include indicators of anxiety, depression and cognitive dysfunction. In contrast, symptoms are defined as clinical changes that are perceptible and apparent to the individual. Similarly, the concept of perceived health status deals with patients' experiences and the impact of disease on everyday life. As such, this is best assessed by patients themselves. Data related to general well being and quality of life will be considered alongside symptoms data.

Initially in Chapter 3 the methodology and results of the literature searches conducted to identify evidence related to the adverse consequences of subclinical hypothyroidism and subclinical hyperthyroidism will be reported. A critical appraisal of a key, recent systematic review collating and examining the data pertaining to the clinical consequences and prognostic implications of subclinical thyroid dysfunction will follow.

CHAPTER 3 PATHOPHYSIOLOGY OF SUBCLINICAL HYPOTHYROIDISM

Overview of chapter 3

It is clear from chapter 1 that overt thyroid dysfunction is associated with significant morbidity and that whilst the symptoms associated with overt thyroid dysfunctions are well established, their clinical presentation is variable. Given the definition of subclinical hypothyroidism it seems reasonable to assume that it is a mild form of overt hypothyroidism and as such is associated with similar, albeit less severe adverse health outcomes.

3.1 Aim of literature review

The aim of the literature search was to identify all research related to investigation of the clinical signs, symptoms and adverse consequences of subclinical hypothyroidism and hyperthyroidism.

3.1.1 Search strategy

A systematic search of the bibliographic database PubMed (which provides access to bibliographic information that includes MEDLINE) was conducted using the medical subject heading terms (MeSH terms) and limited to adult humans. No restrictions were applied to publication date. The initial searches were performed during February 2009. These searches were repeated periodically in order to capture any newly indexed publications, with the final literature search being conducted on 25th January 2011.

Two search strategies were used. Initially each of the search terms were explored independently (Appendix 1 *Electronic search strategies*). In the subsequent searches, each term was systematically combined with the MeSH term 'subclinical hypothyroidism' and re-run. Publications retrieved through the combined searches were saved to file and exported to a reference manager database. Similarly, the second search strategy systematically combined each search terms with the MeSH term 'subclinical hyperthyroidism'. (Appendix 1 *Electronic search strategies*).

3.1.2 Inclusion and exclusion criteria

Publications were included where the primary aim of the study, systematic review or meta analyses was related to the investigation and evaluation of the detrimental health consequences of subclinical thyroid dysfunction. Review papers were excluded if they were non-systematic. Case studies, letters, discussion and position papers were also excluded. Literature related to subclinical thyroid dysfunction in pregnant or post natal women, individuals with drug-induced subclinical thyroid dysfunction or in cohorts defined by a specific chronic condition or medical history (for example a cohort with type 2 diabetes or dementia) were excluded. Furthermore, randomised controlled trials and trials investigating clinical interventions were excluded.

Two reference manager databases were constructed. One comprised the search results for subclinical hyperthyroidism, the other comprising publications contributing data relevant to detrimental health consequences of subclinical hypothyroidism. Where papers reported both, they were filed to both databases. Within each of the databases a search was conducted to identify and remove duplicate publications.

Identification of a recent, systematic review by Biondi et al published in 2008 indicated that significant work had already been undertaken in identifying and summarising the consequences of subclinical thyroid dysfunction. It was therefore determined that this paper would be formally appraised and if deemed to be of high quality would form the core of the current review, supplemented by subsequent evidence retrieved. [91]

Critical appraisal of this publication was undertaken in accordance with the standard checklist from the Critical Appraisal Skills Programme (CASP). [92] Critical appraisal indicated that the Biondi et al review was particularly pertinent to the focus of the current chapter, had been rigorously conducted and was of high quality. In this review, Biondi et al identified, collated and examined all high quality studies published between 1970 and April 2007 pertaining to the clinical consequences and risks associated with subclinical hyperthyroidism and subclinical hypothyroidism. The stated aim of the review was to answer seven questions; each question was clearly focused and the authors reported that the quality of the studies included had been critically assessed by two reviewers and all studies were of high quality. Whilst the search strategy was comprehensive, the inclusion and exclusion criteria for the articles retrieved were not explicit. It is not possible to rule out selection and publication bias as only English language studies were included. Furthermore, whilst the electronic searches were comprehensive, it was not explicit as to whether supplementary hand searches of additional materials were conducted. Hence, the Biondi review was considered to be a key publication and only data reported in meta analyses or systematic reviews or research papers published subsequent to this review were regarded as pertinent to the rationale of the current chapter.

The identification of this key systematic review meant that it was necessary to identify and review all relevant articles published prior to April 2007 that were not cited by Biondi et al, and all relevant articles published subsequent to this review. In order to ascertain whether the literature reviewed by Biondi et al was appropriate and comprehensive, the list of articles retrieved from the PubMed searchers was cross referenced with the articles cited in the review. Additional exploration of studies that had previously been reviewed by Biondi et al was considered unnecessary and therefore these articles are not examined further within the current chapter.

3.1.3 Application of the inclusion/exclusion criteria

The search strategy used to identify publications related to subclinical hypothyroidism retrieved 513 articles (Figure 3.0). Further details of the subclinical hyperthyroidism search results are reported and discussed in chapter 4.0. The abstracts of all retrieved articles were screened to assess the inclusion/exclusion status of each publication. Application of the inclusion/exclusion criteria led to the exclusion of 396 of the articles retrieved from the subclinical hypothyroidism search strategy. The reasons for exclusion are listed in table 3.0. A considerable number of retrieved articles (n=115) were excluded from discussion in the current chapter because the studies were unrelated to investigation of the detrimental effects of subclinical hypothyroidism. A large proportion of reviews were also excluded as they were not systematic in their approach (n=77) or the subject of the review was treatment for subclinical thyroid dysfunction or the study employed an intervention (n=88). A further 62 duplicate articles were excluded because they had been included in the systematic review by Biondi et al and as such would not contribute additional data for examination within the scope of the current chapter.

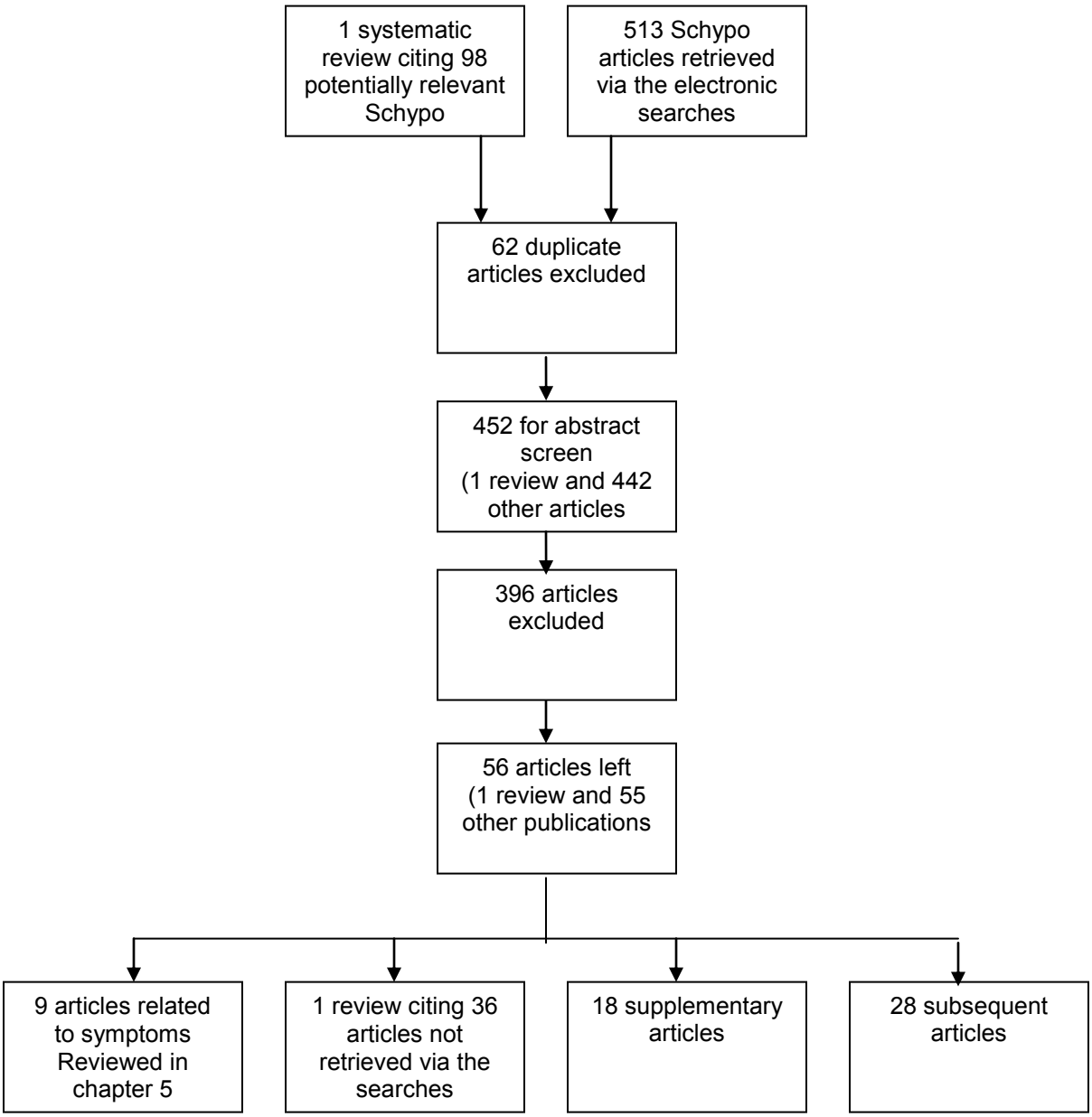
Table 3.0 Exclusion of articles; subclinical hypothyroidism

Reason for exclusion of retrieved publications	Number of articles
Not related to adverse consequences	115
Non systematic reviews	77
Studies of intervention/ RCT/ reviews of treatment	88
Diseased populations	52
Research in children	17
Case studies	15
Pregnant and post natal women only	11
Letters	8
Superseded systematic review and meta analyses	6
Discussion paper/ editorial	5
Included in analyses on mortality	1
Non human subject	1
Total number of articles excluded	396

A large body of the literature retrieved focused upon subclinical hypothyroidism in specific population subgroups with significant disease. Fifty two such articles were retrieved to include studies showing an association between subclinical hypothyroidism and an increased risk of nephropathy and cardiovascular disease in type 2 diabetic patients, [93] insulin resistance in individuals with rheumatoid arthritis [94] and elevated total cholesterol and low-density lipoprotein cholesterol concentrations in cardiology patients. [95] Further examination of this literature has not been undertaken however because the principal focus of this chapter is exploration of the adverse health consequences of subclinical hypothyroidism in a wide ranging, 'normal' population. Despite the application of limits restricting the searches to studies of adult humans it was also necessary to exclude 17 studies of subclinical thyroid dysfunction in children and adolescents and one animal study. Furthermore, 15 case studies, 11 studies of subclinical thyroid dysfunction in pregnancy, eight letters, six superseded systematic reviews and meta analyses and five discussion papers are not examined further within this chapter.

The 46 remaining supplementary articles comprised, the recent systematic review by Biondi et al, 18 articles pre-dating but not cited in the Biondi review and 28 articles post dating the Biondi review (Figure 3.0). The findings of these supplementary and subsequent studies are presented and summarised alongside the conclusions drawn by the Biondi review. Throughout the current chapter, the terminology ‘supplementary’ and ‘subsequent’ will be applied to publications that either pre or post date the systematic review by Biondi et al respectively and the terminology ‘Biondi et al’ will be used to denote the systematic review.

Figure 3.0 Flow diagram: literature related to subclinical hypothyroidism



3.2 Pathophysiological consequences of subclinical hypothyroidism

3.2.1 Cardiovascular risk and subclinical hypothyroidism

Cardiovascular risk is an important consideration for decision making with respect to thyroid function testing, management and treatment of subclinical hypothyroidism. Similar effects on the cardiovascular system have been observed in overt and subclinical hypothyroidism. Based upon evidence available between 1970 and April 2007, Biondi et al reported major discrepancies in data related to cardiovascular risk. Supplementary and subsequent data investigating the relationship between subclinical hypothyroidism and cardiovascular risk do not generally support an association with hypertension. One supplementary cross-sectional exploration of the prevalence of hypertension in a random sample of 257 women aged 50 years or more failed to demonstrate an association between subclinical hypothyroidism and increased risk of hypertension. [96] Similarly, the subsequent Suita study, a large cross-sectional investigation of cardiovascular parameters in a community dwelling Japanese population found no association between subclinical hypothyroidism and hypertension. [97] However, two subsequent cross-sectional studies based in China report contradictory findings. One study of 5669 community dwelling adults demonstrated similar systolic blood pressure, diastolic blood pressure, and pulse pressure in individuals with subclinical hypothyroidism compared with euthyroid individuals after adjustment for age, gender, body mass index (BMI), and smoking status. Sensitivity analysis excluding patients receiving anti hypertensive medication showed similar results. [98] In contrast, the more recent cross-sectional study of 1319 adults aged between 18-85 years demonstrated a

modest yet statistically significant increased likelihood of hypertension in individuals with subclinical hypothyroidism compared with euthyroid subjects (OR 1.7, 95% CI 1.06-2.88, p<0.027). [99] Although the statistical analysis adjusted for age, gender, smoking status and BMI, the results may have been affected by the inclusion of participants receiving antihypertensive medication (Table 3.1).

In general, data supplementary to Biondi et al derived from population based studies do not support an association between subclinical hypothyroidism and hypertension. This evidence is however limited by the cross-sectional study designs and additional prospective, longitudinal studies are required to further clarify the relationship between subclinical hypothyroidism and hypertension.

Table 3.1 Subclinical hypothyroidism and hypertension

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Akbar DH [96] 2004 Saudi Arabia	Case control Outpatients	Random sample of 257 women aged >50 years 90 Schypo	Known thyroid dysfunction, history of neck irradiation, chronic disease, medication known to interfere with TFT	TSH 0.27-4.2 FT4 12-22	Hypertension, systolic blood pressure, diastolic blood pressure	No association with BMI, and hypertension
Takashima N [97] 2007 Japan	Cross sectional, Community	Adults n=3607 377 Schypo 3130 Euth	Patients treated for thyroid dysfunction	TSH 0.43- 3.78 FT4 12.87-21.9 Single TFT	IMT surrogate marker of atherosclerosis Glucose metabolism – Fasting blood glucose (FBG) and lipid metabolism	No association with hypertension, or IMT Associated with increase in FBG
Duan Y [98] 2009 China	Cross sectional, Community	Adults 806 Schypo 5669 Euth	Systemic disease, pregnancy, medicines known to interfere with TF	TSH 0.4-4.5 FT4 10.3-24.5 Single TFT	Hypertension, systolic blood pressure, diastolic blood pressure	No association with blood pressure
Lui D [99] 2010 China	Cross sectional survey Community	Adults, 18-85 yrs 93 Schypo 1226 Euth	History of thyroid disease, overt thyroid dysfunction, medication affecting thyroid function, pregnancy, diabetes,	TSH 0.3-4.8 FT4 10.3-24.5 Single TFT	Hypertension	Moderately icreased risk of hypertension in Schypo (OR 1.5, 95% CI 1.06-2.88, p<0.027)

Mechanisms for an association between subclinical hypothyroidism and hypertension, have been proposed based upon evidence of increased arterial stiffness, increased peripheral vascular resistance and endothelial dysfunction in individuals with subclinical hypothyroidism. One small supplementary case control study reported impaired endothelial function. [100] Cikim et al reported significantly lower values of flow mediated dilation in 25 individuals with subclinical hypothyroidism compared with 23 euthyroid controls after reactive hyperaemia. [100] Disparate findings were reported in two subsequent studies in which peripheral endothelial function was assessed in response to reactive hyperaemia. [101,102] In a subsequent study of flow mediated vasodilatation of the brachial artery in 21 Brazilian females with subclinical hypothyroidism compared with 21 euthyroid controls, endothelial dysfunction was not apparent. [102] Likewise, no differences in endothelial function were detected in 18 females with subclinical hypothyroidism compared with 22 female controls in a supplementary study conducted by Dagre et al. [101] More recently, anomalies in endothelial function that could be indicative of early vascular disease were described following investigation of 20 young and middle aged women with subclinical hypothyroidism and 15 euthyroid controls. In this study, significantly reduced coronary blood flow velocity in the distal left anterior descending artery was observed after sympathetic stimulus using the cold pressor test. [103] Conversely, impaired microvascular function as assessed by coronary flow reserve was described in one supplementary case control study of 50 adults with subclinical hypothyroidism compared with 30 euthyroid controls. [104] Other indicators of atherosclerosis have also been widely studied in individuals with subclinical hypothyroidism. Carotid artery intima media thickness is another useful marker of

atherosclerotic vascular changes that has frequently been used as a cardiovascular endpoint. Biondi et al describe two studies demonstrating significantly increased carotid artery intima thickness in individuals with subclinical hypothyroidism compared with controls. [105,106] In contrast, three supplementary case control studies conducted in the outpatient setting did not corroborate these findings and failed to demonstrate significant differences in carotid artery intima media thickness in cases of subclinical hypothyroidism compared with euthyroid controls. [100,102,107] No association between subclinical hypothyroidism and carotid artery intima-media thickness was observed in an investigation of cardiovascular parameters in 377 community dwelling individuals with subclinical hypothyroidism and 3130 euthyroid individuals. [97] Comparable findings were reported following ultrasound evaluation of the walls of the common carotid, the internal and external carotid and the carotid bifurcations in 2184 subject aged over 45 years. In this population based sample, subclinical hypothyroidism was not associated with carotid artery plaques at any location (Table 3.2). [108]

In terms of arterial stiffness, an established independent predictor of hypertension and coronary artery disease, the evidence generally supports an association between subclinical hypothyroidism and arterial stiffness. Further to the review by Biondi et al, two studies evaluating pulse wave velocity, (a parameter known to represent arterial stiffness) were identified. [105,109] Hamano et al evaluated brachial-ankle pulse wave velocity (baPWV) in 28 individuals with subclinical hypothyroidism, seven individuals with overt hypothyroidism and healthy age matched controls. [109] Increased arterial wall stiffness was evident in both the overt and subclinical individuals compared with the controls. Another subsequent case control study further supports and extends these

findings. [105] This study by Nagasaki et al aimed to establish the affect of subclinical hypothyroidism on arterial stiffness in different arterial segments. Central pulse wave velocity (in heart-femoral segments) and peripheral pulse wave velocity (in femoral-ankle segments) were evaluated in 40 individuals with subclinical hypothyroidism and 50 euthyroid controls. Significant increases in both parameters were described in individuals with subclinical hypothyroidism compared with euthyroid controls suggesting that arterial stiffening of the aorta in addition to the peripheral arteries is present in subclinical hypothyroidism. [105] Both of these studies were conducted in a small sample of Japanese subjects and it remains to be seen whether these data can be extrapolated to other populations (Table 3.2).

In summary, studies to date consistently demonstrate a significant increase in arterial stiffness in individuals with subclinical hypothyroidism compared with euthyroid controls. It is therefore possible that increased arterial stiffness is an additional cardiovascular risk factor in individuals with subclinical hypothyroidism. Additional larger studies are required to determine the external validity of these findings and the potential for extrapolation to other populations. Whether abnormalities in endothelial function occur in subclinical hypothyroidism and augment cardiovascular risk remains to be elucidated. Subsequent study findings both contradict and extend the conclusions drawn by Biondi et al with respect to the association between subclinical hypothyroidism and increased intima media thickness. The Suita study provides good evidence that subclinical hypothyroidism is not associated with increased carotid intima media thickness. On this basis it is reasonable to conclude that subclinical hypothyroidism does not contribute to an increased risk of atherosclerosis. Studies to date are however limited by their cross-

sectional design and by the fact that duration of subclinical hypothyroidism is unknown. It is therefore possible that these cardiovascular parameters are modified over time and become cardiovascular risk factors in individuals with more established subclinical hypothyroidism.

Table 3.2 Subclinical hypothyroidism and other cardiovascular risk factors

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Cikim AS [100] 2004 Turkey	Case control Outpatients	25 Schypo 23 Euth controls matched for smoking, hypertension, CV disease	Atherosclerosis, other cardiovascular disease that could affect endothelial dysfunction, postmenopausal	TSH 0.27-4.2 FT4 11-22	Endothelial function via flow mediated dilation (FMD)	Significantly lower FMD in Schypo (10.68 vs 15.92, p <0.05)
Hamano K [109] 2005 Japan	Outpatients	28 Schypo 28 Age matched euthyroid controls	Not explicit	TSH not explicit FT4	Pulse wave velocity (PWV) as an indicator of arterial stiffness and total cholesterol	Schypo associated with arterial wall stiffness
Tanaci N [110] 2006 Turkey	Case control Outpatients	Female 15 Schypo, 11 BMI, age matched Euth control	Chronic disease, alcohol, drugs abuse lipid lowering medication or known to interfere with TFT	TSH >5.0 FT4	C reactive protein, or homocysteine, glucose or lipids	No difference in any parameters studied
Almeida CA[107] 2007 Brazil	Case control Cross sectional Outpatients	Women, middle aged, 30 Schypo 27 controls	History of TD, treatment for TD, CV disease, hypertension, diabetes and smoking	TSH 0.4-4.0 FT4 10.3-23.2	Ultrasonography of carotid arteries	No significant differences
Baycan S [104] 2007 Turkey	Case control Outpatients	50 Schypo 30 Euthyroid controls	CV disease, alcohol, smoking, chronic disease, medication known to interfere with TD	TSH >4.0 FT4 not explicit	Coronary flow reserve (CFR)	CFR significantly decreased in Schypo 2.23 vs 2.98, p<0.001

Table 3.2 continued

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Dagre AG [101] 2007 Greece	Case control Outpatients	Female Adults 18 Schypo 22 controls	Evidence of CV disease	TSH 0.3-3.7 FT4 4.1-15.8	Endothelial function	No difference in any phase of reactive hyperaemia
Nagasaki T[105] 2007 Japan	Cross sectional, Population based Outpatients	40 Schypo 50 control	Atherosclerosis, chronic disease, medication known to interfere with TF, positive anti thyroid antibody	Not explicit Repeat TFT 1 monthly interval	Central, peripheral pulse wave velocity (PWV) and brachial ankle (ba) PWV and lipid profiles	Significant differences in triglyceride, High density lipoprotein cholesterol (HDL-c), central, peripheral PWV and baPWV significantly increased
Dorr M [108] 2008 Germany	Random sample of 292	>45 years 63 Schypo 1839 Euth	Known or possible thyroid disease	TSH 0.25-2.12 FT4 not explicit	Carotid plaque at 4 locations	No association with carotid plaque using ultrasound or prevalence of stroke self reported physicians diagnosis
Toruner F [112] 2008 Turkey	Case control Outpatients	38 Schypo 44 control	Chronic disease or thyroid medication	TSH not explicit FT4 not explicit	Lipid parameters	Significantly increased total cholesterol, low density lipoprotein cholesterol (LDL-c) and triglyceride concentrations (TG), $p<0.05$

Table 3.2 continued

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Biondi B[103] 2009 Italy	Case control Outpatients	Middle aged, women 20 Schypo 15 controls	Smokers, concomitant vasoconstructive drugs, obesity and dyslipidemia	TSH 0.27-4.2 FT4 12-22 Single TSH	Doppler echo and coronary flow reserve (CFR) after cold pressor test. Multiple measures	E velocity significantly increased (185 vs 169). IVRT (ms) p<0.05 87 vs 74. CRF 1.4 Schypo vs 2 Euth p<0.001
Cabral MD[102] 2009 Brazil	Case control Outpatients	Adult women 21 Schypo 21 controls matched for BMI, age and CV risk	Alcohol use, concomitant illness or medication that could interfere with TF, lipoprotein or endothelial function.	TSH 0.4-4.0 FT4 10.3-24.5	Flow mediated vasodilatation of brachial artery, carotid intima media thickness, lipid parameters	No significant differences between Schypo and euthyroid in any parameters measured.

3.2.2 Traditional cardiovascular risk factors

Whilst plasma lipid profiles have been widely studied, Biondi et al report conflicting data regarding the relationship between lipid profiles and subclinical hypothyroidism. Similarly, supplementary and subsequent data are contradictory. Some studies support an association between subclinical hypothyroidism and abnormal lipid and lipoprotein profiles, [113,114,115] whilst others report similarities in these parameters in individuals with subclinical hypothyroidism compared with euthyroid controls. [102,107,110,116] A large cross-sectional study of 66260 adults in Korea reported significant differences in total cholesterol (TC) and low density lipoprotein cholesterol (LDL-c) between subclinical hypothyroidism and euthyroid groups. [113] Whilst the authors concluded that the observed elevations in these atherogenic parameters lend support to calls for screening and treatment of subclinical hypothyroidism, the degree of elevation demonstrated was small and unlikely to be clinically significant (TC 201.9 ± 39.9 mg/dl versus 197.1±36.3 mg/dl respectively, $p<0.05$; LDL-c 123.7±31.5 mg/dl versus 121.5 ±31.2 respectively, $p<0.0001$) (Table 3.3). Conversely, another large cross-sectional investigation of lipid parameters in a community dwelling adult Japanese population found no association between subclinical hypothyroidism and total cholesterol, high-density lipoprotein cholesterol or triglyceride levels. [97] The discrepancies between these studies may be explained by a lack of adjustment for common confounders and possible inclusion of patients receiving medication for thyroid dysfunction in the Korean study. In a smaller study increased postprandial serum triglyceride concentrations were observed in 15 females with subclinical hypothyroidism compared with 12 age and gender matched euthyroid controls. However these differences were not statistically significant. [110]

Similarly, higher serum concentrations of triglyceride and low density lipoprotein cholesterol and lower concentrations of high density lipoprotein cholesterol observed in 40 cases compared with 30 euthyroid controls failed to reach statistical significance. [102] Likewise, Almeida et al reported no differences in these lipid parameters between 30 female cases and 30 gender matched controls. [107] In contrast, four small studies demonstrated statistically significant differences in some of these parameters in individuals with subclinical hypothyroidism compared with euthyroid subjects. [112,114,115] One study described a significant association between subclinical hypothyroidism and total cholesterol, low density lipoprotein cholesterol and triglyceride concentration when comparing these parameters in 23 cases with 26 female euthyroid controls. Likewise, Erdem et al observed a significant increase in each of these parameters and a significant decrease in high density lipoprotein cholesterol in 40 cases compared with 31 matched controls. [114] In another small case control study, total cholesterol, triglyceride and total cholesterol/high density lipoprotein cholesterol ratio were significantly higher in 30 cases compared with 20 euthyroid controls. [115] Four of the smaller studies also evaluated serum concentrations of lipoprotein A, another marker for assessing risk of atherosclerosis. [100,107,110,112] All four studies demonstrated similar serum concentrations of lipoprotein A in individuals with subclinical hypothyroidism compared with euthyroid subjects.

In terms of the relationship between lipoprotein A and subclinical hypothyroidism, supplementary data fully support the findings of Biondi et al and demonstrate that subclinical hypothyroidism is not associated with abnormalities in lipoprotein A concentration. With respect to other lipid parameters, the data is contradictory. Whilst

the current literature review includes two large population based studies evaluating lipid parameters and Bondi et al provide data from six such studies, no two studies demonstrate the same collection of significant changes in association with subclinical hypothyroidism. In general, where statistcally significant differences in lipid parameters have been observed, the magnitude of change is small and unlikely to be clinically significant at the individual patient level. The clinical impact of subclinical hypothyroidism on lipid metabolism and risk of atherosclerosis requires further clarification in prospective population based studies.

Table 3.3 Subclinical hypothyroidism and traditional cardiovascular risk factors

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Jung CH [113] 2003 Korea	Cross-sectional Population based	375 Schypo 65017 Euth	None	TSH 0.25-5.0 FT4 9.0-25.7	Lipid parameters	Schypo associated with increased triglyceride (201.9 vs 197.1, p<0.015), LDL-c (123.7 vs 121.5, p<0.0001)
Al-Tonsi AA[116] 2004 Egypt	Case control Outpatients	16 Schypo, 16 gender, age matched Euth control	Metabolic disease or medication or hormonal treatment	TSH 0.4-4.6 FT4 4.5-11.7	Lipid parameters	No significant differences in lipid or phosphate concentrations in Schypo compared with 16 controls
Pesic M [115] 2007 Serbia	Case control Outpatients	30 Schypo 20 controls	History of thyroid dysfunction	TSH >4.5 FT4 normal	Lipid parameters	Schypo associated with higher triglyceride and total cholesterol
Erdem TY [114] 2008 Turkey	Case control Outpatients	Women 40 Schypo 31 matched control	Medication known to interfere with thyroid dysfunction	Not explicit	Plasma viscosity	Plasma viscosity significantly decreased

3.2.3 Subclinical hypothyroidism and novel cardiovascular risk factors

More recently, an association between subclinical hypothyroidism and novel cardiovascular risk factors such as homocysteine, C-reactive protein and various coagulation and metabolic parameters have been proposed. With respect to concentrations of homocysteine, Biondi et al describe consistent evidence demonstrating no association between subclinical hypothyroidism and hyperhomocysteinemia. Accordingly, two supplementary studies were also unable to corroborate suggestions that atherogenicity in subclinical hypothyroidism is mediated by abnormal concentrations of homocysteine. [113,117] Turhan et al describe similar concentrations of total plasma homocysteine in 53 individuals with subclinical hypothyroidism compared with 50 euthyroid controls. [117] These findings were corroborated by Jung et al in a cross-sectional study of 66260 adults in Korea. [113] Additionally Jung et al evaluated concentrations of high sensitivity C-reactive protein in individuals with subclinical hypothyroidism and euthyroid subjects and failed to demonstrate significant differences between the groups.

Based upon data from one large population based study and six smaller studies, Biondi et al report significant differences in various coagulation parameters in individuals with subclinical hypothyroidism compared with euthyroid subjects. Accordingly, two supplementary case control studies demonstrated significantly increased mean platelet volume in association with subclinical hypothyroidism. [118, 119] Additionally, Erikci et al reported a significantly higher platelet distribution width in cases of subclinical hypothyroidism compared with controls. [119] In contrast, a third supplementary study described significantly decreased serum concentrations of soluble CD40 ligand, (a

protein expressed mainly by activated platelets) in 22 individuals with subclinical hypothyroidism in comparison to 22 age matched controls (8.24 versus 9.86 ng/ml respectively, $p<0.001$). [120] Elevated levels of sCD40 ligand have been shown to be associated with increased risk of cardiovascular disease. [121]

Another biochemical marker for cardiovascular risk that has recently been associated with subclinical hypothyroidism is retinol binding protein-4 (RBP4). Elevated levels of retinol binding protein-4 have been shown to be positively correlated with insulin resistance, obesity, diabetes mellitus, and cardiovascular disease. [122] In this evaluation of cardiovascular risk factors in 217 randomly selected elderly individuals by Choi et al, 40 patients with subclinical hypothyroidism had significantly greater plasma RBP4 concentrations in comparison with 177 euthyroid individuals. The authors concluded that RBP4 concentration could be used as an index of cardiovascular risk in individuals with subclinical hypothyroidism. However, the clinical significance of elevated RBP4 requires further clarification since it is not known whether increased plasma RBP4 concentrations are a cause or a consequence of subclinical hypothyroidism. [122] In terms of metabolic syndromes, a small case control study demonstrated a significant association between insulin resistance and subclinical hypothyroidism. [123] In contrast, a large cross-sectional investigation (n=3607) of cardiovascular and metabolic parameters in community dwelling Japanese adults found no association between subclinical hypothyroidism and glycosylated haemoglobin. Significantly lower fasting glucose levels were however reported in individuals with subclinical hypothyroidism compared with euthyroid individuals. Once again, the differences observed were small and unlikely to be clinically important. [97] No other differences in cardiovascular or metabolic parameters existed

between the groups. Based upon alterations in glucose metabolism alone, the outcomes suggest that treatment of subclinical hypothyroidism is not warranted (Table 3.4).

In summary, various novel risk factors for cardiovascular disease have been investigated in relation to subclinical hypothyroidism. Supplementary and subsequent literature fully support the findings of Biondi et al and suggest that altered coagulation parameters occur in subclinical hypothyroidism which may be important in the pathophysiology of atherothrombosis and coronary heart disease. The clinical significance of these small, yet statistically significant changes remains to be fully elucidated. Furthermore, these findings require replication reached by Biondi et al and demonstrate that subclinical hypothyroidism is not associated with homocysteine or C-reactive protein. These parameters have not been widely evaluated and available data are generally derived from small cohorts of health seeking individuals recruited from the outpatient setting. Supplementary data therefore cannot be extrapolated to other populations. These data are not robust enough to further reconcile the current disagreement as to whether concentrations of high sensitivity C-reactive protein and homocysteine are adversely affected in subclinical hypothyroidism. In conclusion, studies examining the relationship between subclinical hypothyroidism and novel cardiovascular risk factors do not provide compelling evidence to justify clinical intervention.

Table 3.4 Novel cardiovascular risk factors and subclinical hypothyroidism

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria	Measures	Outcome
Aldasouqi S [124] 2004 Saudi Arabia	Case control Outpatients	47 Schypo 50 Euth controls	Thyroid surgery or radioiodine treatment	TSH 0.27- 4.2 FT412-22	Homocysteine	No significant difference in homocysteine Schypo 7.44 vs Euth 7.22
Akinci B [125] 2007 Turkey	Case control Outpatients	25-62 years 22 Schypo 22 age, match controls	Alcohol, smoking, contraceptives, hormones, chronic disease, multivitamins	TSH>5 FT4 10.29-24.4	Platelet activity, CD40 ligand a protein expressed by activated	CD40 ligand significantly decreased Schypo vs control 8.24-9.86 ng/dl, p<0.001
Coban E [118] 2007 Turkey	Case control Outpatients	36 Schypo 20 age, gender, BMI controls	Hypertension, diabetes mellitus, smoking, alcohol consumption, systemic disease and medication affecting platelet and TD	TSH 0.27-1.2 FT4 0.93-1.7	Platelet activity	Mean platelet volume significantly increased iin Schypo compared with euthyroid 9.9 fl vs 9.2 fl,p <0.001
Choi SH [122] 2008 South Korea	Random sample 217 elderly population based cohort	Elderly 40 Schypo 177 Euth	Diabetes mellitus and dyslipidemia	TSH 0.4-4.1 FT4 9.0-23.2l	Retinal binding protein and lipid parameters	Schypo associated with elevated RBP4
Turhan S [117] 2008 Turkey	Case control Outpatients	53 Schypo 50 Age, gender, BMI matched euthyroid controls	History of thyroid dysfunction, medication known to interfere with TFT, chronic disease, smoking, familial hypercholesterolemia	TSH 0.35-4.94 FT4 9.0-19.0 Repeat TFT	Lipid parameters	No significant difference in homocysteine or lipid parameters

Table 3.4 continued

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria	Measures	Outcome
Ericki AA [119] 2009 Turkey	Case control Outpatients	47 Schypo 30 Euth	Known thyroid dysfunction and medication known to interfere with TFT	TSH>5 FT4 10.29-24.4	Platelet activity	Schypo significantly higher mean platelet volume
Maratou E [123] 2009 Greece	Case control Outpatients	13 Schypo 21 Euth	Concomitant medication, family history of diabetes	Not explicit	Insulin resistance	Association with insulin resistance and therefore associated disorders such as CVD

3.2.4 Subclinical hypothyroidism and cardiac structure and function

Based upon available data, Biondi et al propose a continuum of cardiac changes as grade of thyroid dysfunction increases from subclinical to overt hypothyroidism with left ventricular diastolic dysfunction being the most consistent cardiac aberration described in subclinical hypothyroidism. [91] They describe data concerning systolic function as less consistent however. Further to Biondi et al, two supplementary case control studies using tissue Doppler echocardiography to investigate cardiac function reported impaired right ventricular diastolic function. [125,126] Additionally, one small supplementary case control study described significant impairment in both systolic and diastolic function at rest in individuals with subclinical hypothyroidism. [127] In another subsequent case control study, significantly lower systolic and diastolic indices during exercise were reported in 25 newly diagnosed cases of subclinical hypothyroidism compared with 25 controls (Table 3.5). [128] In contrast, Iqbal et al published findings analysing data from the Tromso studies. [129] These studies employed two research methodologies; a large epidemiological study of thyroid function and left ventricular mass index and a nested case-control study with refined inclusion and exclusion criteria to minimise misclassification of thyroid function status and improve clinical relevance.

The epidemiological study of 2035 adults did not find any statistical or clinical association between thyroid category and left ventricular mass index using conventional and pulse wave tissue Doppler echocardiography. Similarly, the nested case control study of 204 subjects (subclinical hypothyroidism n=66) with two successive thyroid function tests indicating stable thyroid function over a 12 month period also failed to identify any differences between individuals with subclinical hypothyroidism and

euthyroid controls. [129] Abnormalities in cardiac conduction have also been described in subclinical hypothyroidism. Monzani et al described anomalies in myocardial contraction as indicated by prolonged pre ejection fraction (isometric systole) in 14 individuals with subclinical hypothyroidism. [130] In addition, impaired cardiac autonomic activity was reported by Sahin et al following assessment of heart rate variability in 31 individuals with subclinical hypothyroidism compared with 28 controls (Table 3.5). [131]

Cardiopulmonary dysfunction has been described in a subsequent small case control study using the treadmill cardiopulmonary test. A significantly slower recovery time after exercise in cases compared to controls was observed as indicated by a reduction in diastolic blood pressure between the first and third recovery minutes. [132] However, no abnormalities in blood volume or renal function however were reported in eight cases compared to eight controls in a similar supplementary study. [133] The influence of thyroid hormone on serum brain natriuretic peptide (BNP) concentration has also recently been investigated. Natriuretic peptides are produced predominantly in the heart and secreted in response to volume expansion and pressure overload with serum levels being predominantly elevated in systolic heart failure. However, a recent cross-sectional study of 150 outpatients in Turkey reported similar BNP levels in subclinical hypothyroidism and in euthyroid controls (Table 3.5). [134]

To summarise, some supplementary and subsequent data complement the findings of Biondi et al and describe adverse alterations in cardiac structure and impaired cardiac function in individuals with subclinical hypothyroidism. In general, these data come from small, underpowered studies employing numerous exclusion criteria and multiple outcome measures. Since these data have not been corroborated by more recent

epidemiological studies, it is difficult to conclude that subclinical hypothyroidism is associated with impaired cardiac structure and function.

Table 3.5 Subclinical hypothyroidism and cardiac function

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria	Measures	Outcome
Villabona C [133] 1999 Spain	Case control Outpatients	24- 54 years 8 Schypo 15 Euth	No oedema, weight gain, thyroid disease, medication containing iodine	TSH 1.4-4.5 FT4 5.46-12.48mg/100ml	Renal function, ERPF, GRF, circulated plasma volume, packed blood cell mass	No association of Schypo and blood volume or renal function
Kosar F [126] 2005 Turkey	Case control Outpatients	36 Schypo 28 Euth controls	Cardiovascular disease, systematic disease	TSH >4.4	PWTD for ventricular function	Impaired systolic and diastolic function
Sahin I [131] 2005 Turkey	Case control Outpatients	31 Schypo 28 control	Cardiovascular disease, other chronic disease, no medications in the last 2 weeks	TSH 0.4-4.3 FT4 within local reference range	Heart Rate Variability (HRV) used to asses autonomic function	Significantly reduced time and frequency domains in severe Schypo TSH>10 mIU/L
Zoncu S [127] 2005 Italy	Case control Outpatients	Schypo 22 Schypo 13 healthy euthyroid subjects	Not willing to consent	TSH 0.3-3.0 FT4 6.6-16pg/ml	Doppler echo, PWTDI	impaired systolic and diastolic function
Arinc H [126] 2006 Turkey	Case control Outpatients	Adults 63 Schypo 20 age matched Euthyroid	Chronic disease, obesity, alcohol users, smokers, familial hyperlipidaemia, drugs known to affect TF	TSH <5 FT4 10.3-24.5	Tissue doppler to investigate ventricular function	No changes in Schypo observed
Iqbal A [129] 2007 Norway	Population based health survey	Adults >24 n= 2035 118 TSH 0.4-5.25, 66 TSH>5.25	Known cardiovascular disease, valvular heart disease and receiving medication for hypertension	Reference range defined statistically based upon TSH distribution of the sample e.g TSH at 2.5- 97.5 percentiles 0.4- 5.25,No FT4	Left ventricular mass index, hypertension, diastolic blood pressure	Schypo not associated with any parameters

Table 3.5 continued

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria	Measures	Outcome
Iqbal A [129] 2007 Norway	Nested case control study Population based	Adults n=7954 162 Euthyroid 66 Schypo	Patients with historical or active coronary infarction, angina pectoris, stroke, TF4 outside reference criteria, and patients receiving treatment of hypertension or TD, over 80 years	TSH 0.5-3.49 FT4 9-22 Repeat TFT	Echocardiography (ECG) and pulse wave tissue doppler	
Mainenti MR [132] 2007 Brazil	Cross-sectional, Case control Outpatients	Adult women 30-60 years 15 Schypo 16 euthyroid controls matched for smoking and menopause	Drugs that interfere with TFT, presence of disease, MI in the last 3 months, pain or physical problems, hypertension, regular exercise	TSH >4.0 FT4 10.2-24.5 Repeat TFT	ECG, cardiopulmonary exercise test, blood pressure, heart rate, functional capacity	Exercise duration shorter and achieved lower peak workload in Schypo compared to controls (11.5% vs 19%, p<0.0004)
Ertugrul DT [134] 2008 Turkey	Cross sectional, case control, Outpatients	39 Schypo 33 euthyroid	Pregnancy or lactation, Chronic disease, alcohol, drug abuse, malignancy	TSH 0.45-4.5 FT4 not explicit Single TFT	BNP produced in ventricular myocardium = possible marker of cardiac dysfunction/damage	Schypo Brain natriuretic peptide (BNP) similar to controls
Akcakoyun M[128] 2009 Turkey	Case control Outpatients	25 Schypo 25 controls	Pregnancy, chronic disease, AF, medication known to alter heart rate and TFT	TSH 0.4- 4.0 FT4 0.8-1.9ng/ml	Mitral annular systolic and early diastolic velocities during exercise on tissue doppler echo	Systolic and diastolic indices significantly lower in Schypo

3.2.5 Heart failure and subclinical hypothyroidism

Based upon available data from one population based cohort aged 70-79 years, Biondi et al reported a possible link between individuals with subclinical hypothyroidism with serum thyrotrophin concentration greater than 7.0mIU/L and congestive heart failure. [135] Subsequent long term data on heart failure data further substantiate and extend these findings. A recent prospective, community based longitudinal study with approximately 12 years follow-up demonstrated a significantly greater incidence of heart failure in patients with serum thyrotrophin concentration greater than 10mIU/L compared with euthyroid controls. The incidence of heart failure in patients with a serum thyrotrophin concentration between 4.5-9.9mIU/L however was similar to the euthyroid group. Furthermore, two adverse electrocardiographic alterations associated with heart failure were found exclusively in the subclinical hypothyroidism group with serum thyrotrophin concentrations greater than 10mIU/L (Table 3.6). [136]

Table 3.6 Heart failure and subclinical hypothyroidism

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Rodondi N [136] 2008 Switzerland	Longitudinal population based cohort	>65 years n=3044 478 Schypo (n= 428 mild Schypo [4.5-9.9 mIU/L] and n=46 severe Schypo [>10 mIU/L]) 2526 Euth	Receiving treatment for thyroid dysfunction, corticosteroids, amiodarone. Known heart failure at baseline	TSH 0.4-4.5 FT4 9-22 Single TFT	ECG after 5 years and heart failure events during 15 year follow-up	Schypo with TSH >10mIU/L adjusted HR for heart failure 1.88, 95% CI 1.05-3.34.

3.2.6 Coronary heart disease and cardiovascular mortality

Much attention has focused upon the link between subclinical hypothyroidism and coronary heart disease. Biondi et al report an increased risk of coronary heart disease in individuals with subclinical hypothyroidism aged 70 years of age or less, no association in the 70-80 year age group and a possible protective effect in individuals over 80 years of age. [137, 138] More recently, in an attempt to further clarify the cardiovascular risk of subclinical hypothyroidism, the thyroid studies collaboration group analysed individual level patient data from 11 large cohort studies. Results demonstrated no significant impact of subclinical hypothyroidism on coronary heart disease events (harzard ratio (HR) 1.18, 95% CI 0.99-1.42) or on cardiovascular mortality (HR 1.14, 95% CI 0.99-1.32). After exclusion of individuals receiving treatment for thyroid dysfunction a modestly increased risk of coronary heart disease events (HR 2.17, 95% CI 1.19-3.93) was observed in individuals with more severe subclinical hypothyroidism characterised by serum thyrotrophin concentrations greater than 10mIU/L compared with euthyroid subjects. [139] Similarly, risk of cardiovascular mortality was slightly increased in individuals with severe subclinical hypothyroidism compared with euthyroid subjects (HR 1.85, 95% CI 1.13-3.05). As indicated by the relatively wide confidence interval, these data are limited due to the small number of coronary heart disease events (n= 29) and deaths related to cardiovascular disease (n=15) in subjects with serum thyrotrophin 10-19.9mIU/L. These associations did not differ significantly by age. Previously, data related to coronary heart disease and cardiovascular mortality were limited by differential measurement and adjustment of potential confounders across studies, an inability to disqualify selective reporting of outcomes, publication bias and bias associated with use

of aggregate data. Subsequent findings are based upon data at the individual patient level which are not subject to these limitations. These data provide good evidence that subclinical hypothyroidism is not associated with increased risk of coronary heart disease and cardiovascular mortality.

3.3 Bone turnover

While anomalies in bone turnover are generally linked to overt hyperthyroidism, two supplementary studies evaluating bone turnover in relation to subclinical hypothyroidism were retrieved. [140,141] One small all female case control study reported no association between subclinical hypothyroidism and any of the parameters that influence bone turnover. [142] Similarly, increased bone turnover was not significantly different in postmenopausal women with subclinical hypothyroidism compared with postmenopausal women with normal thyroid function. However, significant differences in parameters related to bone structure were described. [141] Biondi et al do not discuss bone turnover in relation to subclinical hypothyroidism (Table 3.7).

Table 3.7 Subclinical hypothyroidism and bone turnover

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Sekeroglu MR [142] 2006 Turkey	Case control Outpatients	Women Adults 16 Schypo 15 age matched controls	Inflammatory or autoimmune thyroid dysfunction	TSH and FT4 not explicit. Single TFT	Markers of bone metabolism to include cytokines interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α).	Schypo not associated with IL-6 and TNF-α
Nagata M [141] 2007 Japan	Case control Outpatients	50-87 years Post menopausal women 22 Schypo 24 control	Historical or current thyroid dysfunction, chronic renal failure, parathyroid or calcium related diseases, history of therapy with glucocorticoids, calcium or vitamin D.	TSH 0.05-4.0 FT4 not explicit	Structural strength of bone using quantitative ultrasound	No association with bone metabolism. Structural strength of bone significantly reduced in Schypo (2.15 vs.2.35 $p<0.001$)

3.4 Neuromuscular function and subclinial hypothryoidsm

In terms of neuromuscular function, Biondi et al describe five studies exploring a wide range of neuromuscular alterations in individuals with subclinical hypothyroidism compared with euthyroid subjects. On the whole, Biondi et al reported considerable disagreement between studies exploring biological parameters that reflect neuromuscular status and muscle metabolism either during or in response to exercise. Two supplementary studies evaluating neuromuscular alterations described a significantly higher prevalence of neuromuscular complaints in individuals with subclinical hypothyroidism compared with euthyroid controls (Table 3.8). [143,144] Furthermore, a greater frequency of reduced muscle strength assessed by an experienced physician using the manual muscle test was observed in those with subclinical hypothyroidism compared with euthyroid individuals. Since these two studies were conducted in an outpatient setting by the same research team and were relatively small (< 57 cases of subclinical hypothyroidism) the findings are unlikely to be applicable to other community dwelling or general populations (Table 3.8). Supplementary findings require replication in larger population based studies before the disagreements regarding the role of subclinical hypothyroidism in neuromuscular function can be reconciled.

Table 3.8 Neuromuscular effects of subclinical hypothyroidism

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Reuters VS 143 2006 Brazil	Cross-sectional, outpatients	18-65 years 57 Schypo 37 euthyroid controls matched by age, gender, socioeconomic status and culture	>20mIU/L, thyroxine replacement therapy, concomitant disease or medication known to interfere with thyroid function, other chronic disease	TSH 0.4-4.0 FT410.3-23.2 Repeat TFT at 4 week interval	Muscle enzymes, signs and symptoms of skeletal muscle dysfunction	Significantly greater prevalence of neuromuscular symptoms and significantly reduced muscle strength. Similar levels of muscle enzymes.
Reuters VS [144] 2009 Brazil	Cross-sectional, case control outpatients	Adults 44 Schypo 24 Euth,	Patients with TSH greater then 20mIU/L, treated for thyroid dysfunction, chronic disease, neuromuscular disorder, use of drugs affecting muscle metabolism and drugs that interfere with thyroid function	TSH 0.4-4.0 FT4 11.58-23.2 Single TFT	Muscle strength and functional capacity	Greater prevalence of muscular complaints and reduced muscle strength. Functional capacity not affected

3.5 Neuropsychological function and subclincal hypothyroidism

With respect to neuropsychological function the reviewers again report discordant findings between studies. Despite smaller studies presenting contradictory findings, Biondi et al described good evidence to demonstrate that subclinical hypothyroidism is not associated with depression, anxiety and cognitive impairment in elderly individuals. [145] In one supplementary study, cognitive function and depressive symptoms in an elderly community dwelling cohort were examined by a psychologist. The results demonstrated an increase in depressive symptoms in individuals with subclinical hypothyroidism compared with euthyroid individuals. The differences observed did not reach statistical significance. Similarly, no significant differences in cognition were reported between these groups. This study was however limited by a response rate of only 10.5% therefore findings cannot be considered representative of the wider population from which the study sample was drawn. [146] A significant increase in the frequency of psychiatric diagnosis based upon structured clinical interview was reported in a cross-sectional study of 94 middle aged outpatients with subclinical hypothyroidism compared with 43 age and education level matched euthyroid subjects. [147] This study also described a significant increase in the prevalence of anxiety symptoms as measured by the Hamilton anxiety and depression scales and a two-fold increased risk of depressive symptoms in individuals with subclinical hypothyroidism compared with euthyroid subjects. The higher prevalence of psychiatric diagnosis in individuals with subclinical hypothyroidism may, however, be subject to investigator bias since all interviews were conducted by one examiner who had knowledge of the subjects' thyroid

function categorisation. On the whole these studies do not demonstrate that subclinical hypothyroidism impacts upon anxiety, depression and cognitive function in elderly individuals. Data are less clear with respect to younger adults (Table 3.9).

Table 3.9 Neuropsychological function and subclinical hypothyroidism

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Manciet G [146] 1995 France	Community based	> 65 yrs 18 Schypo, 18 Schyper, 378 Euth	Under 65 years, unwilling to give consent	TSH 0.5-4.5 FT4 16-29	Symptoms of depression and cognitive impairment	Lower scores in Schypo not significantly different MMSE <23 n=5 Schypo <23
Almeida C [147] 2007 Brazil	Cross-sectional outpatients	94 Schypo 43 controls	Severe chronic illness, drugs that might interfere with TFT, TSH >20mIU/L	TSH >4 FT4 10.3-23.2 Repeat TFT	Psychiatric disease DSM-IV	Schypo associated with symptoms of depression and anxiety on HADS and Beck Inventory

3.6 Natural history and progression to overt hypothyroidism

Individuals with subclinical hypothyroidism are at risk for progressing to overt hypothyroidism, however the natural history is poorly defined. The reviewers describe variable findings with studies providing a range of estimates for spontaneous resolving and evolving serum thyrotrophin concentrations and several prognostic indicators for increased risk of progression. [91] Based on the available data, Biondi et al propose that progression to overt hypothyroidism is related to the cause of thyroid dysfunction, and is correlated positively with increased basal serum thyrotrophin concentration and with older age. Biondi et al recommend monitoring to confirm persistent subclinical hypothyroidism.

Only one supplementary study exploring the natural history of subclinical hypothyroidism was identified. [79] Meyerovitch et al examined data from a large health care database in order to determine progression to overt hypothyroidism over a period of five years in individuals with an initial elevated serum thyrotrophin level and not receiving replacement therapy. The reported rate of progression from subclinical hypothyroidism to overt hypothyroidism over a five year period was only 2.9%. [79] Although subclinical hypothyroidism can lead to overt hypothyroidism, progress is generally slow. (Table 3.10).

Table 3.10 Natural history of subclinical hypothyroidism

Author and date	Design /setting	Participants, age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Meyerovitch J [79] 2007	Retrospective survey health care database	Adults n=422242	Known thyroid dysfunction, treated with drugs known to interfere with thyroid dysfunction, pregnant	TSH 0.35-5.5 FT4 10.3-20	Progression	2.9% progressed to overt hypothyroidism during 5 year follow up period

Summary of chapter 3

In this chapter, evidence from a systematic review which compiled data related to subclinical hypothyroidism from studies published between 1970 and April 2007 and available supplementary data related to the clinical signs and pathophysiological consequence of subclinical hypothyroidism have been reviewed and summarised. In general, the current literature review contributed little additional, robust and generalisable data to further substantiate or significantly alter the conclusions reached by Biondi et al.

Cardiovascular risk seems to be a likely adverse consequence of subclinical hypothyroidism; however the mechanisms for this remain unclear. To date, the evidence for cardiac impairment and development of cardiovascular disease in subclinical hypothyroidism is inconsistent. In general, supplementary evidence generated by multiple small studies has not been corroborated by larger population based studies. Whilst studies of cardiac function have consistently shown alterations in measurable parameters, few studies demonstrate the same constellation of abnormalities. Accelerated atherosclerosis in subclinical hypothyroidism is thought to occur by multiple mechanisms, however the majority of the evidence indicates that lipid parameters in individuals with subclinical hypothyroidism are similar to age and gender matched euthyroid controls. Furthermore, the evidence of a role for novel risk factors for cardiovascular disease in the development of atherosclerosis is weak due to data being derived from small, highly selected samples. These data require replication in larger, more representative groups. In relation to heart failure, coronary heart disease and cardiovascular mortality, supplementary and subsequent studies provide good evidence

which further corroborate and extend Biondi et al's findings that subclinical hypothyroidism is not associated with increased risk of coronary heart disease, heart failure or cardiovascular mortality.

Multiple reasons for the lack of consistent findings reported have been proposed. Differences in the assay methods and diagnostic criteria for subclinical thyroid dysfunction are frequently observed. Other possible explanations for the conflicting data are differences in inclusion and exclusion criteria employed with regard to individuals with known thyroid disease. Furthermore, heterogeneity of the underlying cause and duration of subclinical hypothyroidism may lead to disparate findings. Similarly, differential definition of outcome measures and identification of and adjustment for confounders may contribute to the conflicting results reported.

So far, this work has established that subclinical hypothyroidism, like the overt form of the condition, is a common disorder particularly in the elderly. The pathophysiological consequences of subclinical hypothyroidism are, however, less well established with studies reporting inconsistent findings.

In the current chapter literature relating to the pathophysiological consequences of subclinical hypothyroidism was reviewed and summarised. In the next chapter literature related to the pathophysiological consequences of subclinical hyperthyroidism will be presented.

CHAPTER 4 PATHOPHYSIOLOGY OF SUBCLINICAL HYPERTHYROIDISM

Overview of chapter 4

Research related to subclinical hyperthyroidism covers both endogenous and exogenous subclinical hyperthyroid dysfunction. The terms endogenous and exogenous are used to define the origins of the disease, with endogenous being indicative of spontaneous disease, (endo denotes from within) and exogenous disease defining disease of external origin (exo denoting external). The principal difference between these subgroups of subclinical hyperthyroidism is that the exogenous form has been induced either intentionally or unintentionally, through administration of thyroxine (or other thyroid hormone) replacement therapy. Other important differences also exist between endogenous and exogenous subclinical hyperthyroidism. While the aetiology of exogenous subclinical hyperthyroidism is straightforward and well understood, the endogenous form has a variety of causes which require consideration. Euthyroid status is more easily achieved in exogenous subclinical hyperthyroidism through manipulation of thyroxine replacement therapy and the exogenous form does not carry the risk of progression to overt hyperthyroidism. The duration and degree of exogenous subclinical hyperthyroidism can be more easily calculated and defined. For these reasons, exogenous subclinical hyperthyroidism has been more widely studied. Due to the differences described, extrapolation of findings from one subgroup to the other should be considered with caution. This chapter will therefore focus solely upon endogenous subclinical hyperthyroidism since it is the clinical consequences and characteristics of

the spontaneous form of this diagnosis that are less established and are more frequently problematic for primary care practitioners.

In this chapter, the results of the literature search related to the pathophysiological consequences of endogenous subclinical hyperthyroidism are presented and summarised in conjunction with the recent systematic review by Biondi et al.

4.1 Result of the literature search

The search strategy and inclusion/exclusion criteria have been previously described in chapter 3. The electronic searched retrieved 350 results. Abstracts of these articles were screened to assess the inclusion/exclusion status of each publication. In total 270 papers were excluded (Table 4.0). A considerable number of retrieved articles (n=70) were excluded from discussion in the current chapter because the studies were unrelated to investigation of the detrimental effects of subclinical hyperthyroidism. A large proportion of reviews were also excluded as they were not systematic in their approach (n=67), they focused on treatment for subclinical thyroid dysfunction, or the study employed an intervention (n=51). A further 24 duplicate articles were excluded because they had been included in the systematic review by Biondi et al and as such would not contribute additional data for examination within the scope of the current chapter.

Table 4.0 Exclusion of literature; subclinical hyperthyroidism

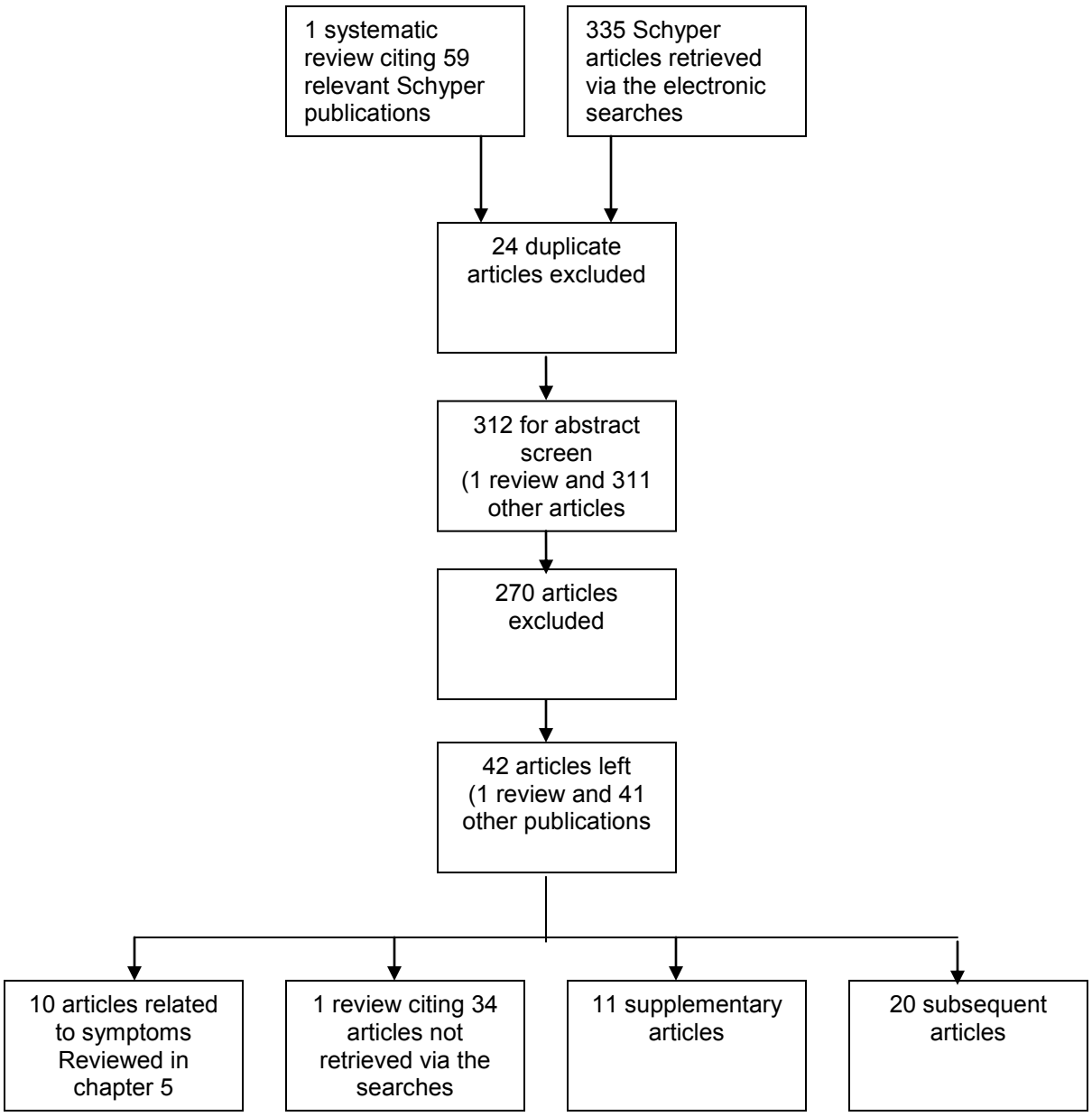
Reason for exclusion of retrieved publications	Articles excluded
Not related to adverse consequences of SCTD	70
Non systematic reviews	67
Studies of intervention or reviews of treatment	51
Diseased populations	35
Case studies	23
Letters	9
Pregnant and post natal women only	6
Research in children	4
Discussion paper/ editorial	3
Superseded systematic review and meta analyses	1
Non human subject	1
Total number of articles excluded	270

A large body of the literature retrieved (n=35) focused upon subclinical hyperthyroidism in specific population subgroups with significant disease. Further examination of this literature has not been undertaken because the principal focus of this chapter is exploration of the adverse health consequences of subclinical hyperthyroidism in a 'normal' population. Despite the application of limits restricting the searches to studies of adult humans it was also necessary to exclude four studies of subclinical hyperthyroidism in children and adolescents and one animal study. Furthermore, 23 case studies, six studies of subclinical thyroid dysfunction in pregnancy, nine letters, three discussion papers and one superseded meta analysis on mortality in subclinical hyperthyroidism are not examined further within this chapter.

Forty two articles remained following application of the inclusion criteria, the systematic review by Biondi et al; 11 supplementary studies published before; but not cited in the review by Biondi et al; 20 subsequently published articles, and 10 publications related to

symptom expression in subclinical hyperthyroidism (Figure 4.0). The findings of all 31 studies are presented and summarised alongside the relevant conclusions drawn by Biondi et al. Throughout this chapter the systematic review will be designated ‘Biondi et al‘and the terminology ‘supplementary’ and ‘subsequent’ respectively will be applied to publications that either pre or post date the systematic review by Biondi et al. Articles related to expression of symptoms in subclinical hyperthyroidism are presented and discussed in Chapter 6.

Figure 4.0 Flow diagram: literature related to subclinical hyperthyroidism



4.2 Cardiovascular consequences of subclinical hyperthyroidism

The effects of overt hyperthyroidism on the cardiovascular system are well established, however, findings from the large body of research evaluating the cardiovascular consequences of subclinical hyperthyroidism are less consistent.

4.2.1 Subclinical hyperthyroidism and atrial fibrillation

In terms of cardiac function, Biondi et al reported substantial evidence indicating a higher risk of atrial fibrillation (AF) in elderly individuals with subclinical hyperthyroidism. [91] The estimates of relative risk reported for atrial fibrillation in individuals with subclinical hyperthyroidism compared with age matched controls ranged from 1.6 to 5.0, with some studies also suggesting a greater likelihood of AF in individuals with more severe subclinical hyperthyroidism (defined by serum thyrotrophin concentrations less than 0.1mIU/L) than individuals with milder subclinical hyperthyroidism (characterised by serum thyrotrophin concentration of between 0.1- 0.4mIU/L). [148, 149,150]

One subsequent cross sectional community based study also revealed an increased likelihood of AF in elderly individuals with subclinical hyperthyroidism compared with euthyroid individuals (OR 1.87, 95% CI 1.01-3.57). [151] In this cohort the prevalence of AF in patients with more severe subclinical hyperthyroidism defined as undetectable serum thyrotrophin concentration and individuals with milder subclinical hyperthyroidism characterized by serum thyrotrophin of 0.1-0.3mIU/L was not significantly different (3.7% versus 11.1% respectively, $p < 0.46$). Data related to the prevalence of AF in these subgroups of subclinical hyperthyroidism should be interpreted with caution however,

because this study was inadequately powered to detect a 7% difference in AF prevalence between these small subgroups of subclinical hyperthyroidism (e.g AF and mild subclinical hyperthyroidism n= 1, AF and severe subclinical hyperthyroidism n= 11). Data from smaller studies evaluating cardiac function by means of ECG lend further support to these findings and further provide biological plausibility to the statistically significant association. Two supplementary case control studies examining cardiac function by means of standard 12-lead electrocardiogram (ECG) also observed differences in markers for AF between individuals with subclinical hyperthyroidism and euthyroid controls. [152,153] In one investigation, significantly longer corrected QT intervals were observed in 32 individuals with subclinical hyperthyroidism compared with 39 euthyroid controls. [152] Likewise, Cetinsarslan et al observed significantly higher P wave dispersion in 36 cases compared with 22 age and gender matched controls. [153] On the whole there is consistent evidence demonstrating an association between subclinical hyperthyroidism and AF in older individuals with severe subclinical hyperthyroidism characterised by serum thyrotrophin of less than 0.1mIU/L (Table 4.1).

Table 4.1 Literature related to subclinical hyperthyroidism and AF

Author, publication date	Design /setting	Participants age and thyroid status	Exclusion criteria	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Cetinarslan B [153] 2003 Turkey	Case control outpatient	Adults ≥18 yrs 36 Schyper 22 age/ gender matched euthyroid controls	Historical or concomitant chronic disease, pregnancy, depression, alcoholism or receiving medication known to affect ECG parameters	TSH and FT4 not explicit Single FTF	ECG parameters predictive of AF Predictive accuracy Pmax = 84% Pdis = 89%	Maximal P wave duration (Pmax) similar. Significantly higher (6 units, p<0.03) P wave dispersion (Pdis=Pmax-Pmin) in Schpyer
Gammage MD[151] 2007 UK	Cross sectional, Community	5881 >65 years 126 Schyper 5519 euthyroid	History of hyperthyroidism, currently receiving treatment for thyroid dysfunction	TSH 0.4-5.5 FT4 9-20 Single TFT	AF on ECG	Higher prevalence of AF in Schyper compared with controls (9.5% vs 4.7%, p<0.01)
Owecki M [152] 2006 Poland	Case control Outpatients	Adults ≥18 years 32 Schyper 39 controls	Unable to source full article however results generated in this small select population is unlikely to significantly alter conclusions of Biondi et al	TSH 0.2-4.0 FT4 7.60-19.67	QTc interval measured by 12 lead electrocardiogram (ECG)r	QT intervals significantly longer in Schyper than in controls 0.434s vs 0.414s respectively p<0.001

4.2.2 Cardiovascular risk factors and subclinical hyperthyroidism

Recent investigation of blood pressure variables in a prospective population based German cohort reported no association between subclinical hyperthyroidism and changes in blood pressure, pulse pressure or incident hypertension. These findings may have limited generalisability since the subgroups excluded and lost to follow-up were significantly older than the final population included in the analysis. [154] Likewise, no association between subclinical hyperthyroidism and hypertension was observed in two cross-sectional, population based studies of Japanese individuals not treated for thyroid disease. [97,98] The Suita study also demonstrated no association between subclinical hyperthyroidism and abnormal carotid artery intima media thickness (a marker of atherosclerosis). In contrast, Dorr et al demonstrated a higher prevalence of carotid plaques in 225 individuals aged 45 years and above with subclinical hyperthyroidism compared with 1839 euthyroid subjects (Table 4.2). [108] Furthermore, results demonstrated a significantly increased likelihood of presence of carotid artery plaques (adjusted OR 1.67, 95% CI 1.11-2.51) and for prevalent stroke (OR 1.98, 95% CI 1.05-3.73) in individuals with subclinical hyperthyroidism compared with euthyroid subjects. The contradictory findings reported by these studies may be explained by differences in study design and genetic background and lifestyles of the populations studied. Since Japan is an iodine replete region and Germany is a formerly iodine deficient area, disparity in dietary iodine intake between the two populations could account for the differences observed. In accordance with one study described by Biondi et al, Coban et al demonstrated a significant increase in the concentration of D-dimer and fibrinogen in 36 individuals with subclinical hyperthyroidism compared with 36 age and gender

matched controls. [155] Elevated concentrations of fibrinogen and D-dimer are potentially clinically important because these coagulation parameters are associated with increased risk of future myocardial infarction, stroke, and peripheral vascular disease. In contrast to one study described by Biondi et al, one supplementary case control study demonstrated significantly elevated concentrations of endothelial markers in individuals with subclinical hyperthyroidism compared with euthyroid controls. [156, 157] Pooling of data on coronary heart disease events originating from five population based, prospective cohort studies failed to demonstrate a significant impact of subclinical hyperthyroidism on coronary heart disease (HR 1.21 95% CI 0.88-1.68). [158]

In summary, Biondi et al and supplementary data demonstrate contradictory findings with respect to the association between subclinical hyperthyroidism and various risk factors for atherosclerosis and cardiovascular disease. Although population based studies have been conducted, findings are inconsistent due to the heterogeneity of the populations studied and outcomes measured. Furthermore, casual relationships are difficult to establish based upon data derived from studies of cross-sectional design. Additional longitudinal investigations of population based cohorts are required to reconcile current disagreement with respect to the relationship between subclinical hyperthyroidism and these potentially important cardiovascular risk factors.

Table 4.2 Cardiovascular risk factors and subclinical hyperthyroidism

Author, publication date	Design /setting	Participants	Exclusion criteria	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Coban E [156] 2006 Turkey	Case control Outpatient	Adults 20 Schyper 20 age, gender, BMI matched controls All antibody positive	Hypertension, diabetes mellitus, smoking, alcohol, systemic disease, medication known to affect TFT and platelet function	TSH 0.27-4.2 FT4 11.97-21.9 Single TFT	von Willebrand factor (vWf) a marker of endothelial damage	Significantly higher levels vWf in Schyper
Takashima N [97] 2007 Japan	Cross sectional, Community based	n=3607 377 Schypo 77 Schypo 3130 Euth	Patients treated for thyroid dysfunction	TSH 0.43- 3.78 FT4 12.9-21.9 Single TFT	IMT surrogate marker of atherosclerosis Glucose metabolism and lipid metabolism	No association with hypertension. Schyper associated with increased HbA1c and Fasting Blood Glucose (FBG) on adjusted analysis
Coban E [155] 2008 Turkey	Case control Outpatients	36 Schyper 36 age, gender and BMI matched euthyroid controls	Concomitant medication chronic and systemic disease, smoking, alcohol, MI, stroke, hypertension, unstable angina and peripheral neuropathy	TSH 0.27-4.2 FT4 11.97-21.9 Single TFT	Biomarkers for endothelial dysfunction	Fibrinogen (296.9 vs 255.0, p=<0.001) and D dimer 261.9 vs 216.4, p<0.001) concentration significantly higher in Schyper than controls
Dorr M [108] 2008 Germany	Population based cohort	>45 years 225 Schyper 1839 Euth	Known or possible thyroid disease	TSH 0.25-2.12 FT4 10-25	Carotid artery plaques using ultrasound / prevalence of stroke reported physicians diagnosis	Significantly elevated odds for presence of carotid artery plaques at any location compared with Euth (adjusted OR 1.67, 95% CI 1.11-2.51) increased odds for prevalent stroke (OR 1.98, 1.05-3.73)

Table 4.2 continued

Author, publication date	Design /setting	Participants	Exclusion criteria	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Duan Y [98] 2009 China	Cross sectional, community	5669 Euth 108 Schyper	Systemic disease, pregnancy, medicines known to interfere with TF	TSH 0.4-4.5 FT4 10.3-24.5 Single FTF	Blood pressure	No association with blood pressure
Volzke H [154] 2009 Germany	Prospective population based cohort	20-79 years n=2910 203 Schyper 2707 Euth	Overt thyroid dysfunction and FT4 > 18.9	TSH 0.25 – 2.12 FT4 <18 Baseline and follow-up TFT for 50% of baseline cohort	BP 5yr Follow-up	No association with blood pressure/pulse pressure or incident hypertension

4.2.3 Subclinical hyperthyroidism and cardiac function

Biondi et al also describe studies evaluating endogenous subclinical hyperthyroidism using ECG and Doppler echocardiography and suggest an increase in heart rate and a higher prevalence of atrial premature beats in individuals with endogenous subclinical hyperthyroidism. In a subsequent study using Doppler echocardiography, Rosario et al demonstrated significant increases in systolic dysfunction in 48 women with endogenous subclinical hyperthyroidism compared with 48 age and BMI matched euthyroid controls. [159] Significant increases in diastolic function in women with subclinical hyperthyroidism compared with controls were also observed. Since all participants were women aged under 65 years, these findings may not be applicable to older women. Left ventricular mass index was also investigated in the Tromso studies. [129] These studies employed two research methodologies; a population based study and a nested case-control study with refined inclusion/exclusion criteria to minimise misclassification of thyroid function status and improve clinical relevance. The epidemiological study which included 2035 adults without known cardiovascular disease did not demonstrate an association between serum thyrotrophin concentration and cardiac function as indicated by left ventricular mass index measured by conventional echocardiography. Similarly, in the nested case control study, no differences in cardiac function between the thyroid function groups were observed via conventional echocardiography. However, data derived from pulse wave tissue Doppler echocardiography of the mitral annulus adjusted for age, gender, body mass index (BMI) and blood pressure demonstrated statistically significant differences in wave velocities between 20 individuals with subclinical

hyperthyroidism compared with 118 euthyroid individuals. [129] The clinical significance of these small increases in wave velocity are as yet undetermined. These alterations may constitute the pathophysiological link between subclinical hyperthyroidism and adverse clinical cardiac events.

Similarly, no differences in left ventricular function were observed in 24 newly diagnosed, untreated individuals with subclinical hyperthyroidism compared with 24 age and gender matched controls. [160] This study, which employed intra-myocardial ultrasonic and colour Doppler imaging techniques to assess cardiac function, did demonstrate impaired systolic function and cardiac contractility in individuals with subclinical hyperthyroidism. However, issues in the study design such as recruitment from an outpatient setting and exclusion of older individuals, smokers and patients with hypertension and abnormal lipid parameters mean that these findings are unlikely to be generalisable to the general population.

More recently a cross-sectional study of 150 outpatients in Turkey reported serum concentrations of brain natriuretic peptide (BNP) in individuals with endogenous subclinical hyperthyroidism almost five times higher than in euthyroid controls. [134] Brain natriuretic peptides which are produced by ventricular myocardium are increased in left ventricular dysfunction and are predominantly used in the diagnosis of systolic heart failure. Although study participants did not have any history or physical signs and symptoms of cardiac dysfunction, left ventricular function was not assessed using echocardiography. It is possible that some of the participants had mild diastolic dysfunction that was not clinically apparent and was present before development of subclinical hyperthyroidism. An independent and statistically significant effect of

subclinical hyperthyroidism on serum BNP concentration was reported, but the clinical significance of these findings has yet to be fully elucidated. [134]

Two small supplementary studies evaluating heart rate variability observed alterations in cardiovascular autonomic balance in individuals with subclinical hyperthyroidism compared with euthyroid individuals. Heart rate variability is a term used to describe variations in the beat to beat interval between heart beats and reflects the balance between the sympathetic and parasympathetic nervous systems. In one of these studies, heart rate variability in 12 individuals with endogenous subclinical hyperthyroidism, 19 with overt hyperthyroidism and 32 euthyroid controls was assessed in order to characterise autonomic control in the lying and standing positions. [161] Although not significantly different to euthyroid or overt hyperthyroid individuals, many parameters in the group with subclinical hyperthyroidism were intermediate between individuals with overt hyperthyroidism and euthyroidism. These observations support the suggestion that there is a continuum of effects as degree of thyroid dysfunction increases. In the second study, heart rate variability in the high frequency and low frequency domains was assessed at rest and after vagal and sympathetic stimulation using the tilt test. Sixteen otherwise healthy women with endogenous subclinical hyperthyroidism and 16 euthyroid controls participated. A significantly lower difference in low frequency and high frequency ratio after tilting and low frequency and high frequency ratio at rest was observed in individuals with subclinical hyperthyroidism compared with controls (Table 4.4). [162] On the whole, supplementary data consistently demonstrate reduced heart rate variability indicative of modified autonomic function in individuals with subclinical hyperthyroidism. However, these data should be interpreted

with caution as they have been derived in small cohorts that are unlikely to be representative of the general population. The long term effects of various echocardiographic abnormalities and the relationship between endogenous subclinical hyperthyroidism and heart failure events were investigated in a large community dwelling elderly cohort. [136] At baseline a significantly impaired diastolic function and significantly increased heart rate was described between individuals with endogenous subclinical hyperthyroidism and euthyroid subjects. After 12 years of follow–up, however, no significant differences in incident heart failure events were observed between the groups, suggesting that these cardiac abnormalities do not result in heart failure in individuals with subclinical hyperthyroidism (Table 4.3). [136] More recently, electrocardiographic investigation of left ventricular function was undertaken at baseline and after five years of follow-up in 107 adults older than 45 years with subclinical hyperthyroidism and 1005 similarly aged euthyroid subjects. Results demonstrated that subclinical hyperthyroidism had no impact upon left ventricular function during this period. [163] Additional longitudinal studies in cohorts covering a wider age range are necessary to further establish the validity of these findings and enable extrapolation of data to younger populations. In summary, a variety of cardiac parameters and cardiovascular outcomes have been examined in relation to subclinical hyperthyroidism. Whether these statistically significant differences translate to clinically significant impaired cardiovascular performance is uncertain. On the whole, representativeness of the populations studied is reduced by stringent inclusion/exclusion criteria and recruitment of small samples from outpatient clinics. Additionally, data derived from larger population based studies often do not corroborate the findings of smaller studies.

Supplementary data fully support the conclusions made by Biondi et al with respect to the relationship between subclinical hyperthyroidism and AF. Whilst there is consistent evidence demonstrating an increased risk of AF in elderly individuals with subclinical hyperthyroidism, risk estimates vary considerably and have yet to be fully established.

Table 4.3 Cardiac function and subclinical hyperthyroidism

Author, publication date	Design /setting	Participants; age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measure	Outcome
Goichot B [161] 2004 France	Case control Outpatient	Adults ≥18 years 12 Schyper 32 controls	Concomitant beta blocker, amiodarone or other anti-arrhythmic medication,	TSH 0.15-4.5 FT4 9.5-18 Single TFT	Heart rate variability	Evidence of changes in autonomic response not significantly different to controls
Di Bello [160] 2007 Italy	Case control Outpatient	Young adults 24 new schyper untreated 24 age/sex matched controls	Patients with hypertension, abnormal lipid parameters and smokers	TSH 0.3-3.8 FT4 7.0-17.0 Single TFT	Cardiac evaluation by ECG Intra myocardial ultrasonic techniques and colour (CDMI)	Modified systolic and diastolic function however no left ventricular hypertrophy in Schyper
Iqbal A [129] 2007 Norway	Population based health survey with	Adults >24 yrs n= 2035 52 TSH < 0.4, 118 TSH 0.4-5.25, 66 TSH >5.25	Known cardiovascular disease, receiving medication for hypertension	Reference range statistically defined by sample TSH 0.4- 5.25 No FT4 measured	Echocardiographic parameters	No association between TSH and LVMI, systolic blood pressure or heart rate after adjusting for age, BMI and systolic blood pressure
	Nested case control study	Adults n=7954 20 Schyper 162 Euthyroid 66 Schypo	Patients with historical or active coronary infarction, angina pectoris, stroke, TF4 outside reference criteria, treatment of hypertension or TD, over 80 years	TSH 0.5-3.49 FT4 9-22 Repeat TFT	Echocardiographic and parameters pulse wave tissue Doppler indices	LVMI similar, S and A wave velocities significantly increased in Schyper

Table 4.3 continued

Author, publication date	Design /setting	Participants; age and thyroid status	Exclusions	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Portella RB [162] 2007 Brazil	Cross sectional, case control study Outpatient	>60 years 16 Schyper 16 euthyroid controls similar socioeconomic status	Those with Schyper for <6 months, concomitant illness or medication TFT or cardiovascular system	TSH 0.4-4.0 FT4 10.3-24.4	Heart rate variability using the tilt test (marker of CV autonomous function)	Cardiovascular modulation significantly affected by Schyper
Ertugrul DT [134] 2008 Turkey	Cross sectional, Case control Outpatient	18-82 years 47 Schyper 33 euthyroid age/ gender/ BMI matched controls	Pregnancy historical or concomitant systemic disease alcohol or drug abuse or malignancy	TSH 0.45-4.5 FT4 not explicit Single TFT	Brain Natriuretic Peptide (BNP) concentration as marker of cardiac function produced by ventricular myocardium	Significant increase in BNP in Schyper (31.2 ng/L vs 23.0, p<0.0001)group compared to controls
Rodondi N [136] 2008 Switzerland	Longitudinal population cohort	>65 years n=3044 44 Schyper 2526 Euth	Receiving treatment for thyroid dysfunction, corticosteroids, amiodarone. Known heart failure at baseline	TSH 0.4-4.5 FT4 9-22 Single TFT	ECG at 5 yrs. Heart failure events 15 yrs follow-up (diagnosis or treatment of heart failure, and by consideration of symptoms, signs, chest radiographs	Increased heart rate (69 vs 64 p<0.05) Schyper not increased risk of heart failure
Rosario PW[159] 2008 Brazil	Case control Outpatient	Women <65 48 Schyper 48 age, menopause, BMI matched controls	Heart disease, hypertension, treated for osteoporosis or using oestrogen or corticosteroids	TSH 0.3-5.0 FT4 9.63-23.17 Repeat TFT	Cardiac morphology and function	Cardiac morphology and function significantly different in Schyper and controls.
Dorr M [163] 2010 Germany	Longitudinal cohort	>45 years 3300 Euth 107 schyper	Known or possible thyroid disease	TSH <0.3 FT4 10-25	Left ventricular function	No association with cardiac mass or development of left ventricular hypertrophy

4.3 Subclinical hyperthyroidism and mortality

Biondi et al describe conflicting data related to increased cardiovascular mortality. [91,137,165] One supplementary meta analysis of mortality data reported a modestly increased risk of mortality from all causes in individuals with subclinical hyperthyroidism compared with euthyroid controls (HR 1.41, 95% CI 1.12-1.79). [165] This meta analysis pooled mortality data for 290 individuals with subclinical hyperthyroidism originating from seven cohort studies exploring mortality from all causes. Excess mortality at 2, 5 and 10 years after diagnosis of subclinical hyperthyroidism was reported by gender and age at the time of diagnosis. At any age, excess mortality after diagnosis was greater in men than women. Moreover, low excess mortality was described in both men and women until the age of 50, beyond which risk more than doubled with each decade. After the age of 80 years, however, excess risks started to decline suggesting a survival effect (Table 4.4). [165] The data related to excess mortality after diagnosis of subclinical hyperthyroidism are inherently limited by the fact that thyroid function may not be stable over time. Findings from another subsequent meta analysis of mortality data derived from five prospective population based cohorts demonstrated no significant impact of subclinical hyperthyroidism on total mortality (RR 1.12, 95% CI, 0.89-1.42) or cardiovascular mortality (RR 1.19, 95% CI, 0.81-1.76). Furthermore no differences by mean age were described. [158] These findings should be interpreted with caution since meta analyses of observational studies cannot prove that a risk does not exist and are subject to ecological fallacy as they are reliant upon aggregate rather than individual patient data. In contrast, a much more recent longitudinal study reported significantly higher hazard ratios for Japanese-Brazilian individuals with subclinical hyperthyroidism

in comparison with euthyroid subjects with respect to all cause mortality (HR 3.0, 95% CI, 1.5-5.9, n=14 (20.3%) versus n=52 (5.7%) respectively) and cardiovascular mortality (HR 3.3, 95% CI 1.4-7.5, n=8 (11.6%) versus n=26 (2.8%) respectively). [166] Due to the small number of cardiovascular deaths (n=8) identified, it is possible that this study was not adequately powered to detect a meaningful association between subclinical hyperthyroidism and cardiovascular mortality. Furthermore, since thyroid function was only assessed at baseline, hazard ratios may be influence by development of overt hyperthyroidism and may not be exclusive to individuals with subclinical hyperthyroidism (Table 4.4). In summary, two meta analyses of mortality data describe conflicting results with respect to increased risk of all cause mortality in individuals with subclinical hyperthyroidism and with advancing age. Estimates of increased risk are generally modest or associated with wide confidence intervals due to the small number of events observed during the follow-up period.

Table 4.4 Subclinical hyperthyroidism and coronary heart disease and mortality

Author and date	Design /setting	Participants	Exclusions criteria	TSH and FT4 reference criteria and frequency of TFT confirming thyroid status	Measure	Outcomes
Sgarbi A [166] 2010 Brazil	Cross sectional	Adults >30yrs Schyper 69 Euth 913	Self reported TD, medication known to affect TFT	TSH 0.45-4.5 FT4 0.7-1.5 Single TFT	All cause and cardiovascular (CV) mortality	All cause Schyper HR 3.0 (1.5-5.9, n=14) and CV mortality HR 3.3 (1.4-7.5, n=8)
Haentjens N[165] 2008 Belgium	Systematic review and meta analyses on mortality	Seven studies 290 Schyper 13039 Euth			All cause mortality	Modestly increased risk in risk of death from all causes HR 1.41 (1.12-1.79)
Ochs P [158] 2008 Switzerland	Systematic review and meta analyses on coronary heart disease and mortality	Five prospective cohort studies			Coronary heart disease and mortality	Modestly increased risk of coronary heart disease RR 1.54 (1.04-2.28) Total mortality RR 1.12 (0.89-1.42)

4.4 Bone mineral density and fracture risk

Biondi et al describe conflicting results from the few small studies that have evaluated bone mineral density (BMD) in relation to endogenous subclinical hyperthyroidism. [91] The primary reason for the scarcity of studies in this area, the small sample sizes and conflicting findings are the difficulties associated with establishing the duration of endogenous subclinical hyperthyroidism and recruitment of individuals with dissimilar disease duration. Despite these difficulties Biondi et al concluded that available data support the hypothesis that reduced bone mineral density can be induced by subclinical hyperthyroidism. Similarly, findings from all supplementary and subsequent studies support this hypothesis. In one supplementary case control study, reduced bone mineral density was shown in postmenopausal women with subclinical hyperthyroidism due to solitary autonomous thyroid nodule compared with age and menopause matched euthyroid controls. [5] Measurements of bone mineral density were, however, similar in premenopausal women with solitary autonomous thyroid nodule with subclinical hyperthyroidism compared to premenopausal age matched euthyroid women. In postmenopausal women, urinary markers of bone resorption (free and total deoxypyridinoline) were significantly higher. This study also demonstrated significantly lower serum concentrations of dehydroepiandosterone (DHEAS) in postmenopausal women with subclinical hyperthyroidism compared with euthyroid controls. Since DHEAS plays an important role in preservation of bone mass, the author suggested that insufficiency of DHEAS may be an additional risk factor for bone loss in postmenopausal subclinical hyperthyroidism (Table 4.5). [167] Likewise, a comparison of markers of bone turnover between 15 women with subclinical hyperthyroidism and 15 healthy age

matched controls described significantly higher serum concentrations of interleukin-6 (a cytokine thought to have a role in bone resorption) and alkaline phosphatase (a marker of bone formation). [142] Similarly, another supplementary study of 60 cases and 60 controls demonstrated a significant increase in markers of bone turnover and a significant decrease in bone mass in pre- and post-menopausal women with subclinical hyperthyroidism due to toxic multinodular goitre. [167] Belaya et al further supported and extended these findings in a study of bone metabolism and bone mineral density in relation to aetiology of subclinical hyperthyroidism in postmenopausal women. [168] Four groups of postmenopausal women were studied; two groups of women with endogenous subclinical hyperthyroidism, a control group and a group with exogenous subclinical hyperthyroidism. Endogenous subclinical hyperthyroidism in one group of women was due to toxic multinodular goitre and the second group had stable subclinical hyperthyroidism for at least six months after antithyroid treatment for Graves disease. Only the two groups of women with endogenous subclinical hyperthyroidism had significantly lower bone mineral density and significantly higher concentrations of biochemical markers of bone turnover compared with the control group. Post hoc analysis demonstrated no differences in bone mass density between the two groups of postmenopausal women with endogenous subclinical hyperthyroidism. [168] Similarly, Rosario et al reported a significant increase in markers of bone formation and resorption in women with endogenous subclinical hyperthyroidism. [159] Additionally, in this evaluation of 48 women with endogenous subclinical hyperthyroidism with 48 age, BMI and menopause matched euthyroid controls bone mineral density in the femoral neck was significantly lower in pre- and post-menopausal women with endogenous subclinical

hyperthyroidism compared respectively with pre- and post-menopausal controls (Table 4.5). Bone mineral density in the lumbar spine was significantly lower only in postmenopausal women with endogenous subclinical hyperthyroidism compared to controls. In terms of fracture risk, Biondi et al described few studies examining fracture risk in subclinical hyperthyroidism, none of which exclusively studied this in relation to endogenous subclinical hyperthyroidism. Furthermore, Biondi et al suggested that study findings may have been affected by inclusion of individuals with overt hyperthyroidism and confounding factors. No supplementary or subsequent studies of endogenous subclinical hyperthyroidism and fracture risk were identified.

In summary, in accordance with the findings of Biondi et al, supplementary and subsequent studies consistently demonstrate an association between subclinical hyperthyroidism and parameters of bone metabolism and bone mineral density. However, the clinical significance of alterations in bone metabolism and bone mineral density remains uncertain. Since findings are generally derived from small studies of predominantly young and middle aged women, data require replication in prospective, population based studies.

Table 4.5 Bone metabolism and subclinical hyperthyroidism

Author and date	Design /setting	Participants, age and thyroid status	TSH and FT4 reference criteria and frequency of TFT	Measures	Outcome
Foldes J [5] 1997 Hungary	Case control study Outpatients	35-64 years 63 Schyper (31 pre and 31 post menopausal) 41 age/ menopause matched controls	TSH 0.3-4.0 FT4 10-25 Repeat TFT	Markers of bone metabolism (DHEAS a marker of formation and Dpd resorption) and bone mass	Bone mass and DHEAS significantly decreased and Dpd significant increased In postmenopausal women with Schyper compared with postmenopausal controls
Tauchmanova L [167] 2004 Italy	Cross-sectional Secondary care	Women ≥18 years 60 SCHyper 60 controls matched for age, menopausal status and duration and BMI	TSH 0.3-3.5 FT4 6.6-18.0 Single TFT	Bone mass density (BMD) using quantitative ultrasonometry (QUS) and dual energy x-ray absorptiometry DEXA and markers of bone metabolism	Significant decrease in BMD and significant increase in markers of bone turnover in Schyper groups compared with controls
Sekeroglu MR [142] 2006 Turkey	Case control Outpatients	Women ≥18 years 15 SCHyper, 15 age matched controls	TSH and FT4 not explicit. Single TFT	Markers of bone metabolism to include cytokines interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α)	Schyper associated with higher Interleukin-6 and alkaline phosphatase supporting a role in bone turnover.
Belaya ZE [168] 2007 Russia	Case control study Outpatients	Postmenopausal women ≥18 years 20 Endo Schyper 21 with Endo Schyper 6 months after treatment 22 age/ menopause matched controls	TSH and FT4 not explicit. Repeated TFT	Bone mass density (BMD), biochemical markers of bone, calcium and phosphorous metabolism	Some markers of bone turnover significantly higher and BMD significantly lower in endogenous Schyper, no difference in calcium or phosphorous metabolism
Rosario PW [159] 2008 Brazil	Case control Outpatients	Women <65 years 48 Schyper 48 age, menopause and BMI matched controls	TSH 0.3-5.0 FT4 9.63-23.17 Repeated TFT	Bone abnormalities using biomarkers of bone turnover and dual energy x-ray absorptiometry (DEXA)	Significant increase in markers of bone turnover and lower BMD in the femoral neck in pre and postmenopausal women with Schyper. Significantly lower BMD in the post menopausal lumbar spine

4.5 Neuropsychological function

Biondi et al suggested that good evidence exists to refute an association between subclinical hyperthyroidism and anxiety, depression or cognitive function in older adults. [145] Despite these findings, based upon available data Biondi et al were unable to draw conclusions about the impact of subclinical hyperthyroidism upon mood and cognitive function in younger populations. Since these data are complicated by numerous confounding factors, it is difficult to determine whether subclinical hyperthyroidism is a causally associated with neuropsychological dysfunction.

In one subsequent study, multiple confounders were evaluated alongside cognition and thyroid function in a large population based sample living in Italy (Table 4.6). [169] This study reported a significantly higher likelihood of cognitive impairment as defined by a Mini-Mental State Examination (MMSE) score of <24 in individuals with subclinical hyperthyroidism compared with euthyroid subjects (HR of 2.26, 95% CI 1.32-3.91). The cut offs used to define cognitive function may also explain the disagreement in findings related to cognitive function reported in this study [160] and the study described by Biondi et al. [145] In a random sample of 192 primary care based individuals aged 60 years or more, a similar prevalence of cognitive dysfunction, dementia, depression and anxiety disorders was described in individuals with subclinical hyperthyroidism compared with euthyroid individuals. However due to the inclusion of a small number of individuals with subclinical hyperthyroidism (n=3), individuals receiving treatment for thyroid dysfunction, and multiple testing, this study lacked adequate statistical power to detect meaningful differences between individuals with subclinical hyperthyroidism and euthyroid individuals. [170] In another supplementary study, Schlote et al examined short-term

memory, affective state, ability to concentrate and psychomotor performance in 35 individuals with subclinical hyperthyroidism, 60 with overt hyperthyroidism and 28 euthyroid controls. [171] Findings demonstrated no impairment in ability to concentrate or short term memory in any group, however self-ratings of affective state tended to be similar in patients with subclinical and overt hyperthyroidism (Table 4.6). In summary, data supplementary to Biondi et al are conflicting with respect to the impact of subclinical hyperthyroidism neuropsychiatric function. Studies in general are limited by a cross-sectional design and multiple confounders. Clinical intervention on the basis of available evidence can not be justified.

Table 4.6 Neuropsychological function and subclinical hyperthyroidism

Author and date	Design /setting	Participants	Exclusions	TSH and FT4 reference criteria and frequency of TFT confirming thyroid status	Measures	Outcome
Ceresini G [169] 2009 Italy	Cross sectional, community based	Adults 65 years or more = 800 Euth 71 schyper Under 65 = 243 Euth 1 schyper	Dementia, treatment known to affect thyroid function	TSH 0.46-4.68 FT4 9.9-28.2 Single TFT	MMSE <24 indicative of cognitive impairment	Schyper independently associated with cognitive impairment in older individuals (HR 2.26,95% CI p<0.003)
Schlote B [171] 1992 Germany	Cross sectional, Outpatients	>18 years 35 Schyper 28 controls	History of psychiatric illness or disease known to effect thyroid function. Concomitant treatment for thyroid dysfunction	TSH 0.2-3.5 FT4 9-24 Single TFT	Affective state, short-term memory, ability to concentrate and psychomotor performance	Schyper increased self reported affective state and significantly impaired psychomotor skills.
Sender Palacios MJ [170] 2004 Spain	Cross sectional descriptive Primary care	192 randomly selected sample 4 Schyper 167 Euth 21 Schypo	Chronic illness	TSH 0.25-6.70 FT4 9-24 Single TFT	Schypo associated with dyslipidemia and increased lipid parameters	Similar prevalence of cognitive dysfunction, dementia, depression and anxiety disorders in schyper and Euth

4.6 Natural history and progression to overt hyperthyroidism

Biondi et al describe uncertainty with regard to the frequency with which subclinical hyperthyroidism progresses to overt hyperthyroidism. Initial lower serum thyrotrophin concentration and the underlying cause of thyroid dysfunction are considered predictive of rate of progression to overt hyperthyroidism. Accordingly, Biondi et al recommend regular monitoring to evaluate whether subclinical hyperthyroidism is persistent or progressive. Four subsequent studies examining the natural history of subclinical hypothyroidism were retrieved. [79, 172,173,174] One retrospective case note review reported a rate of progression to overt hyperthyroidism of 32% within four years in individuals with subclinical hyperthyroidism characterised by serum thyrotrophin concentrations lower than 0.1mIU/L. Survival analyses in this cohort of 75 individuals with no previous history of thyroid dysfunction also indicated that presence of symptoms of hyperthyroidism and level of baseline thyrotrophin are significant predictors of outcome. [173] The reported hazard ratios were 6.05 (95% CI; 2.18-16.84) for serum thyrotrophin concentration <0.10mIU/L and 2.08 (95% CI; 1.03-4.21) for subclinical hyperthyroidism with symptoms of overt hyperthyroidism (Table 4.7). The later supplementary study of 102 elderly women with subclinical hyperthyroidism defined by serum thyrotrophin between 0.1-0.4mIU/L reported a lower rate of progression to over hyperthyroidism of only 1% per year. The authors of this study suggested that in this population spontaneous reversion to euthyroidism may occur, however persistent subclinical hyperthyroidism is more likely. [172] These two supplementary studies report a much lower rate of spontaneous normalisation than earlier studies. [61,175] However, overestimation of spontaneous normalisation in the earlier studies may have occurred due to misclassification of non

thyroidal illness as subclinical hyperthyroidism, based upon one measurement of serum thyrotrophin concentration. Additionally, a supplementary retrospective examination of data from a large health care database suggested that approximately 51% of individuals with an initially decreased serum thyrotrophin concentration who are not treated with anti thyroid medications will revert to euthyroidism within five years. [79] Similarly low progression rates were reported in a more recent retrospective study evaluating progression to overt hyperthyroidism and regression to euthyroid state in a UK based adult population with subclinical hyperthyroidism. Classification of thyroid function five years after diagnosis demonstrated that 67.5% persisted with subclinical hyperthyroidism, 31.5% regressed to euthyroid status and 0.6% progressed to overt hyperthyroidism. Furthermore, the result suggested that older individuals and subjects with more severe subclinical hyperthyroidism (defined by a TSH of <0.1 mIU/L) at diagnosis were less likely to regression to euthyroid status (Table 4.7). [174]

In summary, the literature review identified four studies of the natural history of subclinical hyperthyroidism subsequent to the review by Biondi et al. Based upon available data, progression to overt hyperthyroidism from subclinical hyperthyroidism appears to be slow. In older individuals, progression is more likely than in younger individuals, however in general individuals are more likely to remain with subclinical hyperthyroidism than regress to euthyroid function or progress to overt hyperthyroidism.

Table 4.7 Natural history of subclinical hyperthyroidism

Author and date	Design /setting	Participants	Exclusions	TSH and FT4 reference criteria and frequency of TFT confirming thyroid status	Outcomes
Meyerovitch J [79] 2007 USA	Retrospective survey health care database	Adults n=422242	Known thyroid dysfunction, treated with drugs known to interfere with thyroid dysfunction, pregnant	TSH 0.35-5.5 FT4 10.3-20	Progression rate of 2.9% over 5 years follow-up
Diez JJ[173] 2009 Spain	Retrospective, case note review	>24 years 75 Schyper 2 years follow-up	TD other than schyper. Medication in the last 12 months known to interfere with TFT pregnancy	TSH <0.5 FTT not explicit Repeated TFT	45% progressed to Ohyper.
Rosario PW [172] 2009 Brazil	Prospective, Longitudinal	>60 years Women 102 Schyper 0.1-0.4 1-5 years follow-up	Concomitant or historical treatment for TD, pituitary disease and corticosteroids	TSH 0.4-4.0 FT4 9-23 Repeat TFT assessed at 3 monthly intervals	Rate of progression to Ohyper, 1% per year
Vadiveloo T [174] 2011 UK	Retrospective survey of a health care database	Adults 2024 Schyper	Receiving thyroid medication or known to interfere with TFT, previous, pregnancy	TSH <0.4 FT4 10-25 Repeated 4 month interval	6.1% 1st year after diagnosis. Older subjects less likely to revert than remain Schyper at 2 years (17.2% vs. 81.2%)

Summary of chapter 4

This chapter summarised evidence from a systematic review by Biondi et al and available supplementary data related to the clinical signs and pathophysiological consequences of subclinical hyperthyroidism. In general, the literature review contributed little additional, robust and generalisable data to further substantiate or significantly alter the conclusions made by Biondi et al. The most consistently reported adverse cardiac alteration of endogenous subclinical hyperthyroidism described is atrial fibrillation, but risk estimates vary and have yet to be fully established. There is consistent data to support the hypothesis that reduced bone mineral density can be induced by endogenous subclinical hyperthyroidism. Studies of bone mineral density in general have nevertheless been small, due to difficulties associated with establishing duration of endogenous subclinical hyperthyroidism and in the recruitment of individuals with similar disease duration. These data require confirmation in larger, population based studies.

Four subsequent studies of the natural history of subclinical hyperthyroidism were identified. These data were contradictory with respect to the frequency of progression to overt hyperthyroidism. Subsequent data corroborate rather than significantly alter the conclusions of Biondi et al in this respect. The frequency with which subclinical hyperthyroidism becomes overt hyperthyroidism is uncertain, however older individuals and subjects with lower serum thyrotrophin concentrations have a higher risk of progression than young individuals with less severe subclinical hyperthyroidism. In

general, studies were limited by a retrospective study design or recruitment of small selected samples.

Despite the large body of literature, the clinical importance and adverse health consequences of endogenous subclinical hyperthyroidism remain unclear. Conflicting results have been reported in larger population based studies compared with those described in smaller studies of patient populations. The reasons for disagreement between studies are likely to be similar to those related to evaluation of pathophysiological consequences of subclinical hypothyroidism i.e. heterogeneity of the populations studied, the assays for measurement of serum thyrotrophin and reference criteria by which endogenous subclinical hyperthyroidism is defined.

In conclusion, based upon evidence to date, the most likely pathophysiological effects of endogenous subclinical hyperthyroidism are AF and reduced bone mineral density. Whether intervention to treat underlying thyroid dysfunction is justified or beneficial in this regard remains unclear.

In the next chapter, literature related to expression of symptoms in subclinical hypothyroidism will be presented.

CHAPTER 5 SYMPTOMS AND SUBCLINICAL HYPOTHYROIDISM

Overview of chapters 5-6

Chapters 3 and 4 demonstrated that despite multiple studies there is little compelling evidence upon which screening and treatment for subclinical thyroid dysfunction can be justified. The clinical significance of subclinical thyroid dysfunction however cannot be fully realised until symptoms and perceived health status in individuals with subclinical hypothyroidism and euthyroid subjects have been explored. The following two chapters present and examine the evidence related to symptom manifestation and perceived health status in individuals with subclinical thyroid dysfunction. For the purposes of this thesis, symptoms are defined as clinical changes that are perceptible and apparent to the individual. In contrast, clinical signs are defined as clinical anomalies that are evident on physical examination or assessment by a clinician and include indicators of anxiety, depression and cognitive dysfunction. Data related to general well being, health status and quality of life will be considered alongside data on symptoms since these concepts deal with patient experiences and impact of disease on everyday life and are as such best assessed by patients themselves. Chapter 5 focuses upon subclinical hypothyroidism and chapter 6, on subclinical hyperthyroidism.

Overview of chapter 5

Chapter 5 reviews available evidence evaluating symptoms in individuals with subclinical thyroid dysfunction compared with euthyroid subjects. Since the systematic review by

Biondi et al also described studies evaluating the prevalence and diagnostic utility of symptoms and perceived health status in subclinical thyroid dysfunction the reviewers' findings and supplementary data will be presented in parallel.

Another aim of this thesis is to characterise symptom expression and determine perceived health status in elderly individuals with subclinical thyroid dysfunction compared with euthyroid individuals. This chapter will also describe diagnostic indices and other validated instruments that have previously been used to evaluated symptoms or health status in individuals with subclinical hypothyroidism and euthyroid individuals.

5.1 Results of the literature search

The literature search strategy and results were reported in Chapters 3 and 4. Nine papers evaluating symptoms or perceived health status in individuals with subclinical hypothyroidism compared with euthyroid individuals were identified. Studies were excluded from review in this chapter if they involved individuals receiving treatment for thyroid dysfunction or only included individuals with subclinical hypothyroidism without a control comparison.

5.2 Symptoms in individuals with subclinical hypothyroidism

The majority of studies suggest that consideration of physical symptoms in isolation is associated with very poor diagnostic accuracy for overt hypothyroidism. This is therefore also likely to be true of subclinical hypothyroidism. However, there are a number of studies that have examined the possibility that subclinical hypothyroidism causes mild hypothyroid symptoms. Biondi et al report continuing controversy regarding the

presence of symptoms in subclinical hypothyroidism and suggest that symptoms alone cannot be used to distinguish individuals with subclinical hypothyroidism from euthyroid subjects. Based upon available data, Biondi et al concluded that symptom presentation is related to severity and duration of subclinical hypothyroidism and sensitivity to thyroid hormone deficiency. In the elderly, symptoms are likely to be less specific than in younger individuals.

Using a new clinical scoring system designed to assess severity of thyroid failure, Zulewski et al demonstrated presence of symptoms suggestive of overt hypothyroidism in individuals with subclinical hypothyroidism. [37] In this study, 93 females with subclinical hypothyroidism scored significantly higher compared with 109 euthyroid females (3.4 ±2.0 versus 1.6±1.6, $p<0.001$). The Zulewski symptom scoring system was also used for investigation of symptoms in individuals with subclinical hypothyroidism in two other studies with variable results. [176,177] In one supplementary cross-sectional study, both clinical symptoms and health status were evaluated in 152 women with subclinical hypothyroidism, 14 with overt hypothyroidism and 66 euthyroid controls. [176] The prevalence of individual signs and symptoms in the groups are not reported. Based upon the number of signs and symptoms reported, individuals were classified as either having a normal symptom score (defined as three symptoms or less) or an abnormal symptom score (defined as more than three symptoms). The frequency of abnormal scores was significantly greater in individuals with subclinical hypothyroidism compared with euthyroid subjects (75% versus 32, $p<0.05$). Health status was also evaluated in this cohort using the SF36. The concept of perceived health status deals with patients

experiences and the impact of disease on everyday life and as such is best assessed by patients themselves. Poor health related quality of life or impaired health status may be important factors to consider when making decisions about management of subclinical hypothyroidism. The SF36 is a multi-purpose, generic measure of perceived health status comprising 36 items that make up eight domains. [178] The SF36 measures both negative and positive aspects of health and a range of health status and well being in terms of both physical and mental health. This instrument measures eight parameters of health status: role limitations due to physical problems, physical functioning, social functioning, pain, mental health, general health, energy and role limitations due to emotional problems. A physical health summary score can be derived from the domains of general health, physical functioning, role limitations due to physical problems and pain. The mental health summary score is derived from the energy, social functioning, and mental health and role limitations due to emotional problems domains. The results can be compared between different populations, specific treatments, and across different health care delivery systems. In comparison with euthyroid subjects, perceived health status scores were significantly different in individuals with subclinical hyperthyroidism with respect to three of the eight domains. Individuals with subclinical hyperthyroidism reported significantly reduced median scores for physical function (65 versus 85, $p<0.017$), role physical (50 versus 100, $p<0.017$) and general health (62 versus 82, $p<0.017$) compared with euthyroid individuals. Examination of the relationship between health status and clinical score demonstrated weak correlations (Spearman correlation coefficient ranging from -0.21 to -0.35). Significant negative correlations between clinical scores in individuals with subclinical hypothyroidism and

five domains of health status (physical function, bodily pain, general health, vitality and mental health) were reported. However, these correlations were lost following stratified analysis of serum thyrotrophin and serum free thyroxine according to the classification of clinical score as normal or abnormal. This suggests that serum thyrotrophin and free thyroxine concentration are not independently associated with reduced health status, and deterioration of health status is due to presence of signs and symptoms. [176] The representativeness of the population studied is restricted by the small sample size and inclusion of individuals without concomitant disease. In another recent supplementary case control study, the Zulewski scale was administered in 57 individuals with subclinical hypothyroidism and 37 euthyroid individuals recruited from the outpatient endocrinology clinic. [177] Compared with euthyroid subjects, significantly more individuals with subclinical hypothyroidism reported presence of the symptoms dry skin (14% versus 33%, respectively $p<0.05$) puffy eyes (10.3% versus 36.7% respectively, $p<0.05$), thickened skin (6.9% versus 23.3% respectively, $p<0.05$) and hoarse voice (10.3 versus 37% respectively, $p<0.05$). Furthermore a significantly greater proportion of individuals with subclinical hypothyroidism had a symptom score of ≥3 compared to euthyroid individuals (70% versus 38.7% respectively, $p<0.04$). [177] Again, however, these findings are restricted by recruitment of a small highly selected sample and as such are unlikely to be generalisbable to the general population.

With the intention of evaluating the relationship between thyroid function and symptoms, Canaris et al administered the Colorado symptom survey to approximately 25000 participants at a state-wide health fair in the USA. [56,59] The symptoms of hypothyroidism used in the survey were selected from findings of a previous study which demonstrated

a significant difference in prevalence of these symptoms between individuals with hypothyroidism and euthyroidism. [59] The survey evaluated current presence or absence of 20 symptoms and identified whether any of the symptoms were of recent onset (e.g. in the last 12 months). The response options for each item ranged from one to five with three being a neutral response and each extreme representing either complete absence or marked severity of the symptom. The results demonstrated that individuals with subclinical hypothyroidism reported a significantly greater percentage of recently changed symptoms compared with euthyroid individuals (15.4% versus 13.4% respectively, $p<0.05$). Furthermore, individuals with subclinical hypothyroidism reported a significantly greater mean percentage of total symptoms compared with euthyroid individuals (13.7% versus 12.1% respectively, $p<0.05$). Those with subclinical hypothyroidism were intermediate between the overt hypothyroidism and euthyroidism groups suggesting a positive association between number of symptoms and progressive thyroid failure. Low individual symptom sensitivities for higher serum thyrotrophin concentrations were also reported suggesting that the absence of a particular symptom did not rule out thyroid dysfunction. Accordingly, a high number of false positive individual symptoms were described. The authors also described derivation of a symptom scoring system to establish whether multiple symptoms better distinguish between overt hypothyroidism and euthyroidism than individual symptoms. The final symptom score utilised the most discriminatory current and changed symptoms (current symptoms; constipation, hoarse voice and deep voice and changed symptoms; constipation, hoarse voice, sensitivity to cold temperature, puffy eyes, and weak muscles) to calculate an accumulative score. Results further demonstrated a greater

likelihood of overt hypothyroidism with increasing symptom score. The effectiveness of the symptom score in distinguishing between individuals with subclinical hypothyroidism and euthyroidism however remains to be elucidated. The clinical utility of this symptom score is limited by the complex weighting system required for calculation of final symptom scores. This method of symptom assessment therefore may not be convenient or feasible in the primary care setting. Since only a third of the population were older than 65 years of age and the analysis of symptoms in the thyroid function groups was not stratified by age, additional studies are required to assess the external validity of this symptom scoring system in older age groups. Additionally, the study population was not strictly population based since participants were recruited from a health fair. These individuals are likely to be representative of healthier and potentially more affluent cohorts than the general population.

Contradictory findings were reported by Bemben et al in a retrospective case note review of primary care geriatric clinic records. To determine the utility of 26 clinical signs and symptoms for diagnosis of subclinical hypothyroidism in elderly individuals with no known history of thyroid dysfunction, the records of 272 patients were reviewed. [179] Irrespective of thyroid status, the symptoms lethargy and memory impairment were common in this population. A higher frequency of dry skin and dyspnoea was reported by the group with subclinical hypothyroidism compared with the euthyroid group, however the differences failed to reach significance (dry skin 40.5% versus 36.8% respectively and dyspnoea 42.9% versus 37.6% respectively). No relationship between thyroid function category and prevalence of any individual symptom was reported. Comparisons between the euthyroid and subclinical hypothyroidism groups stratified into

three subpopulations based upon total number of symptoms present (e.g. more than four symptoms, three to four symptoms and one to two symptoms) similarly failed to discriminate between the 230 euthyroid subjects and 42 individuals with subclinical hypothyroidism. Multivariate analysis used a cross validation strategy in which one subset of data was used to construct a logistic regression model, the results of which were then evaluated in the remaining subset of data. Logistic regression models had weak predictive power when applied to cases that were not used to build the model. The authors concluded that the classic clinical signs and symptoms individually or in combination are not present in elderly individuals with subclinical hypothyroidism and therefore do not aid active case finding in this population. The results are, of course, limited by the retrospective study design. Retrospective data collection from primary care records is likely to lead to poor correlation between clinical features and thyroid dysfunction because primary care clinicians do not routinely seek or record standard or specific clinical features in their patients. Another study investigated the presence of 44 non thyroid specific symptoms in individuals with subclinical hypothyroidism compared with euthyroid individuals. [24] The most frequent symptoms in the subclinical hypothyroidism group were fatigue (27.9%), distress (20.9%) weight gain (14.0%) and nervousness (11.6%). These four symptoms were also the most frequently reported symptoms in the group with overt hypothyroidism. Discriminant analysis however failed to identify symptoms distinctive of subclinical hypothyroidism. The main aim of this study was to investigate the effects of thyroid dysfunction on quality of life as assessed using the SF36. [178] The 43 Individuals with subclinical hypothyroidism, scored significantly lower in the mental component summary scores than the 20 controls (43.8 versus 51.5

respectively, p<0.001). [24] Likewise physical component summary scores were significantly lower in individuals with subclinical hypothyroidism compared with euthyroid subjects (41.2 versus 46.7 respectively, p<0.02) The group with subclinical hypothyroidism scored more highly with respect to both component summary scores compared to those with overt hypothyroidism. These findings demonstrate that symptoms suggestive of overt hypothyroidism are present in individuals with subclinical hypothyroidism and suggest a graded effect of hypothyroid dysfunction on perceived health status. All subjects were aware of their thyroid function category before completion of the study questionnaire, therefore results could be subject to reporting bias. Furthermore, due to the relatively small size and limited age range of the participants these data are unlikely to be applicable to older populations. In contrast, a large community based cross-sectional study demonstrated that women with subclinical hypothyroidism have similar perceived health status as euthyroid women. [24] The SF36 was also used to assess perceived health status in this study. [180] The mean mental component summary scores did not differ between 80 women with subclinical hypothyroidism and 240 age matched controls (51.5 versus 50.1 respectively). Likewise the mean physical component summary scores were similar between cases with subclinical hypothyroidism and age matched controls (49.1 versus 49.6 respectively). A key feature of this study was that the women were unaware of thyroid status, removing reporting biases. However the study sample may not be representative of the community from which they were recruited due to the low (11%) response rate (screened n=12544, participated n=1423). Razvi et al compared perceived health status assessed by the SF36 in 71 consecutively diagnosed community dwelling individuals with subclinical

hypothyroidism and age and gender matched UK normative data. [181] The findings demonstrated significantly lower absolute scores on all eight domains of the SF36 in individuals with subclinical hypothyroidism compared with the age and gender matched normative population. Due to limited availability of normative data for older age groups, absolute scores for older individuals with subclinical hypothyroidism (≥ 65 years of age) were compared with the younger group studied. The older group reported significantly lower scores for physical function, role limitations due to physical problems and pain than the younger group with a difference in mean absolute score of 17.72 (95%CI 6.4-29.04) for physical function, 13.93 (95%CI 1.32-26.54) for role physical and 14.93 (95%CI 2.97-26.89) for pain. Although the participants were recruited from the primary care setting the representativeness of the cohort is reduced because these individuals were all actively seeking medical attention and being investigated for thyroid dysfunction. These patients are therefore more likely to have symptoms and/or concomitant disease than the general primary care population. Furthermore, all individuals were aware of their thyroid function categorisation when completing the study questionnaire and this potential new, additional diagnosis may have impacted upon perceived health status. [181] In contrast, a similar study in Italy reported no difference in perceived health status between 45 individuals with subclinical hypothyroidism and age and gender matched Italian population norms as assessed by the Nottingham health profile (NHP) and the SF36. [15] The Nottingham Health profile is intended for use in the primary care setting and evaluates perceived emotional social and physical health problems. The questionnaire comprises two parts. Part one encompasses 38 questions that make up six domains (energy, pain, emotional reaction, sleep, physical abilities and

total isolation). Part two assesses which life areas are affected, work, hobbies, sex life, home life, social life, holidays and looking after the home. The individuals with subclinical hypothyroidism were all aware of their diagnosis and had been referred to a secondary care endocrinology clinic. The difference between these two final studies may be due to the different populations and normative data used in the analysis. [15]

Table 5.0 Symptoms and health status and subclinical hypothyroidism

Author, publication date	Design	Participants/ setting	Exclusions	Serum TSH (mU/L) and FT4 (pmol/L) reference criteria for Schypo	Outcome measures (Instrument used)	Summary of results
Bemben DA[179] 1994 USA	Retrospective case note review Primary care	Elderly >60 yrs 86 Schypo 230 Euth	Previous thyroid dysfunction, referral by inpatient rehabilitation services	TSH <5.0-14.9 FT4 9.0-25.0	26 classical signs and symptoms adapted from an endocrinology text book	No association between Schypo and 26 individual symptoms attributed to overt hypothyroidism. No association between Schypo and totalled number of symptoms reported
Zulewski H[37] 1997 Switzerland	Cross sectional study Outpatients	Adults ≥18 years 93 Schypo, 189 Euth 50 Ohypo	Males	TSH 0.1-4 FT4 8.0-27	14 symptoms and signs of hypothyroidism (Zulewski scale)	Classical sign and symptoms are rare or absent in Schypo.
Canaris GJ [56] 2002 USA	Cross sectional study Statewide health fair	Adults ≥18 yrs 2336 Shypo 22842 Euth 114 Ohypo	Missing or inconsistent data	TSH 0.3-5.1 Total T4	17 signs and symptoms of hypothyroidism and 3 thyroid neutral symptoms (Colorado symptom survey)	Schypo group reported significantly more total symptoms than euthyroid group. Schypo 13.7% total symptoms vs 12.1% Euthyroid
Bianchi GP[15] 2004) Italy	Consecutive, Community based	Adults 45 Schypo 26 Ohyper 2031 population norms	Existing disease	TSH 0.35-4. FT4 8.0 -19	Health status (SF-36) and Nottingham Health Profile Self reported	All aware of diagnosis. Health status not significantly impaired in Schypo compared with population norms
Razvi S [181] 2005 UK	Primary care based	Adults 100 consecutively diagnosed schypo	Existing chronic disease, history of thyroid dysfunction	TSH 0.4-4.0 FT4 9-25	Health status (SF-36) Self reported	Perceived health status significantly impaired in Schypo

Table 5.0 Symptoms, health status and subclinical hypothyroidism continued

Author, publication date	Design	Participants/ setting	Exclusions	Serum TSH (mU/L) and FT4 (pmol/L) reference criteria for Schypo	Outcome measures (Instrument used)	Summary of results
Reuters VS[177] 2006 Brazil	Case-control study Outpatients	≥18 yrs 57 Schypo 37 Euth	TSH >20mIU/L, treatment for thyroid dysfunction, chronic disease, medication known to interfere with TFT	TSH 0.4-4.0 FT4 10.2-23.0	14 symptoms and signs of hypothyroidism (Zulewski scale) Self reported	Schypo group presented with significantly higher clinical score compared with euthyroid group
Gulseren S [24] 2006 Turkey	Prospective follow-up study Outpatients	Women 18-75 yrs 33 Schypo 20 controls 51 Ohypo	Past psychiatric disorder, other chronic disease	TSH 0.35-5.50 FT4 11.45-23.2l	Symptoms checklist developed by researchers Health status (SF 36)	Symptoms identical in Ohypo and Schypo. No individual symptoms distinctive of Schypo. Health status scores in Schypo group were significantly lower than Euth group
Bell RJ [180] 2007 Australia	Community-based cross-sectional study.	Women 18-75 yrs 80 Schypo 240 controls	Pregnancy or 6 weeks postpartum, chronic disease, concomitant treatment	TSH 0.5-4.0 FT4 10.0-19.0	Health status (SF-36) Psychological General Well-being Index (PGWI) Self reported	No association with lower well-being or impaired health-status Schypo compared with control
Vigario P [176] 2009 Brazil	Cross sectional study Outpatients	Women ≥ 18 years 152 Schypo 66 Euth 14 Ohypo	Medication known to affect thyroid function, current hospitalisation, chronic disease	TSH ≥4.0 FT4 10.3-24.5 Repeat TFT 6 week interval	Symptoms (Zulewski scale) Health status (SF36)	Frequency of abnormal clinical scores significantly different between 3 groups. Clinical exam, physicians blind to TF

Summary of chapter 5.0

Nine relevant studies evaluating symptoms or perceived health status in individuals with subclinical hypothyroidism compared with euthyroid subjects were identified. In general, studies were conducted in adults of all ages with the exception of one retrospective study conducted in individuals aged >60 years. The populations sampled were sourced predominantly from the outpatient setting with little data being derived from community dwelling or primary care based study cohorts. Only two of the studies evaluated both symptoms and health status. The assays for measurement of thyrotrophin and the reference criteria upon which subclinical hypothyroidism was defined also varied between the studies. In terms of outcomes, tools employed for evaluation of symptoms were also varied. The available data provides some evidence for the presence of symptoms suggestive of overt hypothyroidism in individuals with subclinical hypothyroidism compared with euthyroid individuals. In general it seems that fewer signs and symptoms are observed in the general population compared with patient populations. Overall, findings are limited by small sample sizes, different outcome measures and heterogeneity of populations studied. There is also a lack of data related to symptoms in elderly individuals and it is unclear whether symptoms in older individuals with subclinical hypothyroidism are a pathophysiological consequence of thyroid dysfunction or merely a physiological alteration due to advancing age. Poor health related quality of life or impaired health status may be important factors to consider when making decisions about the management of subclinical hypothyroidism. More-over, the relationship between symptoms, impaired health status and thyroid function has yet to be fully elucidated since impaired health status may be an outcome

of subclinical hypothyroidism or a consequence of symptoms. In general, studies of outpatient populations demonstrate an association between subclinical hypothyroidism and symptoms and with impaired health status. These findings are unlikely to be applicable to the general population and as yet have not been confirmed in larger community based cohorts. In summary, on the basis of the available evidence, questions related to the presence of symptoms in subclinical hypothyroidism and the impact of subclinical hypothyroidism on perceived health status remain unanswered.

In the current chapter, literature related to expression of symptoms in subclinical hypothyroidism was reviewed and summarised. In the next chapter, literature related to expression of symptoms in subclinical hyperthyroidism will be presented.

CHAPTER 6 SYMPTOMS AND SUBCLINICAL HYPERTHYROIDISM

Overview of chapter 6

As in the previous chapter the articles retrieved in the literature search will be presented and discussed alongside the systematic review by Biondi et al. Since another aim of this thesis is to characterise symptom expression and health status in subclinical hyperthyroidism, diagnostic indices and other instruments previously used for assessment of health status in individuals with subclinical hyperthyroidism and euthyroid subjects will be described in this chapter.

As previously described in chapter 3 this thesis will focus solely upon endogenous subclinical hyperthyroidism since the clinical consequences and characteristics of this spontaneous form of thyroid dysfunction are less established and are more frequently encountered by primary care practitioners. The principal difference between these subgroups of subclinical hyperthyroidism is that the exogenous form has been induced either intentionally or unintentionally through administration of thyroxine replacement therapy. In this chapter, studies which exclusively include individuals with exogenous subclinical hyperthyroidism will not be reviewed because extrapolation of findings to individuals with endogenous subclinical hyperthyroidism may not be appropriate. This is particularly so in relation to symptom expression and perceived health status because individuals with exogenous subclinical hyperthyroidism may have previous experience of ‘thyroid symptoms’ and as such may be more sensitive to changes in their health. Similarly, individuals receiving treatment for overt thyroid dysfunction may have greater health awareness due to frequent contact with the health services.

6.1 Results of the literature search

The literature search strategy and results were reported in Chapters 3 and 4. Ten papers evaluating and symptoms or perceived health status in individuals with subclinical hyperthyroidism and euthyroid individuals were identified. Studies were excluded from review in this chapter if they involved individuals receiving treatment for thyroid dysfunction and only included individuals with subclinical hyperthyroidism without a control comparison.

Biondi et al suggest that symptoms are less specific and less severe in endogenous subclinical hyperthyroidism than those observed in overt hyperthyroidism. This is particularly so in older individuals. Like subclinical hypothyroidism, the intensity of symptoms is likely to be related to the duration of subclinical hyperthyroidism and the individual's sensitivity to thyroid hormone excess.

To asses whether individuals with subclinical hyperthyroidism selected from a non patient population exhibited similar signs and symptoms to those found in patients with subclinical hyperthyroidism Schlote et al measured serum thyrotrophin concentration in 6884 workers. [182] Screening identified 228 (3.31%) with concentrations lower than the reference range (<0.21mIU/L), 65 (0.9%) with concentrations higher than the reference criteria and 6591 within the reference range. Further testing, application of exclusion/inclusion criteria and time constraints lead to the exclusion of approximately 75%. The final sample comprised 16 individuals with exogenous subclinical hyperthyroidism, 15 individuals with exogenous subclinical hyperthyroidism and 27 age

and gender matched euthyroid controls. Signs and symptoms were evaluated in according to the Crooks index of hyperthyroidism. The Crooks clinical index is a diagnostic index developed in the 1950s to facilitate objectivity and improve accuracy of clinical assessment of overt hyperthyroidism. The index comprises eight symptoms (breathlessness on effort, palpitation, lethargy, sensitivity to heat, excessive sweating, nervousness, increased appetite and weight loss) and 11 signs (palpable thyroid, bruit over thyroid, lid retraction, lid lag, exophthalmos [bulging or protruding eyeballs], hyperkinetic movements, fine finger tremor, clammy hands, systolic and diastolic blood pressure and rapid pulse rate). [41,48] Schlote et al failed to demonstrate any significant differences between the three thyroid function groups with respect to total symptom score. A significant increase in the frequency of palpitation was observed in patients with endogenous subclinical hyperthyroidism compared with controls (28.6% versus 3.8% $p<0.025$). Although overall frequency of symptoms reported was low, symptoms of nervousness, excessive sweating and preference for the cold were present in around 33% of subjects in each of the three thyroid function groups. In terms of signs of hyperthyroidism, fine finger tremor was the only clinical sign observed and again this sign was present in each of the thyroid function groups. These study findings are unlikely to be generalisable due to the fact that a large number of the population were excluded from the statistical analysis.

In another study by Schlote et al, the Crooks index was administered to a patient population comprising 35 individuals with subclinical hyperthyroidism, 60 with overt hyperthyroidism and 28 euthyroid individuals. [171] The findings contradict the first study. A significantly greater proportion of the subclinical hyperthyroidism group compared with

the euthyroid group presented with palpitation (50% versus 0%, p<0.001), weight loss (42% versus 15%, p<0.01), breathlessness on effort (25% versus 15%, p<0.05) preference for cold (42% versus 8%, p<0.01) and excessive sweating (58% versus 15%, p<0.01). Three signs were also present in a significantly greater proportion of individuals with subclinical hyperthyroidism compared with euthyroid individuals. Palpable thyroid was observed in 75% of the subclinical hyperthyroidism group compared with 27% of the euthyroid group, p<0.001), fine finger tremor in 50% of those with subclinical hyperthyroidism compared with 15% of euthyroid subjects (p<0.001). Similarly, systolic blood pressure was significantly higher in the subclinical hyperthyroidism group compared with the euthyroid group (130 mmHg versus 120mmHg, p<0.05). Additionally total symptom score was significantly greater in individuals with subclinical hyperthyroidism compared with euthyroid individuals (6.0 versus -4.6; p<0.001). [182] These two studies highlight the difference between patient and non-patient populations and further demonstrate that samples sourced from the outpatient setting are unlikely to be representative of the general population.

The Crooks index was also administered in a prospective UK based study including 15 consecutive elderly patients with subclinical hyperthyroidism, 10 elderly hyperthyroid patients and 10 euthyroid patients. Again, the total symptom score of the group with subclinical hyperthyroidism (-0.7 ±1.6) was significantly higher than the group with euthyroidism (-5.6 ±1.5; p <0.05). [183] Although all patients in the study were aware of their thyroid status, the examiner conducting the clinical assessment was blind to category of thyroid function limiting observer bias. Sgarbi et al reported similar clinical findings in accordance with the Crook index in a study of 10 individuals with subclinical

hyperthyroidism compared with 10 age, gender and BMI matched euthyroid controls. [184] At baseline the Crooks clinical score was significantly higher in individuals with subclinical hyperthyroidism compared with euthyroid controls (12.0 versus -1.0 respectively, $p<0.001$). The clinical index was significantly correlated with serum thyrotrophin but not free thyroxine concentration. The main symptoms present in individuals with subclinical hyperthyroidism were palpitation, tiredness, excessive sweating, nervousness, weakness and preference for cold. The findings of Sgarbi et al and Stott et al demonstrate a significant difference in the prevalence of symptoms in patient populations with endogenous subclinical hyperthyroidism. Patient populations are more likely than the general population to have severe symptoms and/or co-morbid conditions. It is also possible that these patients have different health seeking behaviour and/or better health education and awareness than the general population. Due to the small sample size and outpatient setting these study findings are unlikely to be generalisable.

A more recent study of young and middle aged individuals with endogenous subclinical hyperthyroidism also described an increase in symptoms compared with age matched controls. [185] Biondi et al used the physician administered hyperthyroid symptom rating scale (HSRS) to assess symptoms in 23 patients with untreated, stable subclinical hyperthyroidism and 23 age and gender matched controls. The hyperthyroid symptom rating scale (HSRS) was developed and described in 1988 by Klein et al as an instrument intended for clinical assessment and management of patients with overt hyperthyroidism. [42] Symptom selection for inclusion in the HSRS was based upon two previous studies demonstrating a difference in prevalence of symptoms between

euthyroid and hyperthyroid subjects which used an established diagnostic index to score the presence and absence of symptoms of hyperthyroidism. [41,48] The HSRS scale comprises ten items that rate nervousness, diaphoresis, heat intolerance, motor activity, tremor, weakness, hyperdynamic precordium, diarrhoea, weight loss and appetite. The scale is an observer rated scale with information needed to rate each item obtained through review of medical history and physical examination. This scale has been widely used in studies to assess signs and symptoms of hyperthyroidism. [185, 186,187] Items are scored on a scale of 0-4 and summed to give a total score (0-40). A higher score indicates more severe symptoms suggestive of overt hyperthyroidism. Biondi et al described a significantly greater mean HSRS score in individuals with subclinical hyperthyroidism when compared with euthyroid controls (9.8±5.5 versus 4.3±2.2; $p < 0.001$). As observed in other studies conducted in patient populations, a greater prevalence of palpitations, nervousness, tremor, heat intolerance and sweating was predominantly responsible for the difference in mean symptom score observed between the two groups. [188]

The hyperthyroid symptoms rating scale was also used to assess symptoms in 48 women under the age of 65 years and 48 euthyroid women matched by age, body mass index and menopausal status. Similarly, the mean HSRS score was significantly higher in women with subclinical hyperthyroidism compared with euthyroid controls (9.0 versus 4.2; $p<0.01$). [159] In contrast, a large cross-sectional study with 3790 participants with no previous thyroid dysfunction reported no association between subclinical hyperthyroidism and mental or physical complaints. [189] This study used Von Zersson's

complaints scale to evaluate 38 non thyroid specific symptoms in 61 individuals with subclinical hyperthyroidism and 2244 euthyroid individuals without evidence of goiter. Participants were asked to rate the degree to which they suffered each complaint using a scale of absent, mild, moderate or severe. The symptoms evaluated were back pain, joint pain, weakness, abdominal feeling of fullness, faintness, heartburn, irritability, nervousness, heavy legs, sleeplessness, dizziness, fatigue, headache, deafness, sudden difficulty breathing, feeling of suffocation, palpitation, anxiety, stomach ache, loss of energy, poor concentration, inner tension, sensitivity to weather, depression, numbness to hands or feet, globus sensation, breathlessness, difficulty swallowing, chest pain, nausea, rumination, nervous legs, hypersensitivity to warmth, hypersensitivity against cold, excessive need of sleep, tremor, neck and shoulder pain and loss of weight. Individuals with subclinical hyperthyroidism did not differ from controls with respect to total symptom score (mean symptoms score of 61.8 versus 64.7 respectively; $p<0.14$). Significant differences between the two groups did however exist with respect to four single items with scores for back pain, depression and globus sensation being significantly lower in individuals with subclinical hyperthyroidism compared with controls and weight loss being significantly greater in individuals with subclinical hyperthyroidism compared with controls. The instrument used to evaluate symptoms in this study was not specifically designed to assess symptoms associated with thyroid dysfunction therefore the sensitivity of this tool for detection of symptoms is limited. Whilst all statistical analyses were controlled for age, gender and education further confounding variables associated with other co-morbid conditions were not considered. These findings should therefore be interpreted with caution. [189] In another

study, a 44 item symptoms checklist and the SF36 were administered to 13 patients with subclinical hyperthyroidism attending a hospital endocrinology clinic. [24] Twenty euthyroid patients were also evaluated. The most frequent symptoms in the subclinical hyperthyroidism group were excessive sweating (46.2%), palpitation (30.8%), nervousness (30.8%) and pain at extremities (23.1%). These symptoms were also the most frequent symptoms in the group with overt hyperthyroidism. However, compared with the subclinical hyperthyroidism group, these symptoms were more often present (excessive sweating 55%, palpitation 53%). [24] The frequency of presentation of these symptoms in the control group was not reported. In general, perceived health status was worse in the overt and subclinical hyperthyroidism groups than in the control group. In terms of mean mental component summary scores the subclinical hyperthyroidism group (48.8 ± 9.1) was intermediate between the euthyroid (51.5 ± 9.4) and overt hyperthyroidism groups (39.7 ± 12.9; ANOVA between groups $p<0.001$). Likewise, mean physical component summary score in the group with subclinical hyperthyroidism (46.6 ± 7.9) was better that the group with overt hyperthyroidism (45.0 ± 8.9) however worse than the euthyroid group (50.2± 5.9; ANOVA between group p 0.02). These data are potentially limited because individuals were aware of thyroid function status when completing the symptom and perceived health status questionnaire. Response bias therefore cannot be ruled out. [24]

The mean mental component summary scores did not differ between 52 women with subclinical hyperthyroidism and 156 age matched controls (49.2 versus 49.6 respectively). Likewise, the mean physical component summary scores were similar between cases with subclinical hyperthyroidism and age matched controls (49.2 versus

49.5 respectively). [180] A key feature of this study was that the women were unaware of thyroid status, removing reporting biases. However, this study is limited by a low participation rate (11%) meaning the study sample are unlikely to be representative of the community from which they were sourced and data is unlikely to be generalisable.

Table 6.0 Symptoms and endogenous subclinical hyperthyroidism

Author	Design and setting	Participants	Exclusions	Reference range for serum TSH (mIU/L) and FT4 (pmol/L)	Instrument used/ no of items and completion	Summary
Stott DJ[183] 1991 UK	Prospective, Case control, Outpatients	61-93 yrs 15 Schyper, 10 Ohyper 10 euthyroid controls	No previous thyroid dysfunction	TSH 0.2 FT4 8.8-23.2	Crooks index 17 items (8 symptoms, 9 signs) Physician completed	Clinical score similar in subclinical and overt dysfunction and higher than euthyroid
Sclote B [182] 1992 Germany	Cross sectional, Community based	43-52 yrs 16 EnSchyper, 15 ExSchyper, 27 controls	Hormonal, psychosomatic, psychiatric disease or chronic pain syndrome	TSH 0.21-3.5 Total T4, 45-130	Crooks index Crooks index 17 items (8 symptoms, 9 signs) Physician completed	No association between symptoms and endogenous subclinical hyperthyroidism
Sclote B [171] 1992 Germany	Cross sectional, Outpatients	≥18 yrs 60 Ohyper 35 Schyper 28 age matched, euthyroid controls	History of psychiatric disease, drugs or disease known to affect TFT	TSH 0.2-3.55 TotalT4 45-130	Modified version of the Crooks index, 12 items (6 symptoms, 6 signs). Physician completed	Significantly greater prevalence of 5 symptoms and 3 signs in Schyper. Total modified score significantly greater in Schyper
Biondi B [188] 2000 Italy	Case control, Outpatients	30 -53yrs 23 subclinical, 23 euthyroid controls	Receiving medication without non thyroidal illness	TSH 0.3-3.8 FT4 7.7-20.6	Hyperthyroid symptom rating scale (HSRS) 10 items (9 symptoms, 1 sign) Physician completed	Significantly higher symptom score
Sgarbi JA[184] 2003 Brazil	Prospective, Case control, Outpatients	16-72 yrs 10 subclinical and 10 euthyroid controls	No history of thyroid dysfunction, respiratory, psychiatric, cardiovascular disease or drugs affecting TFT	TSH 0.32-5.2 FT4 10.3-24.5	Crooks index 17 items (8 symptoms, 9 signs) Physician completed	Clinical score significantly greater in Schyper

Table 7.0 Symptoms and endogenous subclinical hyperthyroidism continued

Author	Design and setting	Participants	Exclusions	Reference range for serum TSH (mIU/L) and FT4 (pmol/L)	Instrument used/ no of items and completion	Summary
Bianchi GP [15] 2004 Italy	Consecutive, Community based	Adults 45 Schypo 26 Ohyper 2031 population norms	Existing disease	TSH 0.35-4. FT4 8.0 -19	Health status (SF-36) and Nottingham Health Profile Self reported	All aware of diagnosis. Health status not significantly impaired in Schyper compared with population norms
Grabe HJ[189] 2005 Germany	Cross sectional, Community based	46-59 yrs 61 Schyper 3317 Euth 16 Ohyper	Known thyroid dysfunction	TSH 0.3-3.0 FT4 10-25	Von Zerssen's complaints survey (31 mental and physical complaints). Self completion	No association between symptoms and Schyper, non thyroid specific symptom measure
Gulseren S[24] 2006 Turkey	Prospective follow-up Outpatients	Women ≥18 yrs 13 Schyper 20 controls	Past psychiatric disorder and other chronic disease, cancer	TSH 0.35-5.50 FT4 11.5-23.2	44 item symptom checklist administered by researchers Health status (SF 36)	Reduced mental and physical component scores in Schyper.
Bell RJ[180] 2007 Australia	Cross sectional, Community based,	Women <18-75 yrs 52 Schyper 156 controls	Pregnant, post partum, history of chronic disease, malignancy or cancer treatment	TSH 0.5-4.0 FT4 10.0-19.0	SF36- 36 items PGWI 22 items Self completion	No significant differences in health status summary scores
Rosario PW [159] 2008 Brazil	Case control, Outpatients	Women ≤65 yrs 48 Schyper 48 matched controls	History of or treatment for thyroid dysfunction, drugs interfering with TFT, osteoporosis oestrogen, corticosteroids	TSH 0.3-5.0 FT4 9.63-23.17	Hyperthyroid symptom rating scale (HSRS) 10 items (9 symptoms, 1 sign) Physician completed	Mean symptom score significantly higher in Schyper

Summary of chapter 6

This chapter focused upon literature evaluating symptoms or perceived health status in individuals with endogenous subclinical hyperthyroidism compared with euthyroid subjects.

Ten studies of symptoms or perceived health status in individuals with subclinical hyperthyroidism compared with euthyroid controls were identified and examined. In the main, thyroid specific instruments were used to assess symptoms, namely the Crooks diagnostic index and the hyperthyroid symptoms rating scale. One study used a reduced version of the Crooks index comprising 12 rather than 17 signs and symptoms suggestive of overt hyperthyroidism. Only one study employed a non thyroid specific symptom tool to measure prevalence of symptoms. The majority of studies were performed in outpatient endocrinology clinics with just two studies being conducted in the community setting, meaning findings are not generalisbable to the general population. In general the populations comprised mixed gender, middle aged adults however three studies comprised women only and two studies exclusively included individuals older than 60 years of age. Overall, studies report a greater prevalence of palpitations, excessive perspiration and preference for cold in individuals with subclinical hyperthyroidism compared with euthyroid individuals. The majority of studies investigating symptoms in individuals with endogenous subclinical hyperthyroidism using the Crooks index reported significantly higher symptom scores in individuals with subclinical hyperthyroidism compared with controls. Similarly, the case control studies conducted in the outpatient setting and employing the hyperthyroid symptoms rating

scale demonstrated significantly higher symptom scores in individuals with endogenous subclinical hyperthyroidism compared with euthyroid individuals. Community based studies failed to demonstrate any association between endogenous subclinical hyperthyroidism and symptoms or impaired health status. These findings are limited, however, by a low recruitment rate and use of a non thyroid specific and potentially insensitive instrument for assessment of symptoms. It is therefore difficult to know whether the cohort studied is representative of the population from which they were sourced and it is likely that important symptoms are not being measured.

With respect to perceived health status, data are again generally derived from small studies of highly selected populations. Whilst these data do demonstrate impaired mental and physical health status, these findings are not corroborated in larger community based studies. An additional methodological issue with most of these studies is that participants are aware of their thyroid function status meaning that results may be subject to response bias. Similarly in studies where physical examination was required, the examiners were not always blind to the subjects' thyroid function status meaning that observer bias cannot be entirely ruled out.

In summary, current data suggest that endogenous subclinical hyperthyroidism is associated with symptoms and impaired health status. On the whole, this evidence has been generated by small studies conducted in patient populations and there is a lack of data related to symptom expression and perceived health status in the general population or in older individuals with endogenous subclinical hyperthyroidism. To further clarify the relationship between subclinical hyperthyroidism and symptoms and

health status, findings require replication in larger prospective community dwelling samples.

In summary, on the basis of the available evidence uncertainty remains with respect to the presence of symptoms in subclinical hyperthyroidism and impact of subclinical hyperthyroidism on perceived health status.

In the current chapter, literature related to the expression of symptoms in subclinical hyperthyroidism was reviewed and summarised. In the next chapter, the evidence presented so far in this thesis is reviewed and summarised. In addition the next chapter explores and clarifies the rationale for the cross-sectional study evaluating symptoms in individuals aged 65 years or more with and without subclinical thyroid dysfunction.

CHAPTER 7 STUDY RATIONALE

Overview of chapter 7

This chapter summarises the evidence presented so far in this thesis and clarifies the clinical relevance of subclinical hyperthyroidism and hypothyroidism in terms of pathophysiological consequences and physical signs and symptoms. An additional aim of this chapter is to explore the rationale for evaluating symptoms in community dwelling individuals aged 65 years or more with and without subclinical thyroid dysfunction, in order to further contextualise the thesis.

Evidence presented in the initial two chapters demonstrates that overt thyroid dysfunction is a clinically important disorder commonly encountered in primary care. Biochemical evaluation of serum thyrotrophin and thyroxine concentrations allows further categorisation of thyroid dysfunction as either overt or subclinical thyroid dysfunction. The distinction made between these categories is based upon the concentration of serum free thyroxine (FT4), with concentrations of FT4 inside the reference range in the presence of elevated or depleted thyrotrophin defining subclinical dysfunction, and concentrations of both serum FT4 and thyrotrophin outside the reference range indicating overt dysfunction. In chapters 3 to 6, the large body of literature exploring the clinical presentation and pathophysiological impact of subclinical thyroid dysfunction was described and summarised. These chapters demonstrate that whilst exploration has been widely undertaken, research findings are inconsistent and the clinical importance of subclinical thyroid dysfunction remains largely unclear. This is

mainly attributable to the small sample sizes and heterogeneity of the outcomes studied. In addition to the wide ranging outcome measures, evaluation of the evidence is further complicated by heterogeneity of patient populations. Whilst many of the smaller studies demonstrate statistically significant differences between individuals with subclinical thyroid dysfunction and euthyroid subjects, the clinical significance of these differences is unclear. The use of different assays for measurement of serum thyrotrophin, different reference criteria used to define subclinical thyroid dysfunction and the reduced representativeness of the samples studied make interpretation and extrapolation of findings to community dwelling populations unfeasible. More robust data are needed to determine the clinical impact and relevance of subclinical thyroid dysfunction, especially in terms of impact in an elderly primary care population. Age seems to have significant impact upon both the clinical expression and biochemical profile of thyroid dysfunction. Data support an increase in the prevalence of subclinical thyroid dysfunction with advancing years. However, there is a lack of data related to the clinical consequence of subclinical thyroid dysfunction in the elderly community dwelling population and extrapolation of data derived from young or middle aged cohorts is inappropriate. There are data that demonstrate a decline in the frequency of classical signs and symptoms of thyroid dysfunction in older patients with overt thyroid dysfunction compared with younger subjects suggesting that age also modifies clinical presentation. Diagnosis of subclinical thyroid dysfunction based on symptom presentation is therefore likely to be more difficult in older individuals, not least because many of the traditional symptoms associated with overt thyroid dysfunction accompany normal ageing. Despite these difficulties, recent evidence demonstrates a low prevalence of undiagnosed overt thyroid

dysfunction in the UK community setting. This suggests that GPs have a high index of clinical suspicion and are adept at diagnosing thyroid dysfunction in this population. Some studies, however, suggest that GP knowledge is limited regarding the proper use of laboratory tools and describe variable practice with respect to both testing and treatment of subclinical thyroid dysfunction. Similarly, others report a large number of requests for thyroid function testing being generated by primary care physicians and suggest that thyroid dysfunction is increasingly a laboratory diagnosis. A lack of clear evidence related to which symptoms necessitate further investigation of thyroid function and guidance in relation to the frequency of thyroid function testing in individuals presenting with new or persistent symptoms may be responsible. Current guideline documents and expert opinion are also inconsistent with respect to management of subclinical thyroid dysfunction. The principal reason for this lack of consensus with respect to screening and management of subclinical thyroid dysfunction as chapters 3-6 have shown is an insufficiency of good quality data demonstrating expression of symptoms and other pathophysiological manifestations of subclinical thyroid dysfunction. Evidently, symptoms typical of overt thyroid dysfunction accompany normal aging and are often present in individuals with normal thyroid function. Whether symptoms suggestive of overt thyroid dysfunction in elderly individuals are pathophysiological or physiological in origin therefore requires clarification. Further evidence of an adverse symptom profile in elderly individuals with subclinical thyroid dysfunction would support the need for screening and treatment in this population. Likewise, determination of an adverse impact on general health status may serve as an aid to treatment decision making and management in elderly individuals with subclinical thyroid dysfunction.

Although observation of clinical signs and symptoms alone seems to be neither sensitive nor specific for the diagnosis of thyroid dysfunction, guidance based upon symptom expression would further support GP decision making when ordering thyroid function testing. Characterisation of symptoms associated with subclinical hypothyroidism and subclinical hyperthyroidism in this population could improve GP detection of individuals most likely to benefit from testing and justify treatment. Additionally, unnecessary investigation and/or treatment of subclinical thyroid dysfunction in this population based upon presence of symptoms could be avoided.

As previously stated, the aim of this thesis is to further clarify the pathophysiological consequences of subclinical hyperthyroidism and subclinical hypothyroidism and determine the association between symptoms suggestive of overt thyroid dysfunction and subclinical thyroid dysfunction in the elderly community dwelling population.

In achieving this aim, there are four objectives which have been previously described. In evaluating the pathophysiology of subclinical thyroid dysfunction this thesis has so far reviewed a large body of existing evidence pertaining to the adverse clinical consequences and manifestation of symptoms in subclinical thyroid dysfunction.

CHAPTER 8 STUDY METHODOLOGY

Overview of chapter 8

In order to contextualise the methodology of this thesis, the first section of this chapter focuses on the historical setting and the methodology of the original Birmingham Elderly Thyroid Study (BETS I). After this, the full methodology of the current study; (BETS II follow-up study) is reported. This includes both the methodology of i) the longitudinal follow-up study and ii) the nested cross-sectional study which is the principal focus of this thesis.

8.1 Historical setting and methodology of the first BETS

The first Birmingham Elderly Thyroid Study (BETS I) was conducted between 01/11/02 and 30/11/04 to determine the prevalence of subclinical thyroid dysfunction and unidentified overt thyroid disease in a large (n=5881) UK community based elderly population. [63] In addition BETS I explored the relationship between thyroid function and i) prevalent atrial fibrillation (AF) [151] ii) cognitive function, [145] and subsequently the effect of thyroxine replacement therapy on cognitive function in subjects with subclinical hypothyroidism. [190]

The BETS I population was recruited from 20 general practices in the greater Birmingham area of the UK; this geographical area covers a range of socioeconomic backgrounds and is broadly representative of urban areas of England and Wales. At the time of this initial study, practice registers were searched to identify eligible individuals. To maximise generalisability to routine general practice, all patients aged 65 years or older were invited to participate. Individuals were excluded if they had an active diagnosis of thyroid disease, were receiving therapy for thyroid disease, had undergone thyroid surgery or treatment within the preceding 12 months, were unwilling or unable to give informed consent or if the GP considered contact to be inappropriate (e.g. recently bereaved, terminal illness). All eligible patients received an invitation letter, a study information sheet and an invitation reply slip.

All patients indicating that they were willing to participate were offered a study appointment with the research nurse at their general practice. At the clinic session subsequent to obtaining written informed consent, a 12 lead Electrocardiograph (ECG)

was performed and blood was taken for thyroid function testing (TFT). Thyroid function tests comprised measurement of thyrotrophin (TSH) and FT4. Measurement of FT3 was also undertaken as dictated by the routine laboratory protocol, when levels of thyrotrophin below the lower limit of the reference range were detected. Table 8.0 demonstrates the thyroid status of individuals screened during BETS I. At the time of this initial study, measurement of thyroid function was performed using chemiluminescent immunoassay (Advia Centaur assay produced by Bayer Diagnostics, Newbury, UK). Thyroid status was classified in accordance with standard reference range criteria for thyrotrophin, FT4 and FT3 used at the laboratory performing testing (Regional Endocrine Laboratory at the University Hospital Birmingham National Health Service Foundation) during the period 2002-2004 (Table 8.0).

Table 8.0 Categorisation of thyroid status

Thyroid status	n = 5881 (%)	Serum thyrotrophin (TSH) concentration mIU/L	Serum thyroxine (FT4) concentration pmol/L	Serum Tri-iodothyronine (FT3) concentration pmol/L
Overt Hyperthyroidism	15 (0.3)	< 0.40	> 20	>6.5
Subclinical hyperthyroidism	128 (2.2)	< 0.40	9 – 20	3.5-6.5
Euthyroid total	5538 (94)	0.4 – 5.5	9 – 20	NA
Subclinical hypothyroidism	168 (2.9)	>5.50	9 – 20	NA
Overt hypothyroidism	23 (0.4)	>5.50	< 9.0	NA
Unclassified	9 (0.2)	NA	NA	NA

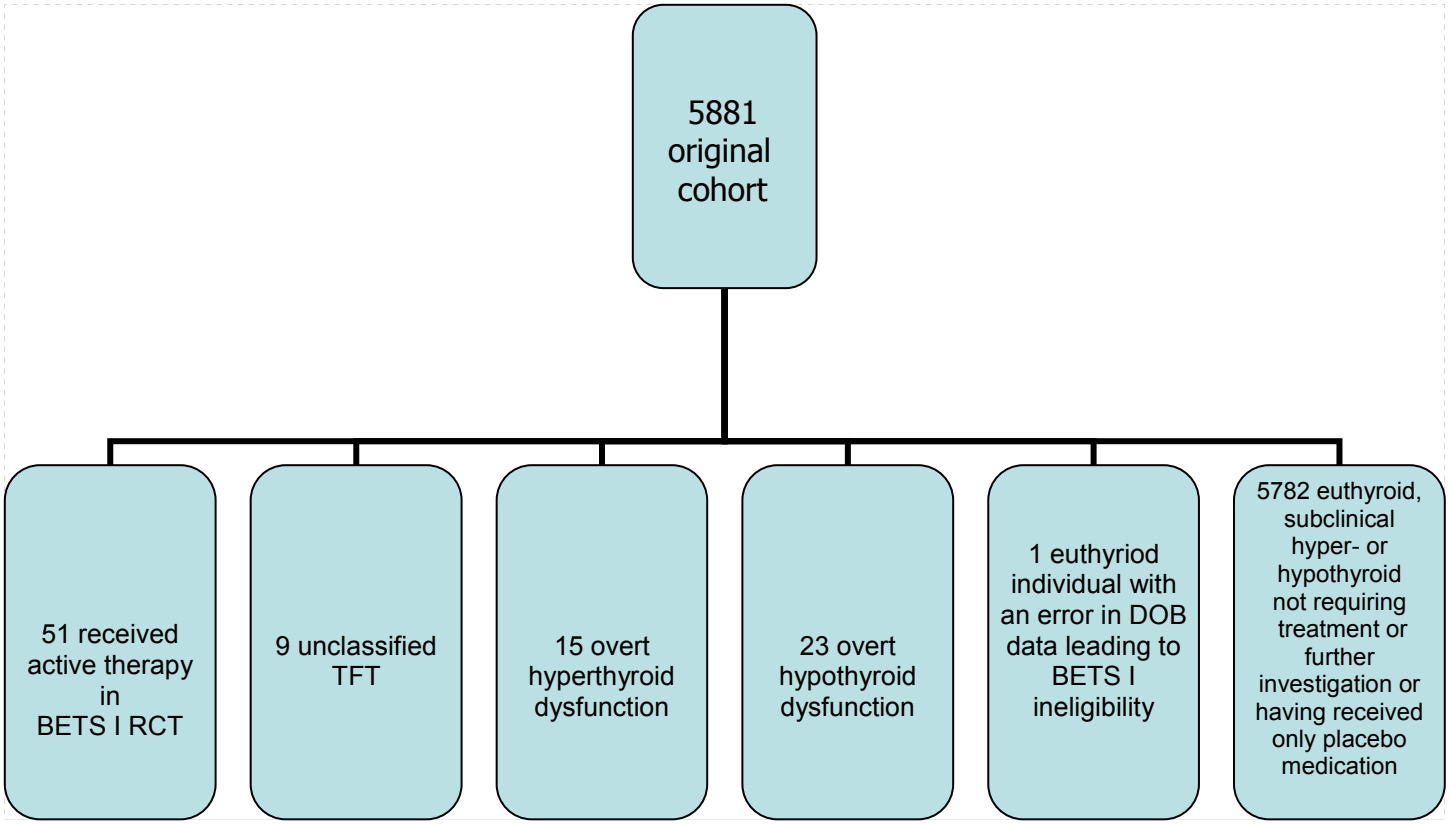
Depression and anxiety and cognitive function were measured using previously validated instruments (Hospital Anxiety and Depression Scale) [191] and standardised tests of cognition (Mini Mental State Examination (MMSE) [192] and the Middlesex Elderly Assessment of Mental State (MEAMS) extensively used with elderly people. [193] In addition all participants completed the EQ5D to provide data on general health and well-being. The research nurse reviewed the practice held medical notes and recorded concomitant disease and medication.

8.1.1 Clinical follow-up as a result of thyroid screening during BETS I.

Patients identified during BETS I screening as having either overt hyperthyroidism (n=15) or overt hypothyroidism (n=23) received treatment for thyroid dysfunction in accordance with routine treatment protocols. Ninety four individuals classified as subclinically hypothyroid gave written informed consent to participate in the BETS randomised controlled trial (RCT) to investigate the effect of thyroxine replacement therapy on cognitive function in subjects with subclinical hypothyroidism. Fifty one of those received the active replacement therapy with the remainder receiving a placebo.

Classification of thyroid status based upon measurements of thyrotrophin, FT4 and FT3 for nine participants was not possible, and these individuals were referred to a thyroidologist for further clinical review. One further patient was excluded as subsequent validation confirmed age ineligibility. Overall, 5782 participants of the original study were classified as having euthyroid function, subclinical hyperthyroidism or subclinical hypothyroidism and did not require or receive further investigation or treatment in relation to thyroid status. This cohort forms the baseline population for the current study (Figure 8.0).

Figure 8.0 Clinical follow-up of the original cohort



8.1.2 Birmingham Elderly follow-up study (BETS II)

The primary objective of the current and second Birmingham Elderly Thyroid Study follow-up study (BETS II) was to re-screen thyroid function in the original cohort and determine the proportion of patients with subclinical thyroid dysfunction in the BETS cohort who revert to a euthyroid state, experience persisting subclinical thyroid dysfunction or develop overt thyroid dysfunction. The principal focus of the thesis is the nested cross-sectional study, the aims and objectives of which have been previously described.

8.1.3 Practice recruitment

All twenty practices that had participated in the original study were invited to participate. One practice was unable to participate at the time of follow up. The other 19 practices expressing an interest were visited by a member of the research team for provision of information about the study to include study background, aims and methods and to discuss issues relating to study organisation. All nineteen practices agreed to participate in the follow-up study.

8.1.4 Confirmation of patient eligibility

A list of patients who participated in the original study was generated from the BETS I database held within the Department of Primary Care Clinical Science (PCCS) at the University of Birmingham. The BETS I database was developed during the original study and contains all previously recorded data including patient characteristics, address and

contact details, medication and disease history and thyroid function test results from the original screening study.

8.1.5 Inclusion criteria

The patient lists were sent to the general practitioners (GPs) for confirmation of eligibility and contained the names of;

- Patients who were identified in the original screening study (BETS I) as having subclinical hyperthyroidism (defined by a TSH < 0.4 mIU/L, FT4 9-20 pmol/L and for FT3 3.5- 6.5 pmol/L) or subclinical hypothyroidism (characterised by a TSH >5.5 mIU/L and FT4 9-20 pmol/L) and who were untreated for thyroid dysfunction in BETS I.
- Patients classified as euthyroid (defined by TSH 0.4 -5.5 mIU/L and FT4 9-20 pmol/L) during the original BETS I study.

8.1.6 Exclusion criteria

The following individuals were excluded from the patient lists sent to GPs for confirmation of eligibility;

- Individuals identified with overt hyperthyroidism (TSH <0.4 mIU/L, FT4 >20 pmol/L and FT3 > 6.5pmol/L) or overt hypothyroidism (TSH >5.5 mIU/L and FT4 < 9 pmol/L) during the original study.
- Patients who received treatment such as thyroid surgery, radio-iodine therapy, anti thyroid medication and/or thyroxine for thyroid dysfunction during the original

study period either due to routine medical care or randomisation to the treatment arm of the BETS I randomised controlled trial.

- Individuals in BETS I for whom classification of thyroid status based upon measurement of TSH and FT4 was not possible.

The patient lists were verified by GPs who confirmed the patients' address, registration status (e.g. currently registered with the practice, no longer registered or deceased). GPs were also asked to make discretionary exclusions from the list if they judged contact with an individual to be inappropriate (e.g. individual recently bereaved, mentally impaired or terminally ill).

GPs returned the patient lists to the research office. Those excluded by the GPs were removed from the list of individuals eligible to receive an invitation to participate in follow-up study.

8.2 Study procedure

8.2.1 Recruitment

All eligible patients were sent an invitation letter, patient information sheet, an invitation reply slip and a freepost envelope. Patients were asked to read the information sheet, and then to complete, sign and return the reply slip indicating whether they wished to participate. Patients willing to participate were asked to provide a contact telephone number. A second invitation letter was sent if no response was received within 3 weeks of the initial letter being sent.

8.2.2 Arranging study appointments

All patients indicating they were willing to participate were telephoned and offered a 30 minute study appointment with a research nurse at their usual general practice. Those indicating that they were not willing to participate were not contacted further.

8.2.2.1 Appointment confirmation

Following the telephone call, patients agreeing to attend received a letter confirming their appointment date and time and a study questionnaire (*Appendix 3 Symptoms questionnaire*). Patients were asked to complete the study questionnaire prior to their appointment and return it to the research nurse during the clinic. Participants were not placed under any restrictions on eating or medication use before their study appointment.

8.2.3 Screening clinics

All clinics were conducted between 06/02/08 and 17/10/08. Research nurses trained in good clinical practice and the study protocol conducted the screening clinics. At each clinic appointment the research nurse explained the study and patients' questions were answered and concerns discussed. Written informed consent was obtained from all patients willing to participate.

8.2.4 Outcome measures

The principle outcomes were:

- Proportions of participants categorised in accordance with current reference criteria defined by the testing laboratory as euthyroid, subclinically hyperthyroid and subclinically hypothyroid.
- Prevalence of 12 current symptoms of overt hypothyroidism and 9 current symptoms suggestive of overt hyperthyroidism in thyroid function groups categorised in accordance with current laboratory reference criteria.
- Prevalence of 12 symptoms of overt hypothyroidism and 9 symptoms suggestive of overt hyperthyroidism that have increased in intensity during the previous 12 months in thyroid function groups categorised in accordance with current laboratory reference criteria.
- Level of perceived health status in thyroid function groups categorised in accordance with current laboratory reference criteria.
- Level of perceived health status in individuals reporting presence and absence of concurrent symptoms suggestive of overt thyroid dysfunction.

8.2.5 Ascertainment of outcomes

8.2.5.1 Case note evaluation

Initial recording of patient data was based upon patient reporting, with validation of data by inspection of medical records. All patients providing written informed consent to participate were asked about their current smoking status (to include the number of cigarettes or weight in grams of tobacco smoked per day) and their average alcohol intake each week. In addition, patients were asked whether they regularly consumed any products, supplementation or preparations of multi vitamins containing iodine or kelp. Details of first and second degree blood relatives who currently have or have previously had a diagnosis of thyroid dysfunction were also collected, including the relationship between them (i.e sibling, parent, or grandparent) and type of thyroid dysfunction if known. Routine general practice medical records were reviewed to collect data. To ensure full data capture for all patients irrespective of when they were screened in BETS I, the start date for the data collection period was defined as 01/11/02 (the start date of the BETS I screening study). All significant disease and major surgery occurring since 01/11/2002 were recorded (Table 8.1). These were diseases previously identified as potentially impacting on BETS I variables (thyroid function) or outcomes. Start dates and current status of treatment related to any of these diseases were recorded along with treatment end date where appropriate. Data related to thyroid surgery, radio-iodine therapy, anti thyroid drugs and thyroxine, start date and duration of treatment occurring since 01/11/02 were also recorded (Table 8.1)

Table 8.1 Concomitant diseases confirmed by review of case notes

Diagnosis
Anxiety
Atrial Fibrillation
Cancer
Cerebrovascular disease / Stroke / TIA
Dementia
Depression
Diabetes
Heart failure / Valve disease
Hypertension
Ischemic or Coronary Heart Disease or Angina
Irregular heart rhythm (other than AF which should be noted above)
Peripheral vascular or artery disease
Pituitary disease
Pulmonary disease / COPD / Asthma
Renal disease (Chronic and grade 3 or 4 only)

Review of the medical records allowed collection of data on use of drug therapies known to influence tests of thyroid function or to be indicative of significant medical diagnoses; this included current use of medications listed in Table 8.2.

Table 8.2 Drug categories

Drug / Drug Group
Amiodarone
Anti-depressant
Anxiolytic
Beta-adrenergic Blockers
Lithium
Major Tranquilizers
Morphine or other opioid analgesics
Glucocorticoids

8.2.5.2 Demographic data

Age was calculated using date of birth and either the date of the initial invitation to participate in screening (for non attendees) or the date of attendance at the screening clinic (for attendees). Socioeconomic status of an individual of retirement age may not be truly represented by measures that rely solely upon employment and education therefore the Index of Multiple Deprivation (IMD) 2004 was employed as a proxy measure of socioeconomic deprivation for this population. [194] IMD is a small area measure of neighbourhood deprivation calculated as the weighted average across seven domains of deprivation using data from the years 2000–2003 with lower scores indicating greater levels of deprivation. IMD scores are calculated at the level of Lower Super Output Areas (LSOAs), these being geographical units of varying size but containing a population of approximately 1500 at the time of the 2001 census which on average is smaller than the ward levels used in other indices such as Carstairs and Townsend (Table 8.3). [195] Furthermore, the use of multiple domains makes IMD a more

valid measure of deprivation in individuals of retirement age. IMD scores were converted into quartiles with quartile 1 representing the most affluent and quartile 4 the most deprived.

Table 8.3 Seven domains of the Index of Multiple Deprivation

Domains of the Index of Multiple Deprivation (IMD) [194]
Income
Employment
Health and disability
Education, skills and training
Barriers to housing and services
Living environment
Crime

8.2.6 Clinical evaluation

8.2.6.1 Venepuncture for thyroid function testing

Venepuncture was undertaken to obtain a blood sample for thyroid function testing. Samples were collected in plastic vacuette 4ml serum separator clot activator tubes. The blood sample and accompanying laboratory request form were labelled with study specific sticky labels. Study labels included the following: the BETS II study logo and study Id number, the patients' unique study Id number, patient gender, date and time of sample collection. The venepuncture protocol dictated that two attempts to obtain a blood sample could be made during the screening appointment. Where the research nurse was unable to obtain blood during the first screening clinic, patients were offered a second appointment for venepuncture only.

8.2.6.2 Transportation of blood sample to the laboratory for testing

Blood samples were collected, treated (gently inverted to activate clotting and stored at room temperature) and transported to the Regional Endocrine Laboratory at the University Hospital Birmingham National Health Service Foundation (UHB) for thyroid function testing in accordance with routine procedure for blood collection. Royal mail safeboxes™ were used to transport samples to the laboratory from general practices where UHB laboratory services were not routinely used (n=8 practices using safeboxes^{TM}). The effectiveness of this system of delivery in terms of receipt of unspoiled samples by the laboratory has been previously demonstrated in other studies conducted in Primary Care Clinical Sciences and was used in BETS I (Personal communication with the authors).

8.2.6.3 Measurement of thyroid function

Measurement of serum thyrotrophin (TSH) and FT4 concentration was undertaken on all individuals that provided written informed consent to participate to include individuals that had received a diagnosis of thyroid dysfunction since the original BETS I screening study. In accordance with the routine laboratory protocol, FT3 measurements were performed only when levels of TSH were below the lower reference limit of 0.3mIU/L. Serum TSH, FT4, and FT3 were measured by electrochemiluminescent immunoassays on the Roche E170 (Roche Diagnostics, Burgess Hill, UK). The TSH assay was calibrated against the second International Reference Preparation 80/558. The lower limit of reporting for the TSH assay was 0.02 mIU/L and the manufacturer's quoted mean functional sensitivity was 0.014 mIU/L. Serum TSH and FT4 concentrations were

determined for all individuals; where a serum TSH below the lower limit of the reference range was identified, serum FT3 was also measured. Laboratory reference ranges for serum TSH, FT4 and FT3 concentration and the associated inter-assay coefficient of variation are shown in Table 8.4.

Table 8.4 Reference range criteria

Thyroid parameter	UHB Reference Range	Intra –assay co-efficient of variation (associated range)
Thyrotrophin hormone	0.3-4.5 mIU/L	1.5% (0.5-33.0mIU/L)
Free Thyroxine	10-22 pmol/L	2.0-2.5% (9.0-66.0pmol/L)
Free Triiodothyronine	3.1-6.8 pmol/L	2.0-3.5% (4.0-21.0pmol/L)

8.2.7 Administration of the study questionnaire

The study questionnaire was enclosed with participant appointment confirmation letters and included an instruction for self completion before attendance at the screening clinic. Study questionnaires comprised two parts with section one evaluating presence of 18 current or recently changed symptoms suggestive of overt thyroid dysfunction and section two assessing perceived health status.

8.2.7.1 Review of the study questionnaire

The nurse reviewed each study questionnaire to ensure all questions had been fully completed, that only one response had been given per question and to ascertain symptoms that had not previously been reported to the GP and/or were considered indicative of other underlying disease. Research nurses received training in all aspects

of completion and inspection of the study questionnaire. Training emphasised the importance of self completion by participants and the nurses were reminded to refrain from selecting questionnaire responses at the request of participants. If for any reason a participant was unable to undertake this activity unaided or where items were incomplete the nurse assisted completion by reading the question to the participant and recording their answer on the questionnaire. Additional copies of the study questionnaire were available in each general practice for administration by the nurses in the event that participants had not received, were unable to complete, or had forgotten to bring the study questionnaire they had been previously allocated.

8.2.8.1 Transfer and feedback of thyroid function test results

Thyroid function test results were electronically transferred from the laboratory to the research office at the end of each day using an electronic transfer system that had been developed during the original study. This system allowed transfer of a file containing the thyroid function test results coded only by the unique patient identifier. Results were imported into the BETS II Microsoft access database, where anonymous TFT results were linked to individual participants based upon their unique study identification number. The TFT results were mail merged to the appropriate results letter and posted to participants and their GPs to be received within 28 days of the screening clinic. Participants with thyroid function tests that required consideration for treatment (with both TSH and FT4 levels outside the reference ranges) were referred back to their GP within 5 working days of results being received by the research office and patients were advised to make an appointment with their GP to discuss their results. Patients with test

results indicating subclinical thyroid dysfunction were advised to discuss their results with their GP at their next consultation. Where the laboratory reported that thyroid function testing had not been possible (due to insufficient or spoiled blood samples being received at the laboratory), patients were offered a second appointment for venepuncture only.

8.3 Development of the study questionnaire

Available tools for assessment of symptoms suggestive of overt hypothyroidism and overt hyperthyroidism and for evaluation of perceived health status were reviewed to identify appropriate instruments for use in the current study. Identification of one questionnaire comprising questions related to symptoms of both hypothyroidism and hyperthyroidism was unlikely therefore amalgamation of two instruments was necessary. The two principle characteristics of these instruments were determined to be suitability for self-completion by elderly individuals and administration to individuals with and without thyroid dysfunction. Additionally, because the thesis aimed to characterise symptoms associated with subclinical thyroid dysfunction as an aid to diagnosis, diagnostic indices specifically designed to distinguish between different grades of thyroid function were considered preferable to tools designed to assess change in symptoms before and after initiation of treatment. Furthermore, instruments that had been previously validated or widely utilised since the introduction of more sensitive third generation thyroid function assays in the 1980s were considered more relevant and therefore favourable.

Disease specific measures of health status and quality of life were excluded from further consideration because application of these tools to a population in which some individuals do not have the relevant disease is inappropriate and would not yield meaningful results. Only generic tools for assessment of perceived health status or health related quality of life were therefore explored.

8.3.1 Review of instruments used to measure health status

Two generic instruments that had previously been used to assess perceived health status in individuals with thyroid dysfunction were identified; the SF8 (a shortened version of the SF36) and the Nottingham Health profile (NHP). [196] The SF36 and the NHP have been extensively used in studies of chronic disease in the general population. The SF36 is also regarded as suitable for use with older adults. [178] More recently these tools were used by Bianchi et al to assess the burden of different grades of thyroid dysfunction on perceived health status. [15] The SF8 comprises eight items which are used to measure a range of health status to include mental and physical function and identifies both positive and negative aspects of health. The NHP comprises 45 items in two parts and measures only negative aspects. The NHP is therefore a less sensitive tool for measurement of how healthy individuals feel. The SF8 was therefore chosen for evaluation of perceived health status in the current study (Table 8.5).

Table 8.5 Evaluation of perceived health status

Instrument/Tool	Administration/ completion	Number of items	English language	Comments
Under active thyroid dependant quality of life questionnaire [198]	Questionnaire/ self completion	18	Yes	Disease specific measure of quality of life in hypothyroidism
Thyroid treatment satisfaction questionnaire (ThyTSQ) [199]	Questionnaire/ self completion	7	Yes	Treatment satisfaction questionnaire suitable for routine clinical monitoring or use in clinical trials
SF 36 [178]	Questionnaire/ self completion	36	Yes	Generic measure of health,widely used, simple to administer, short completion time and assesses positive and negative aspects of health
Nottingham health profile [197]	Questionnaire/ self completion	45 in two parts	Yes	Generic measure of health status, acceptable, short completion time, less sensitive than SF36 in hypothyroidism, assesses only negative aspects of health
Chronic Thyroid Questionnaire [14]	Interview/ clinician assisted	104	Yes	Disease specific measure of health status in hypothyroidism

8.3.2 Review of tools used for evaluation of symptoms

Four instruments that evaluated symptoms of overt hypothyroidism were identified (Table 8.6). [37,39,56,200] The Thyroid Symptom Questionnaire (TSQ) was immediately excluded because it had been specifically designed for monitoring of residual complaints following treatment. [200] The three remaining tools were the Billewicz index, the Zulewski score and the Colorado symptom survey. [37,39] The Billewicz index was excluded because it is an older clinical index that has been shown to be of limited use for detection of early signs and symptoms of hyperthyroidism. [37] For this very reason the Billewicz index was recently modified, re-evaluated and updated by Zulewski et al and has been shown to be useful in distinguishing euthyroid individuals from individuals with overt hypothyroidism. However, the Zulewski score was considered inappropriate for use in the current study however because it requires administration by a trained clinician. [39] Moreover, the Colorado symptom survey fulfilled all of the inclusion criteria and was therefore the most suitable instrument for use in the current study. [56] This questionnaire was specifically designed to assess symptoms suggestive of overt hypothyroidism and has previously been administered for self completion in a large cross-sectional study comprising individuals with and without subclinical thyroid dysfunction. The tool comprises 17 symptoms of hypothyroidism and three other 'thyroid neutral' symptoms. Selection of items was based upon the results of a previous study which demonstrated a difference in symptom prevalence between hypothyroid and euthyroid subjects. The survey is divided into two parts with part one assessing current presence or absence of each symptom and the second part determining whether the symptom is new compared with the previous year. The response option for each item is

1-5 with 3 being a neutral response and each extreme representing either complete absence or marked severity. The key features of this questionnaire are that it is convenient and easily administered and suitable for self-completion by an elderly population.

Despite three instruments for assessing symptoms of overt hyperthyroidism being identified, none of them were diagnostic indices suitable for self completion by an elderly population. [41,42,201] The hyperthyroidism complaints questionnaire (HCQ) was not considered for use in the current study because it had been specifically designed for monitoring of residual complaints following replacement therapy. [201] The two remaining tools; the hyperthyroid symptoms rating scale (HSRS) and the Crooks' index, were both diagnostic indices that have recently been utilised in studies comparing individuals with subclinical hyperthyroidism and euthyroid individuals. [41,42] However, both indices, required administration by a clinician because physical examination is necessary for evaluation of clinical signs of hyperthyroidism.

The Hyperthyroid symptoms rating scale (HSRS) has been widely used in studies to assess signs and symptoms of hyperthyroidism. [159,187,188] Klein et al developed this instrument to aid assessment of symptom severity in hyperthyroidism. [42] Selection of items from the HSRS was based upon two previous studies demonstrating a difference in prevalence of symptoms between individuals with overt hyperthyroidism and euthyroidism. [40,41] The HSRS scale comprises ten items that rate: nervousness, diaphoresis, heat intolerance, motor activity, tremor, weakness, hyperdynamic precordium, diarrhoea, weight loss and appetite. The scale is an observer rated scale with information needed to rate each item obtained through review of medical history

and physical examination. Items are scored on scale of 0-4 and summed to give a total score (0-40) with higher scores indicating more symptoms. Full use of this symptom rating scale was considered unfeasible in the current study due to the requirement for physical examination. Since this scale had been widely used in other studies and the fact that the majority of items it contains are common to other hyperthyroid symptom indices and literature related to symptoms, items were selected from it for use in the current research. [159, 188, 202]

Similarly, the Crooks index is a diagnostic index that was developed to improve accuracy of clinical assessment of overt hyperthyroidism. [41] Whilst it is an older clinical index it has been used recently to assess signs and symptoms that accompany subclinical hyperthyroidism. The index comprises eight symptoms (breathlessness on effort, palpitation, lethargy, sensitivity to heat, excessive perspiration, nervousness, increases in appetite, weight loss) and nine signs (palpable thyroid, bruit over thyroid, lid retraction, lid lag, exophthalmos and hyperkinetic movements, fine finger tremor, clammy hands and rapid pulse rate). A final clinical score of ≥19 is considered to be consistent with overt hyperthyroidism, ≤ 11 indicative of euthyroid status and between 12-18 intermediate. [41]

It was therefore necessary to develop a specific questionnaire for ascertainment of data related to symptoms suggestive of overt hyperthyroidism. This was achieved by amending the Colorado symptom survey for hypothyroid symptoms to incorporate symptoms suggestive of hyperthyroidism as identified from the HSRS and Crook's index. The final questionnaire comprised items from the Colorado symptom survey, the hyperthyroid symptoms rating scale (HSRS) and the Crooks index. [41,42,59] Comparison of

items between these three indices and the literature informed selection of additional symptoms suggestive of hyperthyroidism for inclusion in the current study questionnaire. Since the Colorado symptom survey included six items assessing symptoms (body weight, sensitivity to temperature, speed of thinking, poor memory, muscle weakness and lethargy) which are also consistent with overt hyperthyroidism, it was necessary to add just three additional symptoms (trembling or shaking hands, excessive perspiration and palpitation).

The three new items were inserted into the Colorado survey and arranged in order to preserve the original format of the survey. This format also enabled ascertainment of presence, absence and recent change in each of the three additional items.

Eight items were removed from the Colorado symptom survey; these were depression, sleep, maths skill, coarser hair, irregular menses and three thyroid neutral items related to vision, cough and nausea. These items were removed from the current questionnaire as they had not previously been identified as important discriminators of thyroid dysfunction, were not considered to be clinically relevant or translatable to an elderly UK population and to minimise respondent burden. [59] Similarly, items of the HSRS and Crooks index requiring physical examination were not selected for use. Other items such as appetite, nervousness, hyperactivity, breathlessness on exertion, diarrhoea and daily function were not selected because they were not common to both indices and were not sufficiently supported in the literature to justify inclusion. Choice of questionnaire items for insertion and removal was affirmed by a consultant endocrinologist specialising in thyroid disease. The final symptom questionnaire therefore comprised 15 items, each with two parts relating to overall presence and recent onset of symptoms.

Table 8.6 Evaluation of symptoms and perceived health status

Instrument/Tool	Administration/ completion	Number of items	English language	Comments
Billewicz clinical index [39]	Interview/clinical exam	21	Yes	Developed pre-1980 to aid diagnosis before availability of sensitive assays for TSH and FT4
Zulewski scale [37]	Interview/clinical exam	14	Yes	Updated version of the Billewicz index. Clinical score valuable for assessment of severity
Thyroid Symptoms Questionnaire [200]	Questionnaire/ self completion	12	Yes	Specifically designed for monitoring residual complaints following initiation of therapy
Colorado symptoms survey [56]	Questionnaire/ self completion	17	Yes	Convenient and simple to administer. Clinical scoring system is complex
Hyperthyroidism complaints questionnaire [201]	Questionnaire/ self completion	31	Yes	Designed for measurement of residual complaints following treatment for hyperthyroidism
Hyperthyroid symptoms rating scale [42]	Interview/ clinical exam	10	Yes	Designed to aid assessment of symptom severity and response to therapy

8.3.3 Evaluation of symptoms

The questionnaire utilised 15 items and enabled assessment of 18 symptoms suggestive of overt thyroid dysfunction. In particular, three questionnaire items were unique to assessment of symptoms suggestive of hyperthyroidism, six items to evaluation of symptoms suggestive of hypothyroidism and six items assessing symptoms which can be considered suggestive of either overt hyperthyroidism or overt hypothyroidism. Three of these items (activity, muscle weakness and memory) evaluated symptoms that have a similar clinical presentation in each form of thyroid dysfunction. In contrast, the final three items assess symptoms that exhibit an opposing clinical presentation in overt hyperthyroidism to that observed in overt hypothyroidism. As these three items generate data relevant to both forms of thyroid dysfunction, they are counted in both the total number of symptoms suggestive of overt hyperthyroidism and total number of symptoms suggestive of overt hypothyroidism. The questionnaire therefore enabled evaluation of a total of nine symptoms suggestive of overt hyperthyroidism and 12 symptoms suggestive of overt hypothyroidism (Table 8.7).

Each item consisted of two components; the first to assess the presence of the symptom at the time of questionnaire completion (current symptom) and the second to evaluate change in symptom severity occurring during the previous 12 months (changed symptom). Both components encompassed a five point likert style response scale.

In general, one end of each five point scale reflected the presence of a symptom suggestive of overt thyroid dysfunction and the other extreme exhibited the opposing

symptom not suggestive of overt thyroid dysfunction with a neutral option at the central position (Figure 8.1.1). The position of the symptom suggestive of overt thyroid dysfunction was changed throughout the questionnaire; in six items, the symptom occupied positions one and two and for all other items the symptom was located in positions four and five. The position of the neutral response option remained the same throughout.

Overall, each questionnaire item evaluated only one symptom suggestive of overt thyroid dysfunction, however, for the items thinking, weight and temperature, both ends of the five point scale evaluated a symptom suggestive of overt thyroid dysfunction with location one and two representing high body weight, sensitivity to cold temperatures and slow thinking (symptoms suggestive of overt hypothyroidism) and positions four and five representing low body weight, sensitivity to heat and fast thinking (symptoms suggestive of overt hyperthyroidism) (Figure 8.1.2).

For completion of component one of each questionnaire item (component to evaluate presence of current symptoms), participants were asked to consider their experience of each item, to compare their own experience with others in their age group and indicate the response within the five point scale which best represented them. The five point likert type scale provided two response options representing the presence of the symptom and three options indicated absence of the symptom. This five point scale also allowed severity of the symptom to be evaluated as either mild or severe in accordance with the likert point chosen. For example, hoarse voice at position four of the response scale was considered to be of mild severity whereas very hoarse voice located at point five of the scale was considered to be more severe (Figure 8.1.3).

The second component of each questionnaire item evaluated change in intensity of symptoms over the previous 12 months. Participants were asked to consider whether their current experience of each symptom was different from 12 months ago and to indicate what type of change had occurred, thus the response scale provided an option for no change, two options for an improvement in symptoms and a further two response options reflecting an increase in symptom severity. The five point scale enabled assessment of the level of increase in symptom severity for example the option ‘more hoarse now’ was considered indicative of a mild increase in symptom severity and ‘much more hoarse now’ was considered indicative of a severe increase in symptom severity during the previous 12 months (Figure 8.1.1- 8.1.3).

Table 8.7 Eighteen items of the symptoms questionnaire

Item No.	Questionnaire item	Symptom number and type		Symptom suggestive of hyperthyroidism	Symptoms suggestive of hypothyroidism
1	Perspiration/ sweating	**1**	Excessive perspiration	X	
2	Trembling/shaky hands	**2**	Trembling hands	X	
3	Palpitation	**3**	Frequent palpitation	X	
4	Temperature*	**4**	Sensitivity to heat *	X	
5	Thinking *	**5**	Fast thinking*	X	
6	Weight*	**6**	Weight loss*	X	
7	Activity **	**7**	Lethargy**	X	X
8	Muscles 1**	**8**	Weak muscles**	X	X
9	Memory**	**9**	Poor memory**	X	X
10	Voice	**10**	Hoarse voice		X
11	Tone of voice	**11**	Deep voice		X
12	Skin	**12**	Dry skin		X
13	Eyes	**13**	Puffy eyes		X
14	Muscles 2	**14**	Muscle cramps		X
15	Constipation	**15**	Constipation		X
4	Temperature*	**16**	Sensitivity to cold*		X
5	Thinking *	**17**	Slow thinking*		X
6	Weight*	**18**	Weight gain*		X
				9 symptoms	12 symptoms

* denotes symptoms suggestive of overt thyroid dysfunction that have a dissimilar and opposing clinical presentation in overt hyperthyroidism and overt hypothyroidism

** indicates symptoms suggestive of overt thyroid dysfunction that have a similar presentation in both overt hyperthyroidism and overt hypothyroidism.

Figure 8.1 Questionnaire components

8.1.1 Symptom suggestive of hypothyroidism

Is your voice generally …	Very clear	Clear	Average	Hoarse	Very hoarse
Likert scale position	1	2	3	4	5
Symptom present or absent	*(absent)*	*(absent)*	*(absent)*	*(present)*	*(present)*
Symptom intensity	Absent	Absent	Absent	Mild intensity	Severe intensity

8.1.2 Symptom suggestive of hypo and hyperthyroidism at likert position 4 and 5

Is your memory?	Very good	Good	Average	Poor	Very poor
Likert scale position	1	2	3	4	5
Symptom present or absent	(*absent/both)*	(*absent/both)*	*(absent/both)*	*(present/both)*	*(present/both)*
Symptom intensity	Absent	Absent	Absent	Mild intensity	Severe intensity

8.1.3 Symptoms of hypo and hyperthyroidism at opposite end of the likert scale

Question: Are you generally …	Very sensitive to cold	Sensitive to cold	Average	Sensitive to heat	Very sensitive to heat
Likert scale position	1	2	3	4	5
Symptom present or absent	*(Present/Hypo) (Hyper/absent)*	*(Present/Hypo) (Hyper/absent)*	*(Both absent)*	*(Present/Hyper) (Hypo/absent)*	*(Present/Hyper) (Hypo/ absent)*
Symptom intensity	Severe/Hypo	Mild/Hypo	Absent	Mild/Hyper	Severe/Hyper

8.3.4 Evaluation of perceived health status

Perceived health status was evaluated using the SF8 to enable comparison of disease burden between individuals with subclinical thyroid dysfunction and euthyroid individuals. The SF8 is a shortened version of the SF36 and as such is a multi purpose generic measure of perceived health status. The SF8 comprises 8 questions (one question to measure each of the eight SF36 domains), measures both negative and positive aspects of health and measures a range of health status and well being in terms of both physical and mental health. Table 8.9 demonstrates the single health measures and summary measures assessed using the SF8. The physical health summary measure comprises the four domains, general health, physical functioning, role physical and bodily pain and the mental health summary the four domains; vitality, social functioning, mental health and role emotional. (Table 8.8)

Table 8.8 Items and domains of the SF8

SF8 single item health measures	SF8 single item health measures
General Health	Physical component summary score
Physical functioning	
Role Physical	
Bodily pain	
Vitality	Mental component summary score
Social functioning	
Mental health	
Role emotional	

8.3.5 Piloting of the symptoms questionnaire

To evaluate face validity the questionnaire was piloted in 10 individuals over the age of 65 years and was reviewed by a consultant endocrinologist specialising in thyroid dysfunction. The pilot population commented on the clarity of layout, format and content of the questionnaire as well as the relevance of the questions and appropriateness of the terminology used. The questionnaire design and content was refined in accordance with feedback obtained from piloting.

8.4 Management of data

All data recorded on the case report forms during the screening clinics and all completed study questionnaires were returned to the study office for data entry. Data were entered onto a password protected Microsoft Access (2003) database, stored on the secure network within Primary Care Clinical Sciences, University of Birmingham. The database was constructed with restrictions on each field to limit entry of implausible data and aid data validation.

8.4.1 Data validation

Validation exercises were performed on all data fields to identify implausible values and conflicting data. Reference was made to source documents to resolve queries. A duplicate Access data base was set up to enable dual data entry of 10% of the symptoms questionnaires. Access database queries were set up to compare the two versions of the database (single and double data entry) and identify discrepancies arising from the double data entry. Discrepancies identified between the two data sets were checked against the paper questionnaires to verify the data. The database was amended as appropriate and error rates confirmed to be at acceptable levels (<5 errors per 1000 data points). The database was backed-up daily and once all data had been entered, cleaned and validated the study database was locked.

8.4.2 Transformation of symptoms data for analysis

Data were subsequently transformed for the purposes of data analysis. Preliminary transformations were made to ensure that higher values represented symptom presence. Recoding of the items, weight, thinking and temperature was necessary, since these items represented symptoms that exist in overt hyperthyroidism and overt hypothyroidism, albeit with opposing clinical presentation. Two separate variables were created; one to reflect overt hyperthyroidism and another for overt hypothyroidism.

A binary variable was created to reflect the presence or absence of each current and changed symptom, with a code of 1 indicating presence and 0 reflecting absence of the symptom. A third variable was constructed for each item of component one and component two to reflect the severity of each symptom. The presence of a more severe symptom was allocated a value of 2 (e.g. very dry skin), a mild symptom a value of 1 (dry skin) and all other options were coded as zero to reflect the absence of the symptom (i.e. response options; average skin, oily skin, very oily skin).

8.4.3 Health status data entry and coding

Data obtained using the SF8 were also transformed for the purposes of statistical analysis. The initial coding scheme assigned for items, general health and social function were coded 1 - 6 from left to right; and items physical functioning, role physical, bodily pain, vitality, mental health and role emotional were coded 1 - 5 from left to right. The first step in transformation of the ordinal scales to continuous data was application of scale means based upon the standard metrics of the SF36 to each of the eight domains. Each item of the SF8 was then assigned a regression co-efficient weight as

published in the SF8 user manual. An aggregate score for the physical and mental component summary scores was calculated by multiplying each SF8 item by its respective regression weight and summing all the products. Higher physical and mental compenent summary scores are indicative of greater perceived health status with scores ranging from 0–100). Data obtained using the case report forms were coded as detailed in Table 8.9.

Table 8.9 Coding schedule of the case report form

Variable	Coding
Gender	1 Male, 2 Female
Any current alcohol use	1 Yes, 0 No
Current smoker	0 non smoker, 1 smoker
Any current iodine intake	1 Yes; 0 No
Family history of thyroid dysfunction	1 Present; 0 Absent
Amiodarone Anti-depressant Anxiolytic Beta-adrenergic Blockers Lithium Major Tranquilisers Morphine or other opioid analgesics Glucocorticoids	0; treatment not prescribed 1;treatment prescribed
Anxiety Atrial Fibrillation Cancer Cerebrovascular disease / Stroke / TIA Dementia Depression Diabetes Heart failure / Valve disease Hypertension Ischaemic or Coronary Heart Disease or Angina Irregular heart rhythm Peripheral vascular or artery disease Pituitary disease Pulmonary disease / COPD / Asthma Renal disease (Chronic and grade 3 or 4 only) Rheumatoid arthritis Neurological disease Knee replacement Hip replacement Osteoarthritis Anaemia Goitre	0; no diagnosis, 1; disease diagnosed

8.4.4 Ethical approval

Ethical approval for the study was obtained from the North Staffordshire Local Research Ethics Committee; reference number: 07/H1204/136, approval date; 19/12/2007 prior to commencement of the research. R&D approval was obtained from the Birmingham and Solihull PCT Consortium (Ref: 153/1108/P) and Coventry Teaching PCT (Ref: COV100907).

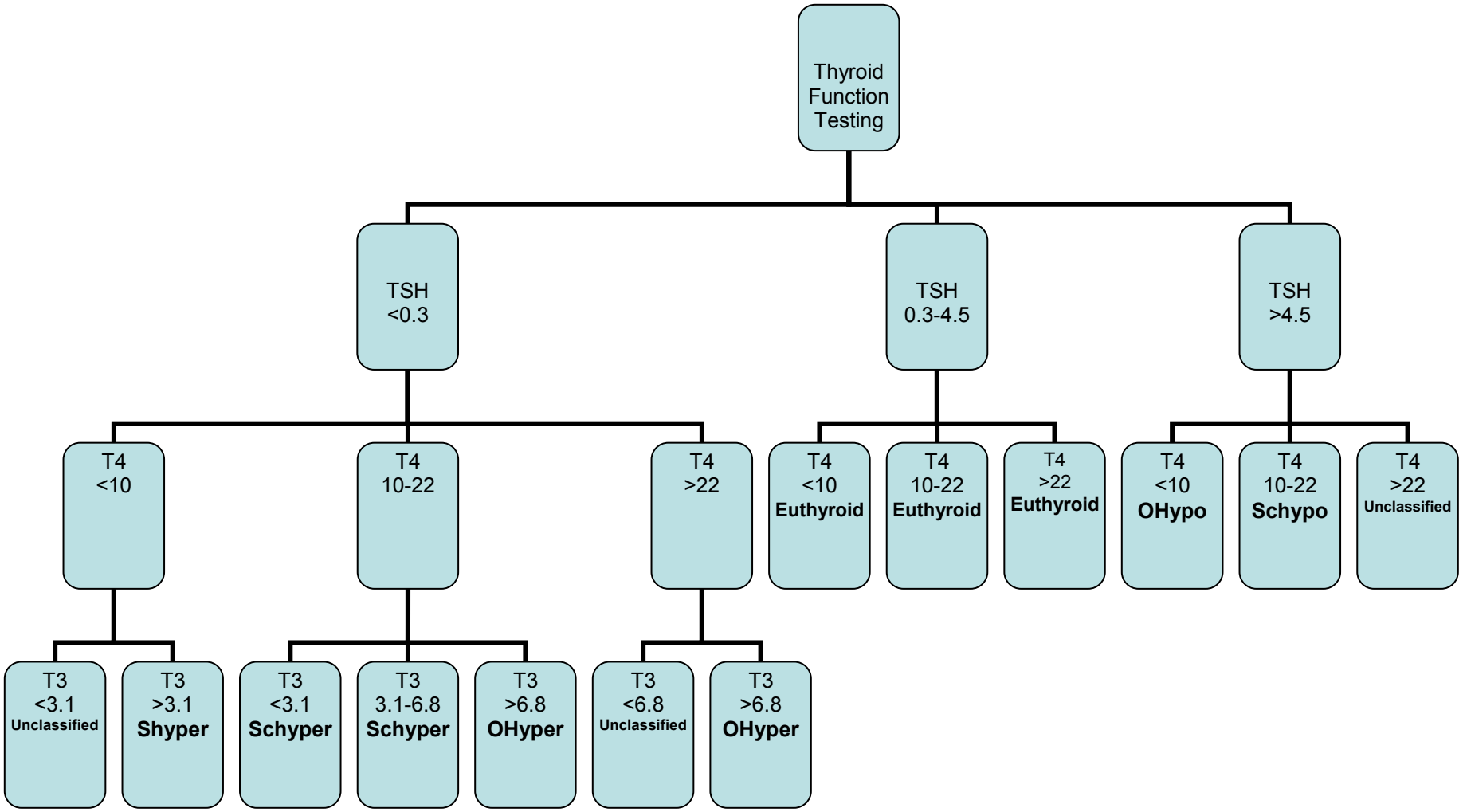
8.4.5 Sample size

Formal sample size (power) calculations were not undertaken during protocol development due to this research being nested within a longitudinal study design and therefore limited to follow-up of an existing cohort. However the large nature of the initial cohort (n=5881) and the anticipated loss to follow-up (10%) suggested that 5293 individuals would be available to the study.

8.4.6 Categorisation of thyroid function

The results of the thyroid function tests (TFT) conducted at screening were used to categorise thyroid function in accordance with the algorithm detailed in Figure 8.2.

Figure 8.2 Algorithm used to categorise thyroid status



8.5 Statistical analysis

The focus of this thesis is the characterisation of symptoms suggestive of overt thyroid dysfunction in individuals with subclinical hyperthyroidism and subclinical hypothyroidism. The statistical analysis plan was designed to allow exploration of the relationships between i) category of thyroid function and symptoms, ii) category of thyroid function and health status, iii) symptoms and health status, iv) symptoms and serum thyrotrophin (thyroid stimulating hormone [TSH]) concentration and v) symptoms and serum free thyroxine concentration.

In its evaluation of the clinical impact of subclinical thyroid dysfunction this study collated thyroid function test results and self reported data on the presence of current symptoms suggestive of hyperthyroidism and hypothyroidism as well as data on recent change in severity of these symptoms and current health status. Demographic data collated comprised age, gender and deprivation score as well as medical history and concomitant medication pre-specified as likely to be associated with thyroid function, recorded symptoms or to interfere with tests of thyroid function.

Descriptive and statistical analyses were undertaken using SPSSv15. In general, descriptive analysis included mean (with standard deviation) for data that followed a normal distribution or median with inter quartile range for data that did not follow a normal distribution and confidence intervals for proportions in categorical data where appropriate.

Details of statistical tests used at each stage of analysis are provided in chapters 9-15 along with the results obtained. The Kolmogorov-Smirnov test for normality was applied to establish if data were normally distributed, where relevant. Appropriate statistical tests were determined after assessment of data distribution. Given the fact that multiple testing was used, Bonferroni adjusted alpha values were used to control for type 1 error where appropriate and are reported where relevant in the results chapters (Chapters 9-15).

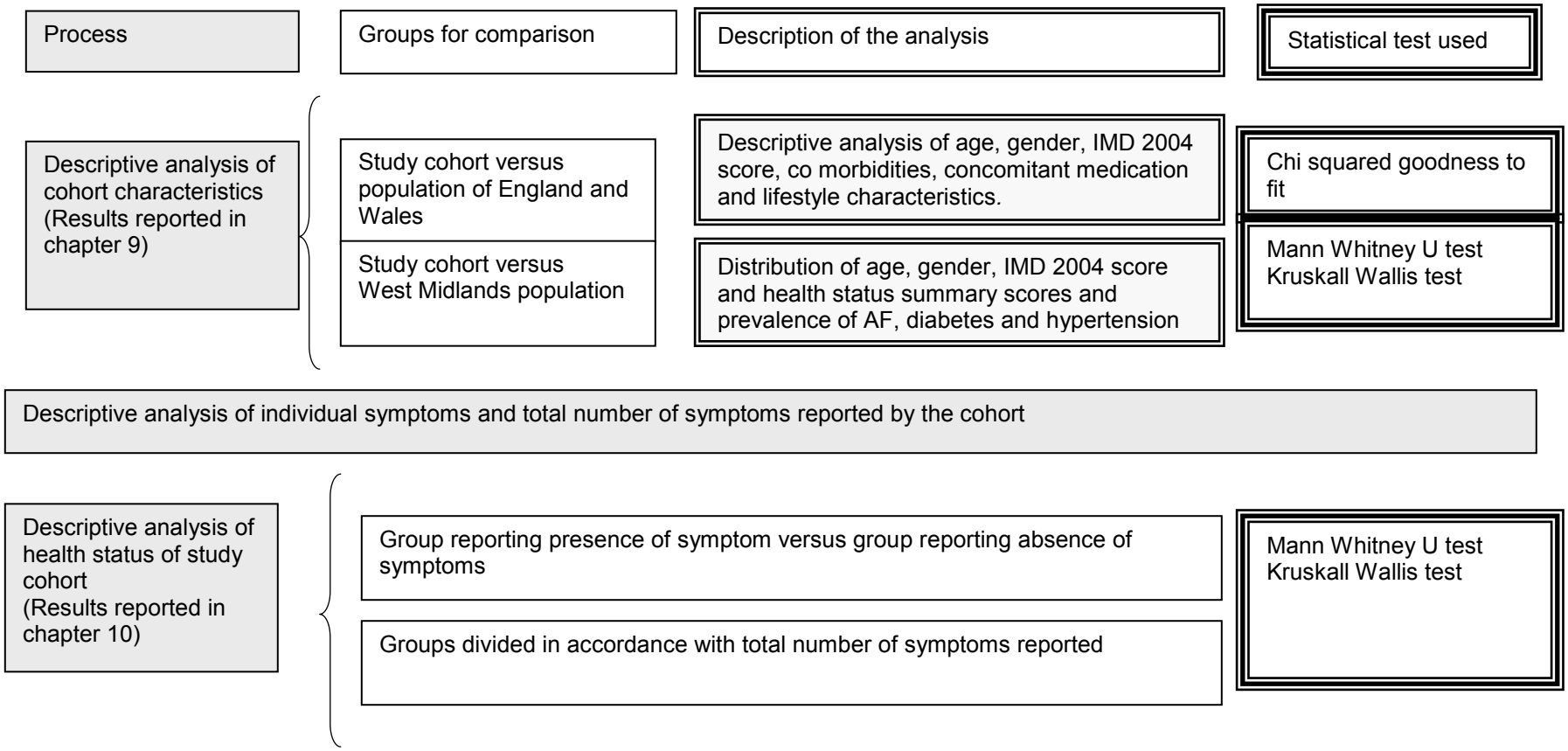
8.5.1 Representativeness of the study population

A consort diagram was constructed to describe the cohort in terms of eligibility, response rate, loss to follow-up and participation in screening of thyroid function. The full characteristics of the study population are described and demographic factors explored (Figure 8.3).

8.5.2 Symptom expression and health status of the cohort

To further characterise the study cohort with respect to expression of individual symptoms suggestive of overt thyroid dysfunction, the prevalence of symptoms reported was calculated and tabulated. To determine the relationship between individual symptoms suggestive of overt thyroid dysfunction and health status, the Mann Whitney U test was used to compare distribution of mental and physical component summary scores between groups reporting presence and absence of individual current and changed symptom (Figure 8.3).

Figure 8.3 Statistical analysis; description of the cohort



8.5.3 Categorisation and description of subgroups

Participants were categorised into three groups indicative of thyroid function in accordance with the standard reference criteria used by the Regional Endocrine Laboratory University Hospital Birmingham. Descriptive statistics were used to describe the thryoid function groups with respect to age, gender, IMD 2004 score, lifestyle characteristics, medical history, concomitant medication, serum concentration of thyrotrophin, TF4 and FT3 and mental and physical component summary scores. (Figure 8.4)

8.5.4 Expression of symptoms in the thyroid function groups

Initially exploratory univariate analyses were undertaken to examine the relationship between thyroid function category and expression of symptoms and to identify potentially clinically important symptoms for inclusion in the multivariate analysis (Figure 8.4). To evaluate the potential clinical importance of pairs of symptoms, each possible combination of two symptoms was defined. The purpose of defining a new variable for each pair of symptoms was two-fold. Firstly, to enable comparison of the prevalence of symptom pairs across thyroid function groups. Secondly, to allow examination of interactions between symptoms; that is to determine whether the relationship between category of thyroid function (as the dependent variable) and each individual symptom (as an independent explanatory variable) was modified by the presence or absence of another symptom. Interactions between pairs of symptoms were examined using binary logistic regression analysis. Individual and pairs of symptoms were selected for inclusion

in the multiple logistic regression analyses if a statistically significant difference in symptom prevalence existed between the thyroid function groups (e.g. euthyroid versus subclinical hyperthyroidism and euthyroid versus subclinical hypothyroidism). Similarly, where a statistically significant interaction between two symptoms was identified, the interaction term and individual symptoms were selected for inclusion in the logistic regression model.

Since the univariate analysis was exploratory in nature and intended to enable selection of potentially important symptoms appropriate for inclusion in the multivariate analysis, where necessary the Bonferroni adjusted alpha level was substituted for a more conventional and less conservative alpha level of 5%.

8.5.4.1 Multivariate analyses and thyroid function category

Binary logistic regression analysis was undertaken to determine if cases of subclinical thyroid function could be predicted from individual symptoms, combinations of symptoms, interactions between symptoms and from other demographic variables (medical history, concomitant medication, age and deprivation score) (Figure 8.4). Demographic variables were excluded from the logistic regression analysis if there were data missing for 1.0% or more of the population or where the outcome of interest was present in less than 1.0% of the population. Two separate models were constructed. One model was constructed to identify factors predictive of subclinical hypothyroidism and incorporated all individuals with subclinical hypothyroidism and euthyroid function. The second model was constructed for identification of factors predictive of subclinical

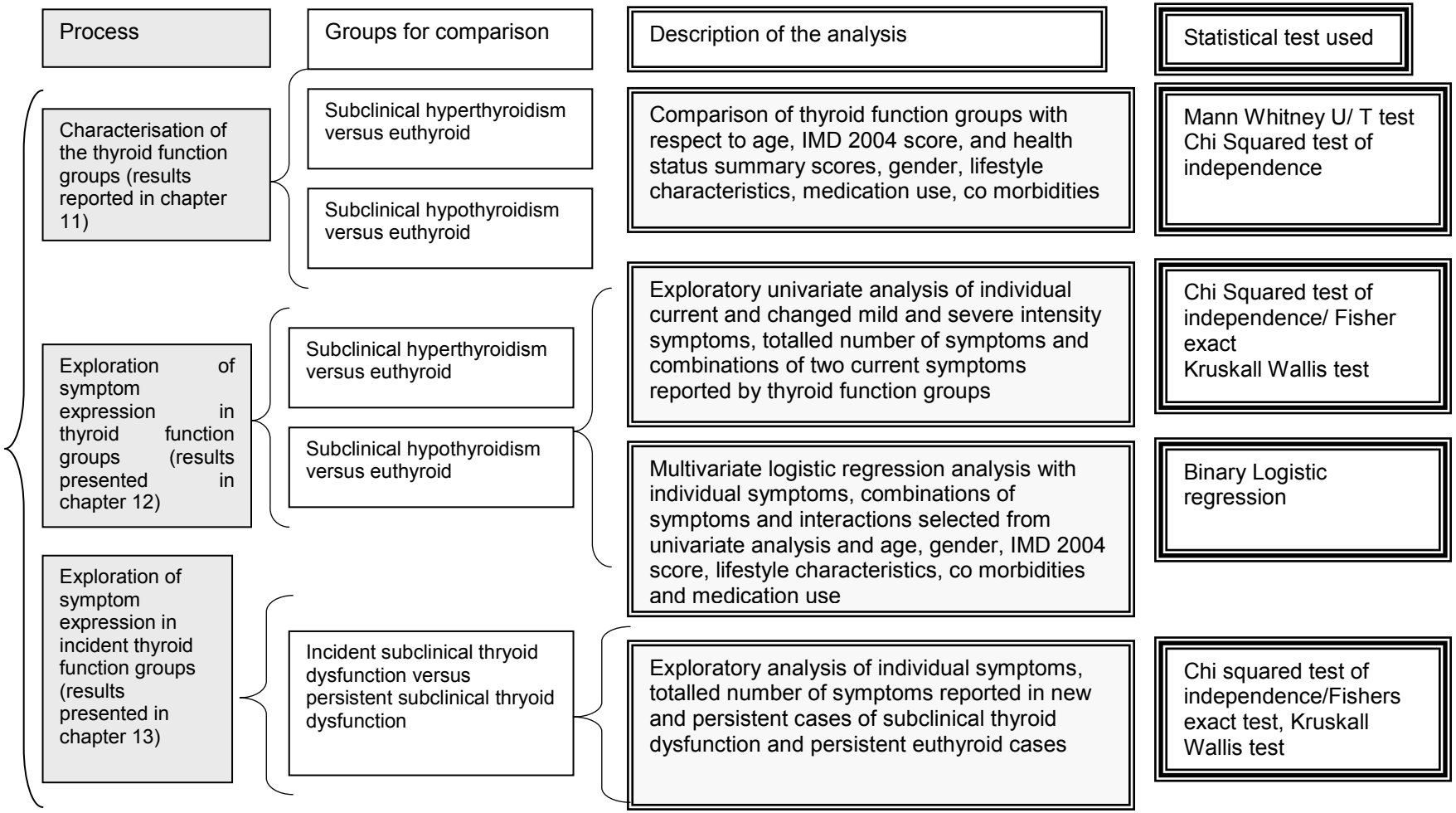
hyperthyroidism and comprised all individuals with subclinical hyperthyroidism and euthyroid function. The final model employed the forward Likelihood Ratio (LR) method of variable selection with a significance level of 5% for variable inclusion and 10% for variable removal. Tests for multicolinearity were conducted to confirm absence of high levels of intercorrelation between explanatory variables. Using this approach to model construction, each of the explanatory variables and each of the statistically significant two way interactions were entered sequentially. The significance of each variable already in the model was reviewed at each step and variable removal was based upon the likelihood ratio test statistic which indicated whether or not a variable was significant in explaining some of the variability in the response. Non significant variables were removed. The final model was selected based upon the highest fulfilment of goodness to fit as indicated by Nagelkerke R^2 (range of 0 to 1, with 1 indicating that the model fully explains the variation in the dependant variable) and the greatest ability to predict the correct category for each case compared with step 0 (i.e the initial model constructed before entry of any of the independent variables). Logistic regression analysis provided co-efficients to indicate the effect of each explanatory variable upon the response variable when controlling for all other variables entered in to the model.

8.5.5 Symptom expression in the incident cases

Characterisation of symptoms in individuals with new and persistent subclinical thyroid dysfunction was undertaken because it is possible that incident cases experience a greater symptom burden than those with persistent subclinical thyroid dysfunction. To enable categorisation of the incident and persistent thyroid dysfunction subgroups it was necessary to draw upon historical study data. All study participants were categorised as either persisting within their baseline thyroid function category or changing from baseline thyroid function category during the interval period. Individuals remaining within the baseline thyroid function category during the interval period were categorised to either, persistent euthyroidism (defined by a baseline and follow-up categorisation of euthyroidism) or persistent subclinical thyroid dysfunction (defined by a baseline and follow-up classification of subclinical thyroid dysfunction). Those that changed from baseline thyroid function category were similarly categorised to one of two groups, with group one comprising those that reverted to euthyroid function (defined by a baseline classification of subclinical thyroid dysfunction and a follow-up classification of euthyroidism) and group two comprising incident cases of subclinical thyroid dysfunction (defined by a baseline classification of euthyroidism and a follow-up classification of subclinical thyroid dysfunction). The prevalence of individual and totalled hyperthyroid and hypothyroid symptoms reported in subgroups of the study population with incident and persistent thyroid function were compared. The proportion of the incident and persistent subclinical thyroid dysfunction groups reporting presence of each individual symptom were compared using the chi squared test for independence or the Fisher's exact test where appropriate (Figure 8.4). Given the fact that multiple comparisons were

being made between groups, a Bonferroni adjusted alpha value of $p<0.003$ was used to control for type 1 error. The prevalence of symptoms reported by cases with persistent euthyroid and persistent subclinical thyroid dysfunction were explored and compared in an identical manner.

Figure 8.4 Statistical analysis; symptoms in the subgroups



8.5.6 Symptom expression and serum thyrotrophin concentration

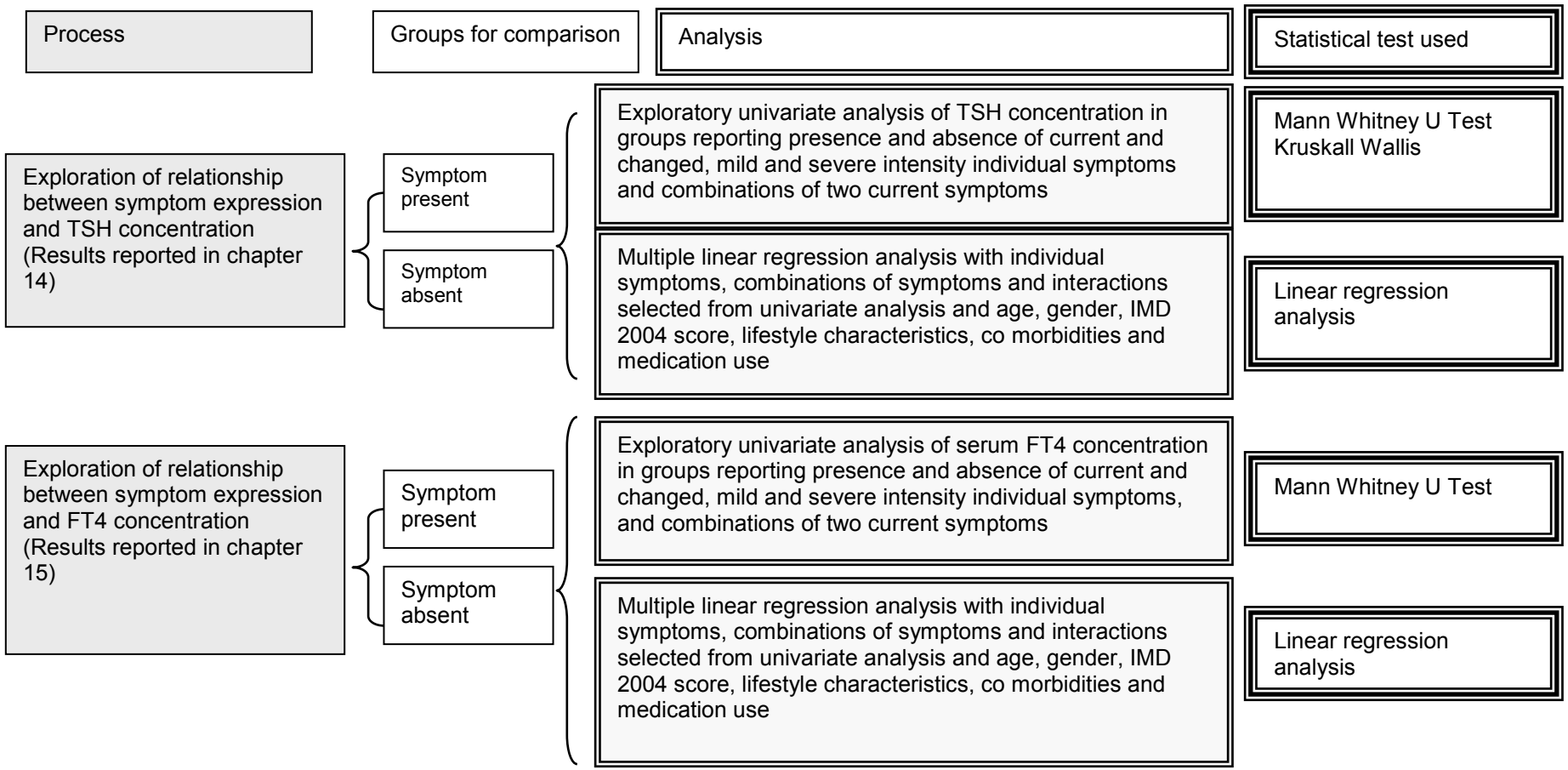
Univariate analyses were undertaken to explore the relationship between serum thyrotrophin concentration and individual symptoms, combinations of symptoms and interactions between symptoms and to enable selection of variables for inclusion in the multivariate analyses (Figure 8.5). Since serum thyrotrophin concentrations did not follow a normal distribution and transformations (including logarithmic) failed to achieve normal distribution, non-parametric tests were employed. Multiple linear regression analysis (forward stepwise) was performed to establish models for predicting serum thyrotrophin concentration. As an extension of simple linear regression, multiple linear regression aims to find a linear relationship between a response variable and a combination of several possible explanatory variables, thereby enabling prediction of a value of the response variable from knowledge of the explanatory variables. The linear regression model incorporated all individuals in the final cohort. Variables were selected for inclusion in the linear regression model if the univariate analysis had demonstrated a statistically significant difference in serum thyrotrophin concentration between groups reporting presence and absence of individual symptoms, combination of symptoms or where a statistically significant interaction between symptoms had been observed. Demographic variables were excluded from the linear regression analysis if there were data missing for 1.0% or more of the population or where the outcome of interest was present in less than 1.0% of the population. Multiple linear regression analysis provided co-efficients to indicate the average effect of each explanatory variable upon the response variable when controlling for all other variables entered in to the model. The final model was selected based upon goodness to fit as indicated by the R-squared

coefficient (range from 0 to 1) with larger R-squared values indicating better fit of the model to the data and therefore a greater ability of the model for prediction of serum thyrotrophin concentration (the dependant variable).

8.5.7 Symptom expression and serum free thyroxine concentration

Serum FT4 concentration in the cohort demonstrated a normal distribution, however for reasons of consistency (and since mean and median values of normally distributed data are similar), non parametric statistical tests were employed for analysis of serum FT4 concentrations between groups reporting the presence and absence of individual and pairs of symptoms. Multiple linear regression analysis was performed to establish a model for predicting serum FT4 concentration as previously described.

Figure 8.5 Statistical analysis; symptoms and biochemical parameters



This chapter of the thesis has described the methodology of the cross-sectional survey evaluating symptoms, perceived health status and thyroid function in a large UK based community dwelling cohort of individuals aged 65 years and over. In this chapter full details of the statistical data analysis were also provided.

The results of the study are presented and summarised in the next seven chapters. Details of statistical tests used at each stage of analysis are provided in Chapters 9-15 along with the results obtained.

CHAPTERS 9-16 RESULTS OF THE CROSS-SECTIONAL STUDY

Overview of chapters 9-16

Although the longitudinal data do not address the aims of this thesis, it is nevertheless necessary to present these data in the current chapter to aid description of the cohort. The current chapter begins with a consort diagram with accompanying text to describe the cohort in terms of eligibility, response rate, loss to follow-up and participation in screening of thyroid function. To further enable consideration of the representativeness of the study cohort, the findings from comparisons between the study population and the general populations of two regions of the UK in terms of demography and presence of common co-morbidities are presented. Thereafter the results will be divided into six chapters in accordance with the statistical analysis plan presented in chapter 8.

Chapter 10: Symptom expression of the cohort

This chapter aims to characterise the study population with respect to reported presence, intensity and change during the previous 12 months in 18 symptoms suggestive of overt thyroid dysfunction and health status.

Chapter 11: Categorisation and description of subgroups

Chapter 11 focuses upon characterisation of the thyroid function subgroups with respect to demography, lifestyle, medication use, medical history and health status.

Chapter 12: Symptoms expression in subgroups

Chapter 12 further explores the thyroid function subgroups with respect to prevalence of current and changed individual symptoms, pairs of symptoms and total number of symptoms.

Chapter 13: Symptoms in incident cases of subclinical thyroid dysfunction

This chapter explores symptoms expression in individuals that developed subclinical thyroid dysfunction during the interval period between baseline and follow-up thyroid function screening.

Chapter 14: Symtpoms and serum thyrotrophin concentration

The aim of chapter 14 is to present the findings of the univariate and multivariate analyses exploring the relationship between serum thyrotrophin concentration and symptom expression.

Chapter 15: Symptoms and serum free thyroxine concentration

Lastly, chapter 15 describes the findings of the univariate and multivariate analyses exploring the relationship between serum thyroxine concentration and symptom expression.

CHAPTER 9 DEMOGRAPHICS OF THE COHORT

The aim of the current chapter is to consider the representiveness of the study cohort.

9.1 Implication of the changes during the interval period

As described in chapter 8, reclassification of the baseline thyroid function test results and subsequent classification of thyroid function were undertaken before data were reviewed. In terms of the cross-sectional study, these changes had no impact. Correction of the BETS I thyroid function test results (TFT) led to reclassification of thyroid status in 139/5881(2.4%) of the BETS I participants. A consequence of the reclassification was that four individuals were recategorised as overtly hypothyroid (two previously classified as having subclinical hypothyroid status at BETS I and two euthyroid) and were therefore no longer eligible for inclusion and were excluded from statistical analyses.

9.2 Follow-up

Of the original cohort of 5881 BETS I participants, 103 individuals did not fulfil the inclusion criteria for the follow-up study. As described in section 9.1, reclassification of baseline thyroid function category due to changes in assays and reference criteria led to the exclusion of four individuals. A further 38 had received a diagnosis of overt thyroid dysfunction during the original study (15 with a diagnosis of overt hyperthyroidism and 23 with overt hypothyroidism) and 51 had been allocated to the treatment arm of the BETS randomised controlled trial (RCT). Thyroid function was unclassifiable for a further

nine individuals and one individual was excluded following identification of an error in the data pertaining to date of birth.

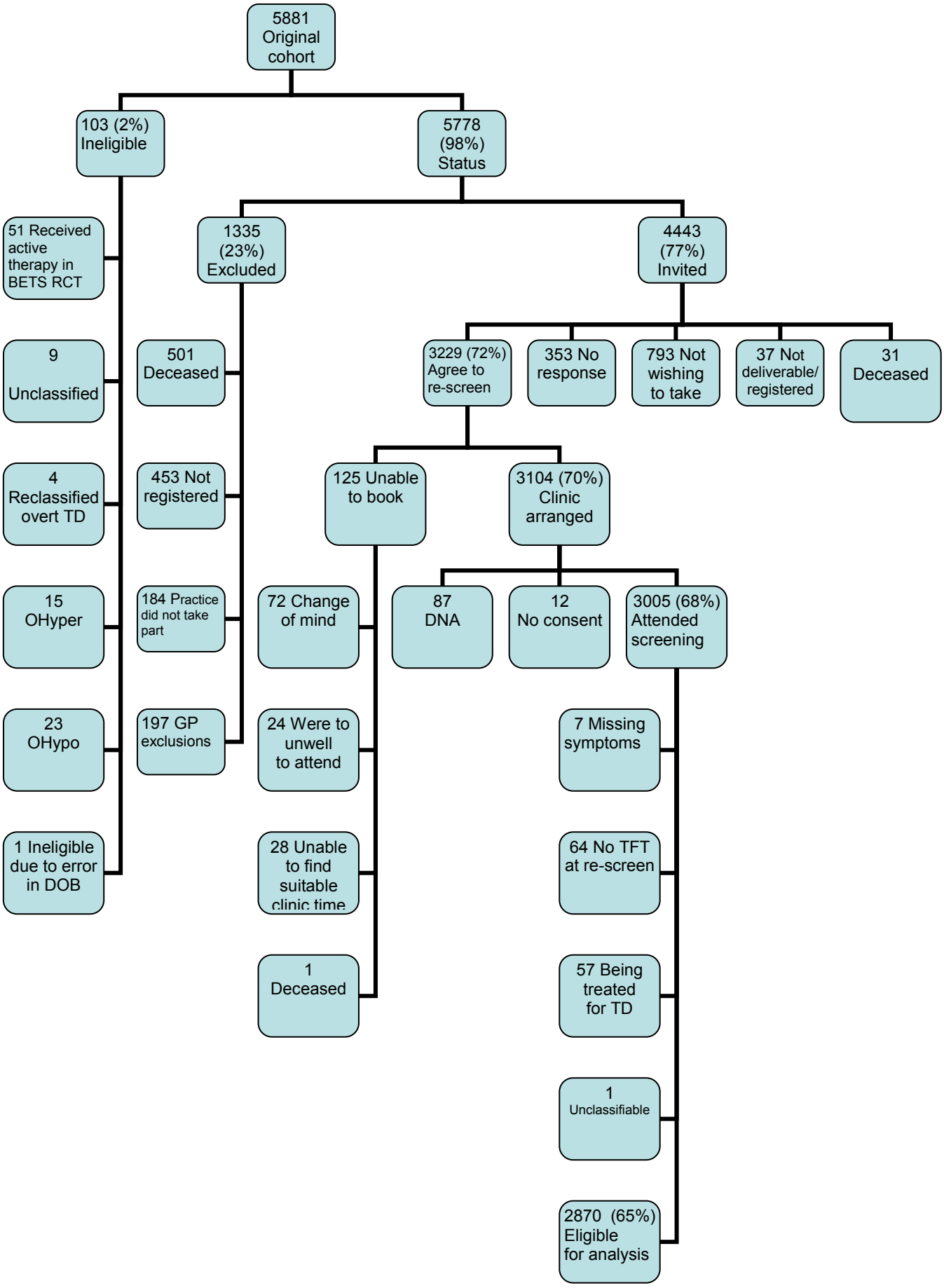
Overall, 98.2% (n=5778) fulfilled the inclusion criteria and were eligible for follow-up. Follow-up of 184/5778 (3.2%) of the potentially eligible cohort was not possible because the general practice with which they were registered was unable to participate. Status verification by GPs led to the exclusion of a further 1151/5778 (20%); 501 were unavailable for follow-up because they were deceased and 453 because they were no longer registered with the practice. GPs considered a further 197 to be inappropriate for follow-up; therefore 4443 individuals were invited to participate (Figure 9.1).

9.2.1 Response rate

After invitation a further 68 (1%) individuals were excluded as not known at address or deceased. A further 793/4443 (18%) declined the invitation to participate and no response was received from 353/4443 (8%). The remaining 3229/4443 (73%) agreed to participate and appointments were arranged for 96% of these individuals (3104/3229). Of the 3104 individuals accepting a screening clinic appointment, 99 (3.2%) were lost to follow-up with 87/3104 (2.8%) not attending and 12/3104 (0.4%) being unable or not wishing to provide written informed consent to participate. An additional 124/3229 (3.8%) individuals expressing an interest in taking part in the screening clinics were lost to follow-up because the screening clinic times were inconvenient for them (n=28), they were too unwell to attend (n=24) or changed their minds about participating (n=72) (Figure 9.1). Overall, 68% (3005/4443) of those invited to participate attended a study clinic and consented to screening of thyroid function.

A further 4.5% (135/3005) of those that attended screening were excluded, 64/3005 (0.02%) had missing thyroid function tests results either because venepuncture was unsuccessful or the blood sample received by the laboratory was insufficient or not viable for testing and 0.002% (7/3005) failed to return a fully completed questionnaire and therefore had missing symptoms data. A further 58/135 were excluded from the final analysis population; 57/135 due to receiving treatment for thyroid dysfunction and a further one because thyroid status could not be determined (TFT results were unclassifiable most likely due to assay artefacts and/or drug interactions). The thyroid function test results for six individuals indicated overt thyroid dysfunction, with four individuals being categorised with overt hypothyroidism and two with overt hyperthyroidism. The final population available for analysis therefore comprised 2870 individuals.

Figure 9.1 Consort diagram



9.3 Demographics of the cohort

The age range of the final study population was 68.7 – 96.4 years with a mean of 76.9 years (SD 5.01). The socioeconomic status of the final population ranged from 3.2 (least deprived) to 74.4 (most deprived) giving a mean IMD score of 21.67 SD (15.06) (Table 9.1).

Table 9.1 Characteristics of the final cohort

Variable	n 2870	Mean (SD)	Median (IQR)
Age (years)	2870	76.90 (5.01)	76.10 (7.48)
IMD score 2004	2869	21.67 (15.06)	17.70 (18.70)

Individuals aged between 65 and 74 years made up 42.3% of the final population with 49.8% (n= 1429) of the final cohort being aged between 75-84 years of age and 8.0% aged 85 years or more (Table 9.2).

Table 9.2 Age and gender distribution of the cohort

Variable	England and Wales n (%)	West Midlands n (%)	Expected frequency in accordance with census data 2001 n (%)	Study population n (%)	χ^2 test for goodness to fit, p value
Male	25,325,926 (48.7)	1,095,207 (48.6)	1406.3 (49.0)	1485 (51.6)	χ^2 = 8.636, df 2, p <0.003
Female	26,715,990 (51.3)	1,159,537 (51.4)	1463.7 (5.10)	1391 (48.4)	
≥65 yrs	8,316,298 (15.98)	353,769 (15.69)		2870 (100)	
65-74 years	4,366,316 (52.5)	190,075 (53.7)	1536.5 (53.0)	1214 (42.3)	χ^2 =263.37, df 3, p <0.001
75-84 years	2,935,164 (35.3)	124,687 (35.2)	1014.6 (35.0)	1429 (49.8)	
≥ 85 yrs	1014816.0 (12.1)	390007 (11.0)	1429 (11.0)	227 (8.0)	

The age and gender distribution of the final cohort was compared with the census data 2001 for England and Wales and the West Midlands region. [203] The age and gender distribution of the final population were significantly different to the age and gender distribution of England and Wales and of the West Midlands region (χ^2 263.37; df 3; p<0.001). The study population comprised a greater proportion of individuals aged between 75 -84 years (49.8 %) than England and Wales (35.3%) and the West Midlands region (35.2%). A smaller proportion of individuals in the final cohort were aged between 65-74 years compared with these age groups in the West Midlands region and England and Wales (42.3) versus 53.7 and 52.5 respectively. In part this is an artefact of the study inclusion criteria (minimum age of 65 years in the initial study of 2002-2003). This

data should be taken into account by anyone wishing to apply findings at a population level (Table 9.2).

In terms of gender distribution, the final cohort was significantly different (χ^2 8.636; df 1; $p<0.003$) to that of the other two groups and comprised a significantly smaller proportion of women (48.4%) than the West Midlands region (51.4%) and England and Wales (51.3%) (Table 9.2). Given that this thesis aims to explore the association between thyroid function and symptom expression at the individual level, these dissimilarities are unlikely to be of great importance but are presented for completeness and to allow representativeness to be determined by any reader wishing to extrapolate this data.

To further demonstrate the nature of the study population and report upon the representativeness of the cohort, the study population were subdivided in accordance with the published IMD quartiles for England and Wales and for the West Midlands (Table 9.3). The chi squared goodness of fit test was used to explore the proportion of study cases that fell into the published IMD quartiles for these two regions and compare these proportions with the expected value of 25%. The study population were significantly different to the population of England (χ^2 75.68; 3 df, $p<0.001$) and the population of the West Midlands (χ^2 85.66; df 3, $p<0.001$). The study population was significantly more deprived than the general population of England and significantly more affluent than the population of the West Midlands (Table 9.3). Again, this should not impact on the association with symptoms reported but may require further consideration by anyone wishing to translate overall symptom burden to a population level.

Table 9.3 Representativeness in terms of deprivation

Study population stratified in accordance with IMD quartiles for England % (n= 2869)				
IMD quartile	Range of IMD scores within each quartile	Expected frequency (%)	Frequency in study population 2869 (%)	$\chi^{2;}$ df, p value
1 Least deprived	1-9.62	717.3 (25.0)	664 (23.1)	75.7 df 3 <0.001
2	9.63-17.0		632 (22.0)	
3	17.01-30.0		918 (32.0)	
4 Most deprived	30.01-85.0		655(22.8)	
Study population stratified in accordance with IMD quartiles for the West Midlands				
IMD quartile	Range of IMD scores within each quartile	Expected frequency (%)	Frequency in study population 2869 (%)	χ^{2} df, p value
1 Least deprived	1-11.20	717.3 (25.0)	841 (29.3)	85.7 df 3 <0.001
2	11.21-19.2		768 (26.8)	
3	19.21-35.1		749 (26.1)	
4 Most deprived	35.11-78.8		511 (17.8)	

*1 missing IMD score 2004

9.4 Clinical characteristics of the study cohort

In terms of thyroid function test (TFT) results, the mean serum concentration of thyrotrophin was 2.1mIU/L, median 1.8mIU/L and ranged from <0.01-19.30mIU/L. Serum free thyroxine concentrations of the study population demonstrated normal distribution and as such the mean and median free thyroxine concentration was 14.9pmol/L, ranging from 9.1-30.1pmol/L. Likewise, free tri-idothyronine concentrations demonstrated a normal distribution in this population with a mean and median of 5.1pmol/L and range from 3.9- 7.0pmol/L (Table 9.4).

Table 9.4 Thyroid function test results for the cohort

Variable	n	Mean (SD)	Median
Thyrotrophin (mIU/L)	2870	2.1 (1.4)	1.8
Free thyroxine (pmol/L)	2870	14.9 (2.1)	14.9
Tri –idiothyronine (pmol/L)	37	5.1 (0.7)	5.1

Review of the medical records held by the general practice enabled collection of medical history and co morbidities. The most prevalent co-morbidity was hypertension, with 51.2% (n=1470) of the cohort having a diagnosis of hypertension documented in their medical records. Approximately 18% (n=525) of the cohort had a diagnosis of renal disease or a glomerular filtration rate of between 15-59 ml/min/1.73m^2 documented in

their medical records. This finding may in part be due to the introduction of the 2008 National Service Framework for chronic kidney disease, which advocates routine primary care measures of glomerular filtration rate as an indicator of renal status (with chronic renal disease defined by a glomerular filtration rate of between 15-59 ml/min/1.73m^2). [204] Approximately 11% (n=300) of the final cohort had a known history of cancer and 202 (7.0%) a previous diagnosis of AF (Table 9.5).

Table 9.5 Medical history of the cohort

Disease category	Present %, 95% CI (n)	Absent %, 95% CI (n)	Missing data %
Hypertension	51.2,49.9-53.0 (1470)	48.8,47.0-50.6 (1400)	0
Renal disease	18.3, 16.9-19.7 (525)	2345, 80.3-83.1 (81.7)	0
Ischaemic heart disease	12.6,11.5-13.9 (363)	87.4, 86.1-88.5 (2507)	0
Pulmonary disease	12.4,11.2-13.6 (355)	87.6, 86.4-88.8 (2515)	0
Diabetes	11.7, 10.6-12.9 (336)	88.3, 87.1-89.4 (2534)	0
Cancer	10.5,9.4-11.6 (300)	89.1, 87.9-90.2 (2558)	(12)0.4
Depression	7.8, 6.9-8.8 (224)	92.2,91.2-93.1 (2646)	0
Atrial Fibrillation	7.0, 6.2- 8.0 (202)	93.0,92.0-93.8 (2668)	0
Anxiety	6.0, 5.2-6.9 (172)	94.0,93.1-94.8 (2698)	0
Stroke/TIA	5.5, 5.0-6.8 (157)	94.5,93.6-95.3 (2713)	0
Heart failure	4.4, 3.7-5.2 (126)	95.6, 94.8-96.3 (2744)	0
Peripheral vascular disease	3.4, 2.8-4.1 (98)	96.6,95.9-97.2 (2772)	0
Irregular heart rhythm	3.4,2.8-4.1 (97)	96.6, 95.9-97.2 (2773)	0
Knee replacement	3.1, 2.5-3.8 (89)	96.9, 96.2-97.5 (2781)	0
Rheumatoid Arthritis	2.4,1.9-3.0 (69)	97.6,96.2-97.5 (2801)	0
Hip replacement	2.3,1.8-2.9 (66)	97.7,97.1-98.2 (2804)	0
Osteoarthritis	1.8,1.4-2.4 (53)	98.2, 97.1-98.6 (2817)	0
Neurological disease	0.9, 0.6-1.3 (26)	99.1, 98.7-99.4 (2844)	0
Dementia	0.7, 0.4-1.0 (19)	99.3, 99.0-99.6 (2851)	0
Anaemia	0.5, 0.3-0.8 (13)	99.5, 99.2-99.7 (2857)	0
Pituitary disease	0.3, 0.1-0.5 (8)	99.7, 99.7-100 (2867)	0
Goitre	0.2, 0.1-0.4 (5)	99.8,99.6-99.9 (2865)	0

When compared with the general population of England and the West Midlands, a greater proportion of the current study cohort were identified with atrial fibrillation (5% versus 7% respectively) χ^2 25.1, df 1, p<0.001. [205] Additionally, the chi squared goodness of fit test indicated a significant difference in the proportion of the study cohort with a history of hypertension (51%) as compared with the value of 38% for England (χ^2 212.9, df 1, p<0.001) and 42% for the West Midlands (χ^2 100.1, df, p<0.001) that was obtained in the Health survey for England 2005. [206] There were, however, no significant differences in the proportion of individuals identified in the current sample with a history of diabetes (11.7%) as compared with the health survey obtained value of 11.5% for England and the West Midlands (χ^2 0.12, df 1, p<0.728). The publication of evidence based guidance for identification and diagnosis of AF and for hypertension in adults in primary care in 2006 may be responsible for the larger proportions of hypertension and atrial fibrillation identified in the current study cohort compared with previously published data. [207,208] Clinical guidelines for diabetes were published by the Department of Health in 2001 and published data is likely to be more complete. It is therefore likely that the disease burden of the cohort is largely representative of the population.

In terms of lifestyle characteristics of the study population, approximately 64% (n=1844) of the final population reported that they currently and regularly consume alcohol and 6.2% (n=175) reported that they were current smokers. Around 15% (n=421) reported having a family history of thyroid dysfunction and 6.2% reported taking kelp or iodine supplementation (Table 9.6).

Table 9.6 Self-reported lifestyle characteristics and family history

Characteristic	Characteristic present n (%, 95%CI)	Characteristic absent n (%, 95%CI)	Missing data n (%)
Regular alcohol intake	1844 (64.3,62.5-66.0)	999 (34.8, 33.1-36.6)	27 (0.9)
Current smoker	175 (6.1, 5.1-7.0)	2675 (93.2, 92.2-94.2)	20 (0.7)
Kelp or iodine supplementation	179 (6.2, 5.4-7.2)	2624 (91.4, 90.3-92.4)	67 (2.3)
Family history of TD	421 (14.7, 13.4-16.0)	2409 (83.9, 82.5- 85.2)	40 (1.4)

With regard to medication prescribed by the GP, beta-adrenergic blockers were being prescribed to around 14% of the cohort, 5% were receiving glucocorticoids and 5% antidepressants. A small number of individuals in the final cohort were being prescribed major tranquilisers (n=13; 0.5%) and a smaller proportion (0.1%) were receiving treatment with lithium. (Table 9.7)

Table 9.7 Prescription medication use within the cohort

Medication	Characteristic present n (%, 95%CI)	Characteristic absent n (%,95%CI)
Amiodarone	11 (0.4, 0.2-0.7)	2859 (99.6, 99.3-99.8)
Antidepressant	151 (5.3, 4.5-6.1)	2719 (94.7, 93.9-95.5)
Anxiolytic	57 (2.0, 1.5-2.6)	2813 (98.0, 97.0-98.5)
Beta-adrenergic blocker	397(13.8,12.6-15.1)	2473 (86.2, 84.9-87.4)
Lithium	4 (0.1, 0.1-0.4)	2866 (99.9, 99.6-99.9)
Major tranquiliser	13 (0.5, 0.3-0.8)	2857 (99.5, 99.2-99.7)
Morphine or other opioid	25 (0.9, 0.6-1.3)	2845(99.1, 98.7-99.4)
Glucocorticoids	145 (5.1, 4.3-5.9)	2725(94.9, 94.1-95.7)

Summary of chapter 9

The aim of this chapter was to demonstrate the nature of the study cohort and report upon the representativeness of the sample for readers wishing to utilise symptom prevalence data. This chapter demonstrates a good response rate with 68% of those invited taking part in screening of thyroid function. The final cohort available for analysis comprised 2870 individuals for whom data collection had been fully completed and thyroid categorisation was possible.

Compared with the general population of England and Wales and the West Midlands, the study cohort had a larger proportion of 75-84 year olds, a smaller proportion of women and a greater prevalence of AF and hypertension. Additionally, whilst being more deprived then the general population of England and Wales, the study cohort was less deprived than the population of the West Midlands. In terms of medical history and co-morbidity the populations were similar with respect to the prevalence of diabetes. These differences are largely an artefact of historical cohort establishment and inaccuracy of published data which is outdated in the light of recent changes in policy and guidelines. These difference do not impact upon the cross-sectional study results which are the primary aim of this thesis but are worthy of consideration if extrapolating findings to other populations.

CHAPTER 10 SYMPTOM EXPRESSION AND HEALTH STATUS OF THE COHORT

Overview of chapter 10

Initially, this chapter describes the prevalence and intensity of symptoms present at the time of questionnaire completion (current symptoms), followed by a description of the prevalence and intensity of symptoms that have changed in the preceding 12 months (changed symptoms).

In addition, this chapter presents data related to perceived health status of the study population and reports upon the relationship between both the mental and physical components of health status and symptom expression. The effect of total number of symptoms on mental and physical health status summary scores is presented graphically and the findings from comparisons of median physical component and mental component summary scores between groups reporting presence and absence of each individual symptom are presented.

10.1 Symptom expression of the cohort

The final cohort of 2870 individuals self reported presence, intensity and recent change in 15 symptoms suggestive of overt thyroid dysfunction. Weight gain was the most prevalent current symptom, with 48.6% (n=1396) of the cohort reporting presence of this symptom at the time of questionnaire completion. The most prevalent symptom suggestive of hyperthyroidism reported by 22.8% (305/2870) of the cohort was fast thinking and the most prevalent symptom suggestive of hypothyroidism other than weight gain was sensitivity to cold temperatures. Dry skin was reported by 32% (n=924) of the cohort (Table 10.1).

10.1.1 Intensity of current symptoms

Severe symptoms were reported less frequently than mild symptoms with 42.3% of the cohort (1213/1398) reporting mild weight gain and just 6.4% (n=185) severe weight gain. Severe dry skin was reported by 5.0% (n=143) of the final population and mild dry skin by 27.2% (n=781) of the cohort. Prevalence of severe symptoms ranged from 0.1% to 6.4% whereas the prevalence of mild symptoms ranged from 2.5% to approximately 42.2% (Table 10.1)

Table 10.1 Prevalence of current symptoms reported by the cohort

					Intensity of current symptoms	
Classification symptom		Missing data n (%)	Absent n (%,95%CI)	Present n (%,95%CI)	Mild n (%,95%CI)	Severe n (%,95%CI)
Suggestive of hyperthyroidism	Excessive perspiration	2 (0.1)	2778 (96.9,96.1-97.4)	90 (3.1,2.6-3.8)	73 (2.5,2.0-3.2)	17 (0.6,0.4-0.9)
	Trembling hands	1 (0)	2749 (95.8,95.0-96.5)	120 (4.2, 3.5-5.0)	90 (3.1,2.6-3.8)	30 (1.0,0.7-1.5)
	Frequent palpitation	6 (0.2)	2693 (93.8,93.1-94.8)	171 (6.0, 5.1-6.9)	145 (5.1,4.3-5.9)	26 (0.9,0.8-1.3)
	Sensitivity to heat	48 (1.7)	2518 (87.7,86.5-88.9)	304 (10.6,9.5-11.8)	277 (9.7,8.6-10.8)	27 (0.9,0.6-1.4)
	Fast thinking	4 (0.1)	2211 (77.0,75.5-78.5)	655 (22.8,21.2-24.4)	595 (20.7,19.3-22.3)	60 (2.1,1.6-2.7)
	Weight loss	4 (0.1)	2660 (92.7,91.0-93.6)	206 (7.2, 6.3-8.2)	190 (6.6,5.8-7.6)	16 (0.6,0.3-0.9)
Either form of TD	Lethargy /lethargy	2 (0.1)	2408 (83.9,82.5-88.2)	460 (16.0,14.2-17.4)	380 (13.2,12.0-14.5)	80 (2.8,2.2-3.5)
	Weak muscles	4 (0.1)	2458 (85.6,84.3-86.9)	408 (14.3,13.0-15.5)	375 (13.1,11.9-14.3)	33 (1.1,0.8-1.6)
	Poor memory	1 (0)	2596 (90.5,89.3-91.5)	273 (9.5,8.6-10.7)	253 (8.8,7.8-9.9)	20 (0.7,0.5-1.1)
Suggestive of hypothyroidism	Hoarse voice	5 (0.2)	2688 (93.7,92.7-94.5)	177 (6.2,5.3-7.1)	170 (5.9,5.1-6.8)	7 (0.2,0.1-0.5)
	Deep voice	8 (0.3)	26794 (93.2,92.4-94.2)	188 (6.6,5.7-7.5)	184 (6.4,5.6-7.4)	4 (0.1,0.1-0.4)
	Dry skin	6 (0.2)	1940 (67.6,65.9-69.3)	924 (32.2,30.5-33.9)	781 (27.2,25.6-28.9)	143 (5.0,4.2-5.8)
	Puffy eyes	5 (0.2)	2475 (86.2,84.9-87.4)	390 (13.2,12.4-14.9)	373 (13.0,11.8-14.3)	17 (0.6,0.4-0.6)
	Muscle cramps	3 (0.1)	2434 (84.8,83.4-86.1)	433 (15.1,13.8-16.4)	368 (12.8,11.6-14.1)	65 (2.3,1.8-2.9)
	Constipation	7 (0.2)	2485 (86.6,85.3-87.8)	378 (13.1,12.0-14.5)	288 (10.0, 9.0-11.2)	90 (3.1,2.6-3.8)
	Sensitivity to cold	48 (1.7)	1837 (64.0,62.2-65.7)	985 (34.3,32.6-36.1)	849 (30.0,27.4-31.3)	136 (4.7,4.0-5.6)
	Slow thinking	4 (0.1)	2638 (91.9,90.0-92.9)	228 (7.9,7.0-9.0)	215 (7.5,6.6-8.5)	13 (0.5,0.3-0.8)
	Weight gain	4 (0.1)	1470 (51.3,49.4-53-0)	1396 (48.6,46.8-50.5)	1211 (42.2,40.4-44.0)	185 (6.4,5.6-7.4)

10.1.2 Prevalence of changed symptoms reported by the cohort

In terms of change in presence and intensity of symptoms during the preceding 12 months, the most frequently reported changed symptom was lethargy with 19% reporting that they were less active now than they were 12 months ago. Around 16% of the cohort reported having weaker muscles and 16% poorer memory than 12 months before. The most frequently reported 'changed' symptom suggestive of hyperthyroidism was weight loss (12.7%) and weight gain (15.3%) the most prevalent changed symptom suggestive of hypothyroidism (Table 10.2).

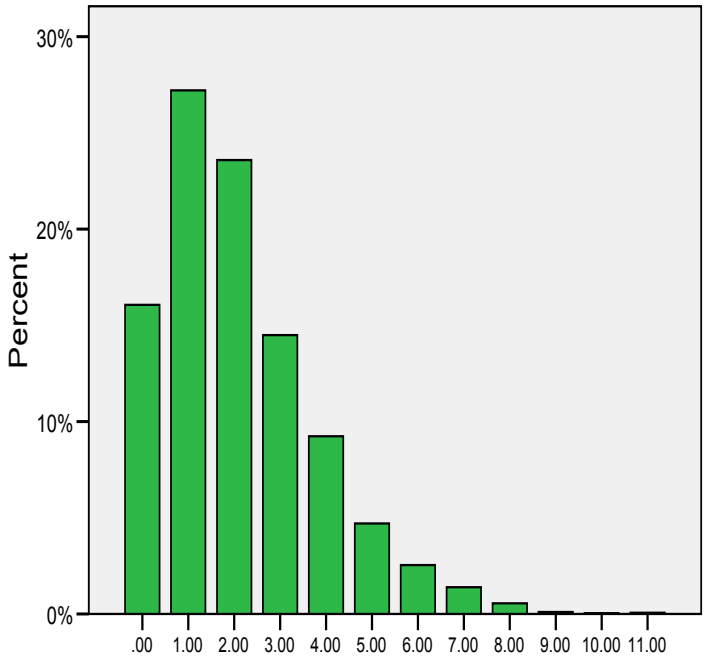
10.1.3 Intensity of changed symptoms

In terms of intensity of symptoms, a minimum of 0.1% and a maximum of 2.0% of the cohort reported presence of a severe change in symptom intensity during the previous 12 months whereas a mild change was reported by between 0.4% and 16.6% of the cohort. Overall, severe changes in individual symptoms were reported less frequently than mild changes in symptoms, with respect to the changed symptom lethargy, 2.0% (n=57) reported experiencing a severe change and 16.5% (n=475) of the cohort reported a mild change. (Table 10.2)

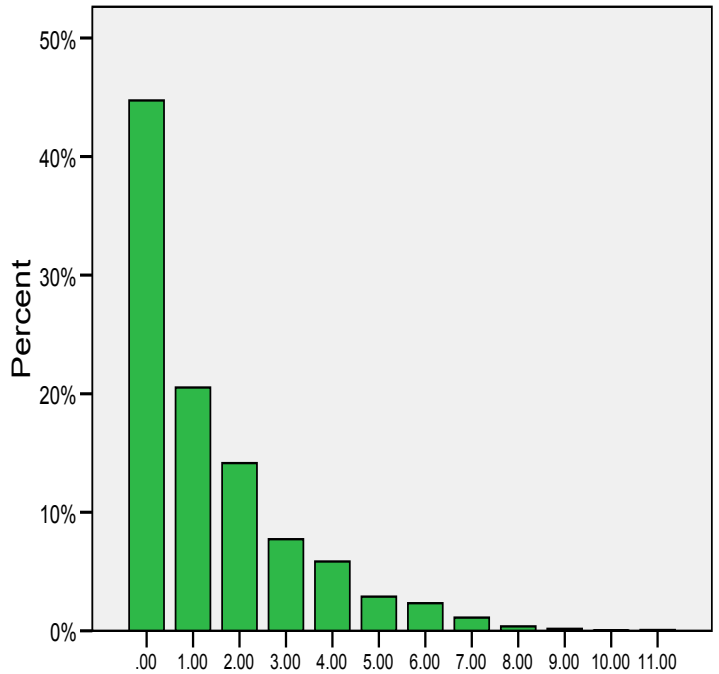
Table 10.2 Prevalence of changed symptoms reported by the cohort

					Intensity of changed symptom	
	Symptom classification	Missing data n (%)	Absent n (%,95%CI)	Present n (%,95%CI)	Mild n (%,95%CI)	Severe n (%,95%CI)
Suggestive of hyperthyroidism	Excessive perspiration	8 (0.3)	2802 (97.6,97.0-98.1)	60 (2.1,1.6-2.7)	56 (2.0,1.5-2.5)	4 (0.1,0.1-0.4)
	Trembling hands	11 (0.4)	2719 (94.7,93.9-95.8)	140 (4.9,4.1-5.7)	129 (4.5,2.8-8.3)	11 (0.4,0.2-0.7)
	Frequent palpitation	14 (0.5)	2728 (95.0,94.2-95.8)	128 (4.5,3.8-5.3)	122 (4.3,3.6-5.1)	6 (0.2,0.1-0.5)
	Sensitivity to heat	13 (0.5)	2798 (97.5,96.9-98.0)	59 (2.1,1.6-2.6)	48 (1.7,1.3-2.2)	11 (0.4,0.2-0.7)
	Fast thinking	8 (0.3)	2847 (99.2,98.8-99.5)	15 (0.5,0.3-0.9)	12 (0.4, 0.2-0.7)	3 (0.1,0-0.3)
	Weight loss	2 (0.1)	2489 (86.7,85.4-87.9)	379 (13.2,12.0-14.5)	362 (12.7,11.4-13.9)	17 (0.6,0.4-0.9)
Either form of TD	Lethargy	8 (0.3)	2330 (81.2,79.7-82.6)	532 (18.5,17.2-20.0)	475 (16.5,15.2-18.0)	57 (2.0,2.1-3.3)
	Weak muscles	8 (0.3)	2397 (83.5,82.184.8)	465 (16.2,14.9-17.6)	443 (15.5,14.2-16.8)	22 (0.8,0.5-1.2)
	Poor memory	3 (0.1)	2394 (83.4,82.0-84.7)	473 (16.4,15.2-17.9)	457 (15.9,14.6-17.3)	16 (0.6,0.3-0.9)
Suggestive of hypothyroidism	Hoarse voice	37 (1.3)	2692 (93.8,92.8-94.6)	141 (4.9,4.2-5.8)	134 (4.7,4.0-5.5)	7 (0.2,0.1-0.5)
	Deep voice	24 (0.8)	2789 (97.2,96.5-97.7)	57 (2.0,1.5-2.6)	55 (1.9,1.5-2.5)	2 (0.1,0-0.3)
	Dry skin	7 (0.2)	2495 (86.9,85.7-88.1)	368 (12.8,11.6-14.1)	337 (11.7,10.7-13.0)	31 (1.1,0.8-1.5)
	Puffy eyes	12 (0.4)	2685 (93.6,92.6-94.4)	173 (6.0,5.2-7.0)	164 (5.7,4.9-6.6)	9 (0.3, 0.2-0.6)
	Muscle cramps	5 (0.2)	2488 (86.7,85.4-87.9)	377 (13.1,11.9-14.1)	347 (12.1,10.9-13.3)	30 (1.0, 0.7-1.5)
	Constipation	14 (0.5)	2662 (92.8,91.7-93.6)	194 (6.7,5.9-7.7)	168 (5.9, 5.1-6.8)	26 (0.9,0.6-1.3)
	Sensitivity to cold	13 (0.5)	2492 (86.8,85.5-88.0)	365 (12.7,11.5-14.0)	339 (11.8,10.7-13.0)	26 (0.9,0.6-1.3)
	Slow thinking	8 (0.3)	2529 (88.0,88.6-89.3)	337 (11.7,10.6-13.0)	327 (11.4,10.3-12.6)	10 (0.3,0.2-0.6)
	Weight gain	2 (0.1)	2405 (83.8,82.4-85.1)	465 (16.1,14.9-17.6)	440 (15.3,14.1-16.7)	23 (0.8, 0.5-1.2)

Figure 10.1 - 10.2 Prevelance of multiple hypothyroid symptoms reported by the cohort

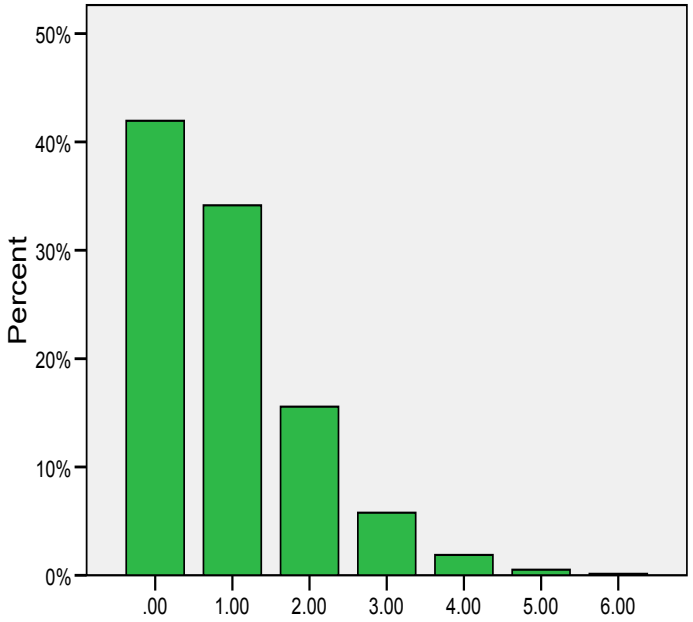


Total number of current symptoms suggestive of hypothyroidism reported by the cohort

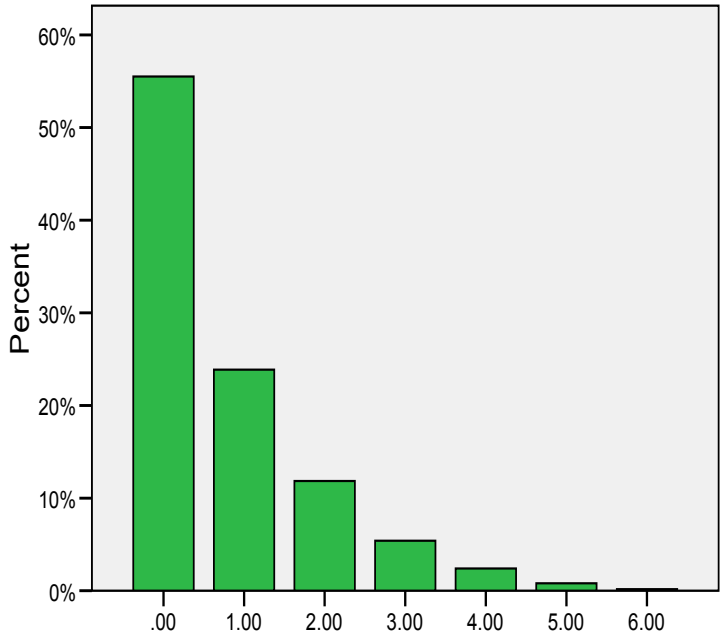


Total number of changed symptoms suggestive of hypothyroidism reported by the cohort

Figure 10.3 - 10.4 Prevelance of multiple hyperthyroid symptoms reported by the cohort



Total number of current symptoms suggestive of hyperthyroidism reported by the cohort



Total number of changed symptoms suggestive of hyperthyroidism reported by the cohort

10.2 Health status of the cohort

Health status was measured using the SF8 which is a multi purpose generic measure of health status that includes both a physical and mental health component. The physical health component score is a summary score of four measures of physical health, (general health, physical functioning, role physical and bodily pain) and the mental health component score is a summary score of four measures of mental health, (vitality, social functioning, mental health and role emotional). Mental and physical component summary scores range from 0-100, with 0 reflecting worst possible health status and 100, the best possible health status. Overall health status data were available for 2817/2870 (98%) of the study population with 53 individuals failing to return fully completed SF8 questionnaires. In general, the population demonstrated better overall mental health status than physical health status, scoring higher for the mental component summary score with an overall median of 51.86 compared with a median physical component summary score of 46.55.

Physical and mental health status at an individual symptom level was examined in order to identify those symptoms with the greatest impact upon health status. The Mann Whitney U test was used to compare median health status summary scores between two subgroups with group 1 representing those reporting presence of the symptom and group 2 defined by those reporting an absence of the symptom.

10.2.1 Impact of individual symptoms and health status

A significant difference in median physical component score between the two subgroups existed for 16 of the 18 symptoms ($p<0.001$ for all 16 symptoms). With respect to 15 of these 16 symptoms, a significantly lower median physical component summary score was attained by those expressing symptom presence compared with those stating absence of the symptom ($p<0.001$ in all 15 cases). In contrast those reporting current presence of the symptom fast thinking attained significantly higher physical component summary score compared with those that reported an absence of current fast thinking (48.8 versus 46 respectively, $p<0.001$). There were no significant differences in physical component summary score observed between groups with respect to current symptoms deep voice or weight gain (Table 10.3).

Table 10.3 Presence versus absence of current symptoms; comparison of physical component summary scores

Symptom classification		Median physical component summary score		
		Absence of symptom %,95%CI (n)	Presence of symptom %,95%CI (n)	Z* (p value)
Suggestive of hyperthyroidism	**Excessive perspiration**	46.7,46.2-47.6 (2727)	38.8,35.4-42.6 (88)	-5.6 (<0.001)
	Trembling hands	47.0,46.3-47.7 (2697)	38.0,35.4-48.7 (119)	-6.4 (<0.001)
	Frequent palpitation	47.3,44.9-46.4 (2643)	37.0, 23.9-24.6 (168)	-9.9 (<0.001)
	Sensitivity to heat	47.0,46.3-47.7 (2470)	45.0,43.3-46.4 (300)	-3.0 (<0.001)
	Fast thinking	46.0,44.9-46.6 (2174)	48.8,46.4-50.0 (639)	-3.9 (<0.001)
	Weight loss	46.6,45.9-47.8 (2609)	46.0,44.4-46.7 (204)	-0.2 (0.754)
Either form of TD	**Lethargy**	49.1,48.6-49.7 (2367)	32.7,31.6-34.0 (448)	-24.5 (<0.001)
	Weak muscles	48.7,48.0-49.2 (24.4)	35.8,34.5-37.3 (399)	-18.8 (<0.001)
	Poor memory	47.4,46.5-47.9 (2550)	41.1,39.1-43.0 (267)	-6.9 (<0.001)
Suggestive of hypothyroidism	**Hoarse voice**	47.0,46.3-47.7 (2638)	41.7,38.2-44.2 (174)	-5.7 (<0.001)
	Deep voice	46.5,45.8-47.4 (2624)	47.0,45.1-50.5 (185)	-.07 (0.577)
	Dry skin	48.2,47.5-48.9 (1901)	44.0,43.2-44.9 (910)	-8.1 (<0.001)
	Puffy eyes	47.2,46.4-47.9 (2426)	43.8,42.1-45.1 (386)	-4.6 (<0.001)
	Muscle cramps	48.1,47.5-48.8 (2386)	39.1,37.6-40.5 (428)	-12.9 (<0.001)
	Constipation	47.6,45.3-48.2 (2438)	40.8,39.2-42.3 (372)	-8.8 (<0.001)
	Sensitivity to cold	48.4,47.7-49.2 (1799)	44.4,43.3-45.0 (971)	-8.1 (<0.001)
	Slow thinking	47.2,46.4-47.9 (2589)	39.7,37.9-42.7 (224)	-7.4 (<0.001)
	Weight gain	48.2,47.1-49.3 (1436)	45.0,44.3-45.6 (1377)	-5.6 (<0.001)

* associated with the Mann Whitney U test

In terms of mental component summary score a significant difference was observed between the two subgroups with respect to 15 of the 18 symptoms. The median mental component summary score was significantly lower in the group reporting current symptom presence compared with the group reporting absence of the symptoms for 14 of the symptoms (Table 10.4). A significantly higher median mental component score however was observed in those reporting current presence of fast thinking compared with those not reporting presence of this symptom. No significant differences were observed between the groups with respect to presence of current symptoms deep voice or weight gain (Table 10.4).

Table 10.4 Presence versus absence of current symptoms; comparison of mental component summary scores

Symptom classification		Median mental component summary score		
		Absence of symptom %,95%CI (n)	Presence of symptom %,95%CI (n)	Z (p value)
Suggestive of hyperthyroidism	**Excessive perspiration**	52.0,51.5-52.5 (2727)	46.3,33.4-51.4 (88)	-3.9 (<0.001)
	Trembling hands	52.1,51.6-53.1 (2698)	47.5,44.7-49.5 (119)	-5.5 (<0.001)
	Frequent palpitation	52.2,51.7-52.8 (2643)	44.0,41.4-46.9 (168)	-8.0 (<0.001)
	Sensitivity to heat	52.2,51.7-52.8 (2470)	51.0,48.5-51.4 (300)	-3.1 (0.001)
	Fast thinking	51.2,50.6-51.7 (2174)	53.6,52.9-54.8 (639)	-5.8 (<0.001)
	Weight loss	52.0,51.5-52.5 (2609)	51.2,49.5-52.2 (204)	-2.2 (0.030)
Either form of TD	**Lethargy**	52.1,51.3-53.3 (2367)	45.5,44.3-47.3 (448)	-11.9 (<0.001)
	Weak muscles	52.9,52.3-53.3 (2414)	45.2,44.1-47.3 (399)	-11.9 (<0.001)
	Poor memory	52.4,51.8-53.1 (2550)	47.2, 44.8-49.2(267)	-8.5 (<0.001)
Suggestive of hypothyroidism	**Hoarse voice**	52.1,51.6-52.7 (2624)	48.9,46.9-50.7 (174)	-4.4 (<0.001)
	Deep voice	51.9,51.5-52.5 (2624)	51.2,50.1-52.0 (185)	-0.9 (0.717)
	Dry skin	52.8,52.2-53.4 (1901)	50.8,49.8-51.3 (910)	-7.0 (<0.001)
	Puffy eyes	52.4,51.9-53.1 (2426)	49.4,48.2-50.9 (386)	-6.0 (<0.001)
	Muscle cramps	52.5,51.9-53.1 (2386)	48.3,46.9-49.6 (428)	-8.0 (<0.001)
	Constipation	52.5,52.0-53.2 (2438)	47.6,45.5-49.1 (372)	-8.7 (<0.001)
	Sensitivity to cold	53.1,52.2-53.4 (1799)	51.1,50.5-51.4 (971)	-5.9 (<0.001)
	Slow thinking	52.4,52.0-52.8 (2589)	45.0,34.6-37.2 (224)	-9.6 (<0.001)
	Weight gain	51.7,51.5-52.5 (1436)	52.0,51.5-52.6 (1377)	-0.4 (0.874)

* associated with the Mann Whitney U test

Mann Whitney U tests were similarly used to compare median health status summary scores between groups reporting changed symptoms suggestive of overt thyroid dysfunction. In terms of physical component summary score and prevalence of individual changed symptoms reported by the cohort, a significant difference in median physical component summary score between groups reporting presence and absence of symptoms was observed for 17 symptoms. In each case, those reporting recent change in the symptom attained a significantly lower median physical component summary score than those reporting no change in the symptom ($p<0.001$ in all cases). The differences in median component summary score observed between groups reporting recent change and no change in fast thinking however failed to reach significance (Table 10.5).

Table 10.5 Presence versus absence of changed symptoms; comparison of physical component summary scores

Symptom classification		Median physical component summary score		
		Absence of symptom %,95%CI (n)	Presence of symptom %,95%CI (n)	Z (p value)
Suggestive of hyperthyroidism	**Excessive perspiration**	46.6,45.5-47.5 (2750)	39.3,35.0-45.1 (59)	-3.3 (<0.001)
	Trembling hands	47.0,46.5-47.8 (2670)	38.2,37.2-41.3 (136)	-6.5 (<0.001)
	Frequent palpitation	47.0,46.4-47.1 (2675)	39.0,35.1-41.9 (128)	-6.9 (<0.001)
	Sensitivity to heat	46.6,46.1-47.6 (2745)	41.1,37.6-44.5 (59)	-3.6 (<0.001)
	Fast thinking	46.5,45.9-47.3 (2796)	44.8,38.8-56.51 (14)	-0.54 (0.396)
	Weight loss	47.0,46.3-47.6 (2443)	44.2,42.3-45.9 (373)	-3.6 (<0.001)
Either form of TD	**Lethargy**	49.1,48.5-49.7 (2284)	36.5,35.5-37.6 (525)	-20.0 (<0.001)
	Weak muscles	48.4,47.7-49.1 (2354)	38.0,36.8-39.1 (455)	-15.4 (<0.001)
	Poor memory	47.5,46.6-48.2 (2347)	43.2,42.2-44.8 (467)	-6.5 (<0.001)
Suggestive of hypothyroidism	**Hoarse voice**	47.0,46.3-47.7 (2647)	41.2,37.6-42.4 (136)	-5.8 (<0.001)
	Deep voice	46.6,46.1-47.6 (2739)	38.2,34.7-44.7 (55)	-3.5 (<0.001)
	Dry skin	47.7,47.0-48.4 (2446)	41.1,34.6-42.0 (364)	-9.3 (<0.001)
	Puffy eyes	47.1,46.4-47.8 (2634)	41.1,39.2-43.7 (171)	-6.1 (<0.001)
	Muscle cramps	47.8,47.0-48.6 (2440)	39.8,38.3-41.4 (373)	-11.1 (<0.001)
	Constipation	47.0,46.3-48.9 (2612)	41.1,39.2-43.6 (191)	-5.4 (<0.001)
	Sensitivity to cold	47.7,46.8-48.0 (2443)	42.0,40.0-43.0 (361)	-8.1 (<-0.001)
	Slow thinking	47.6,46.6-48.2 (2477)	42.2,39.6-43.8 (333)	-7.5 (<0.001)
	Weight gain	47.5,46.5-48.0 (2361)	43.8,42.4-44.9 (455)	-5.0 (<0.001)

* associated with the Mann Whitney U test

Similarly, a significant difference in median mental component summary score between the groups existed for 17 (p<0.001) of the 18 changed symptoms. (Table 10.6).

Table 10.6 Presence versus absence of changed symptoms; comparison of mental component summary scores

Symptom classification		Median mental component summary score		
		Absence of symptom %,95%CI (n)	Presence of symptom %,95%CI (n)	Z (p value)
Suggestive of hyperthyroidism	**Excessive perspiration**	52.0, 51.6-52.5 (2750)	43.6,39.2-48.7 (59)	-5.1 (<0.001)
	Trembling hands	52.1,51.6-52.7 (2670)	47.6,45.0-50.5 (136)	-5.1 (<0.001)
	Frequent palpitations	52.1, 51.7-52.7 (2675)	44.7,42.1-46.8 (128)	-6.9 (<0.001)
	Sensitivity to heat	52.1,51.6-52.6 (2745)	44.0,40.5-47.8 (59)	-5.6 (<0.001)
	Fast thinking	51.9,51.5-52.4 (2796)	50.8,34.4-58.1 (14)	-0.4 (0.71)
	Weight loss	52.3,51.6-52.4 (2443)	49.2,48.1-50.9 (373)	-6.1 (<0.001)
Either form of TD	**Lethargy**	53.2,53.6-53.4 (2284)	45.5,44.8-47.3 (525)	-13.9 (<0.001)
	Weak muscles	52.0,52.4-52.3 (2354)	46.1,44.9-47.3 (455)	-11.9 (<0.001)
	Poor memory	52.7,52.1-53.3 (2347)	49.0,47.7-49.9 (467)	-8.9 (<0.001)
Suggestive of hypothyroidism	**Hoarse voice**	52.1,51.7-52.7 (2647)	47.0,45.0-49.3 (136)	-4.9 (<0.001)
	Deep voice	52.0,51.6-52.5 (2739)	46.5,42.2-49.3 (55)	-3.7 (<0.001)
	Dry skin	52.5,51.9-53.1 (2446)	48.2,46.4-49.8 (364)	-8.4 (<0.001)
	Puffy eyes	52.1,51.7-52.7 (2634)	48.2,45.3-50.2 (171)	-5.1 (<0.001)
	Muscle cramps	52.5,51.9-53.1 (2440)	48.2,46.9-49.6 (373)	-7.6 (<0.001)
	Constipation	52.2,51.7-53.1 (2612)	48.3,45.5-49.6 (191)	-6.1 (<0.001)
	Sensitivity to cold	52.5,51.9-53.1 (2443)	48.1,46.3-49.2 (361)	-7.6 (<0.001)
	Slow thinking	52.6,52.1-53.2 (2477)	47.4,45.2-50.0 (333)	-9.6 (<0.001)
	Weight gain	52.1,51.7-52.8 (2361)	51.0,49.8-51.5 (455)	-3.2 (<0.001)

* associated with the Mann Whitney U test

10.2.2 Summary of findings related to individual symptoms and health status

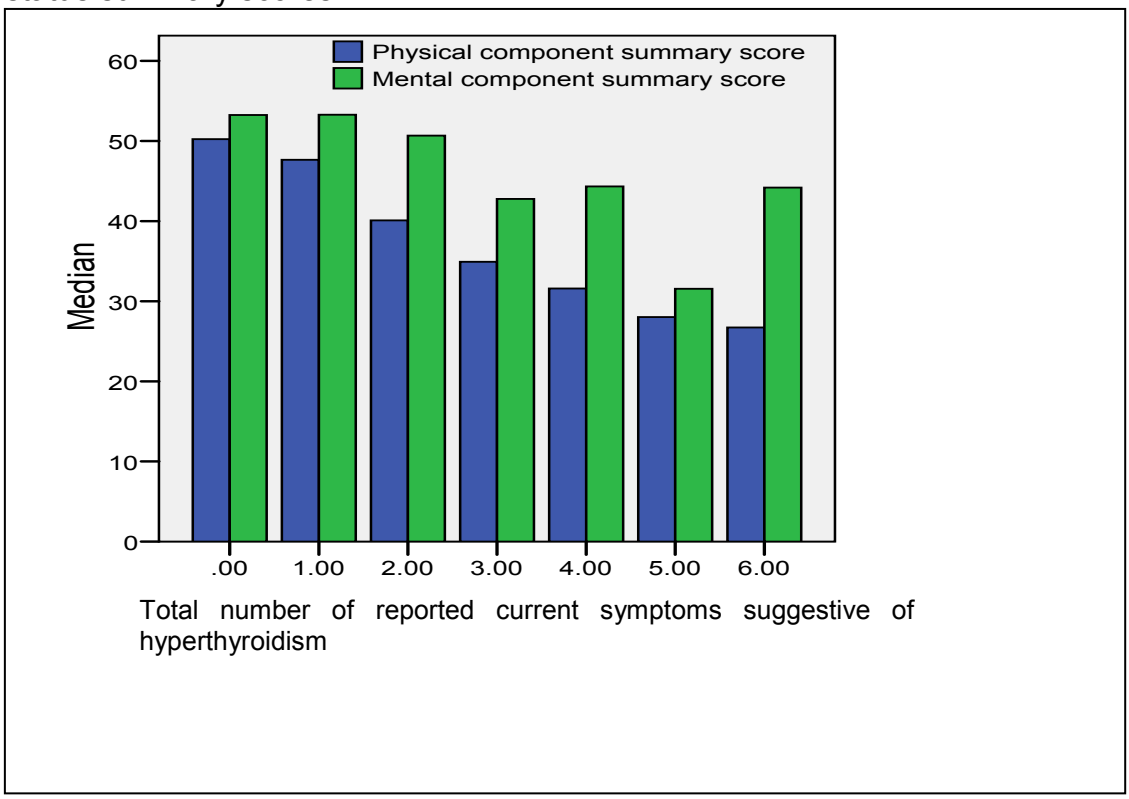
In general, individual symptoms appear to have a statistically significant impact upon health status of the cohort. The size of the changes in health status observed were, in general, small (<10 units) and are unlikely to be clinically meaningful.

10.3 Multiple symptoms and health status

10.3.1 Multiple hyperthyroid symptoms and health status

The impact of individual symptoms on health status was relatively small and unlikely to be of clinical significance**.** It is possible that multiple symptom presentation increases the magnitude and clinical significance of changes in health status. Therefore, the impact of multiple symptoms on health status was examined. To further explore the relationship between symptoms expression and health status, totalled number of symptoms reported was plotted against median physical and mental component summary scores. As the totalled number of reported current symptoms suggestive of overt hyperthyroidism increased, median physical component summary scores decreased (Figure 10.5).

Figure 10.5 Relationship between multiple current hyperthyroid symptoms and health status summary scores



A Kruskal Wallis test revealed a statistically significant difference in physical and mental component summary score across the four totalled current hyperthyroid symptom groups (group 1; n=1187: no symptoms reported, group 2; n=1395: one to two symptoms reported, group 3; n =216, three to four symptoms reported and group 4; n= 19: five or more symptoms reported) χ^2 (df3, n=2817) = 355.26, p<0.001 and χ^2 (df3, n=2817) = 175.55, p>0.001, respectively). Group four reporting the greatest number of totalled symptoms suggestive of hyperthyroidism recorded a lower median physical component summary score (28.0) than the other three groups (median score group 1; 50.2, group 2; 45.3 and group 3; 34.4 respectively) (Table 10.7). With respect to mental component summary scores, the results demonstrated a similar trend with group four reporting the greatest number of totalled symptoms suggestive of hyperthyroidism attaining the lower median mental component summary score (33.30) than the other three groups (median score group 1; 53.3, group 2; 51.9 and group 3; 43.2, respectively).

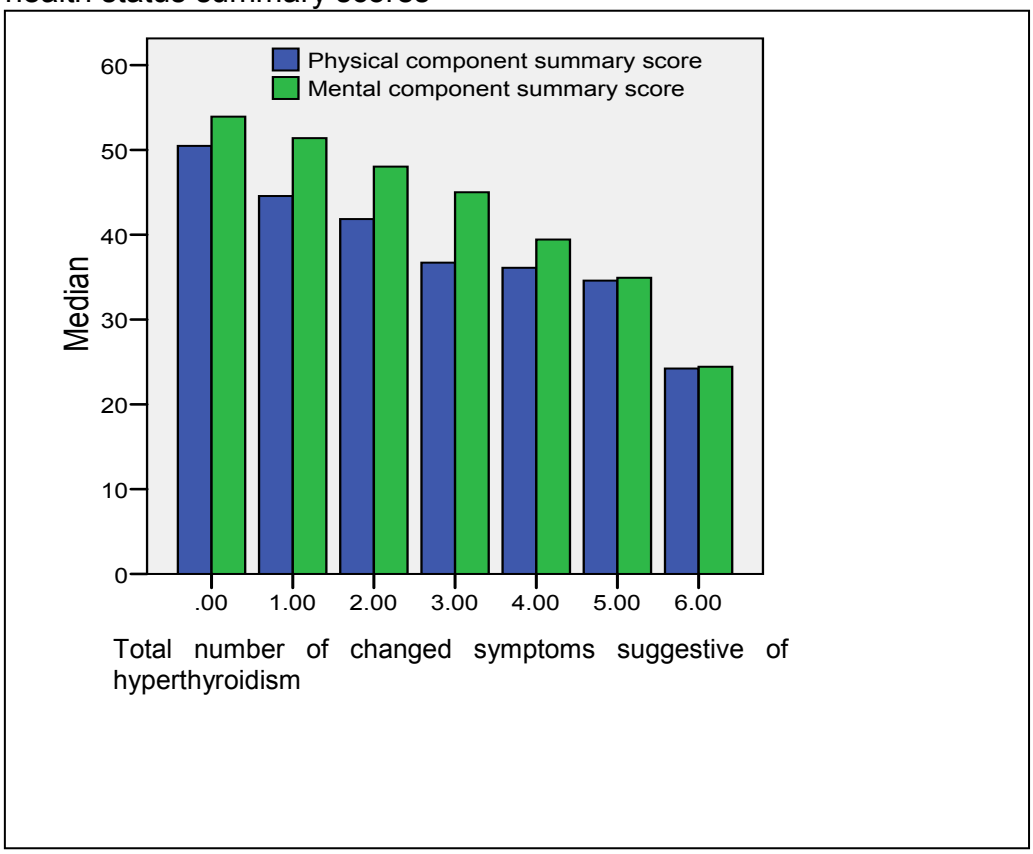
Table 10.7 Effect of multiple current hyperthyroid symptoms on health status summary scores

Totalled current hyperthyroid symptoms	Median physical component summary score	χ^2 (p) df = 3	Median mental component summary score	χ^2 (p) df = 3
None (n=1187)	50.2	355.3 (<0.001)	53.3	175.6 (<0.001)
1-2 (n=1395)	45.3		51.9	
3-4 (n=216)	34.4		43.2	
5 or more (n=19)	28.0		33.3	

10.3.2 Multiple changed hyperthyroid symptoms and health status

As the totalled number of reported changed symptoms suggestive of overt hyperthyroidism increased, median physical component summary scores decreased. In the same way, as the totalled number of changed symptoms suggestive of overt hyperthyroidism increased median physical component summary score decreased (Figure 10.6)

Figure 10.6 Relationship between multiple changed hyperthyroid symptoms and health status summary scores



In terms of changed symptoms suggestive of hyperthyroidism, a significant difference in median mental and physical component summary score also existed between the four totalled hyperthyroidism symptom groups. Again, the group with the highest number of totalled symptoms reported significantly lower levels of physical and mental health than any of the other three groups (Table 10.8).

Table 10.8 Impact of multiple changed hyperthyroid symptoms on health status summary scores

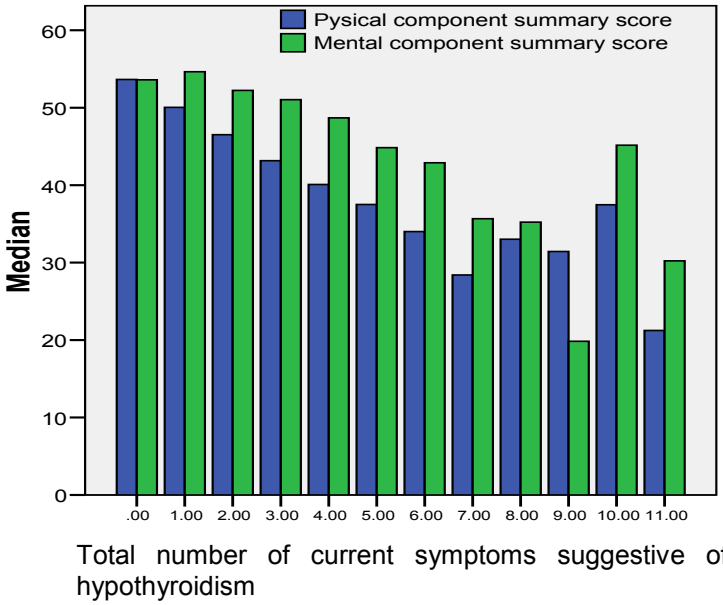
Totalled changed hyperthyroid symptoms	Median physical component summary score	χ^2 (p) df = 3	Median mental component summary score	χ^2 (p) df = 3
None (n=1563)	50.5	349.7 (<0.001)	53.9	275.2 (<0.001)
1-2 (n=1005)	43.6		50.7	
3-4 (n=221)	36.7		43.6	
5 or more (n=28)	34.2		34.7	

10.3.3 Multiple current hypothyroid symptoms and health status

The impact of multiple current and changed hypothyroid symptoms on mental and physical component summary scores was similar to that observed due to multiple hyperthyroid symptoms (Figures 10.7 and 10.8).

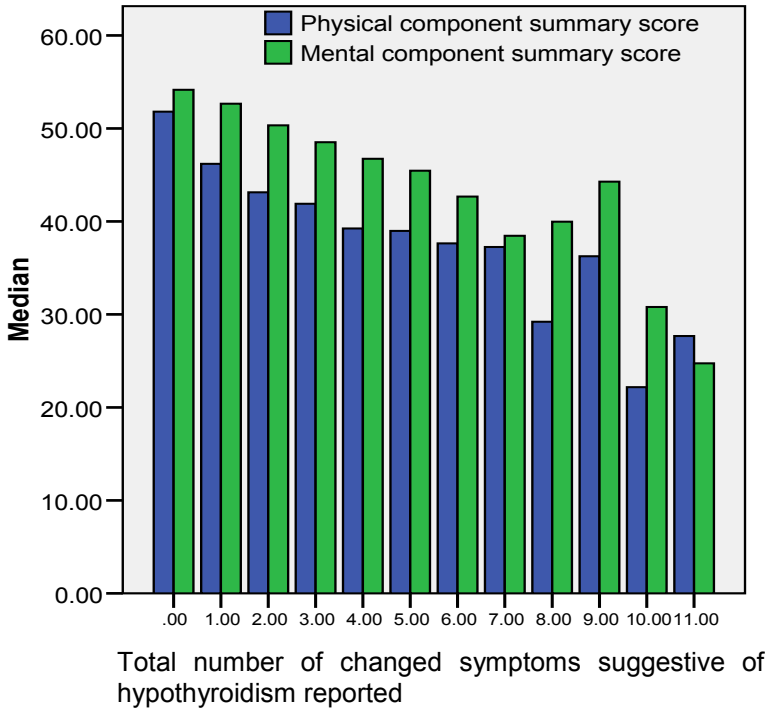
As the totalled number of reported current symptoms suggestive of overt hypothyroidism increased, median physical component summary scores decreased. (Figure 10.7)

Figure 10.7 Relationship between multiple current hypothyroid symptoms and health status scores score



Likewise, as the totalled number of changed symptoms suggestive of overt hypothyroidism increased, median physical component summary score decreased (Figure 10.8).

Figure 10.8 Relationship between multiple changed hypothyroid symptoms and health status score



Kruskal Wallis tests also revealed a statistically significant difference in median mental and physical component summary score between the four totalled current hypothyroidism symptom groups, ($p<0.001$) (Table 10.9).

Table 10.9 Effect of multiple current hypothyroid symptoms on health status summary scores

Totalled current hypothyroid symptoms	Median physical component summary score	χ^2 (p) df = 3	Median mental component summary score	χ^2 (p) df = 3
None (n=447)	53.7	509.3 (<0.001)	53.6	248.0 (<0.001)
1-2 (n=1434)	48.8		53.4	
3-4 (n=670)	41.9		50.4	
5 or more (n=266)	34.2		42.5	

In terms of multiple changed hypothyroid symptoms and health status summary scores, those reporting the highest number of symptoms suggestive of hypothyroidism scored significantly lower on both the physical and mental component summary scores ($p < 0.001$ in each case). (Table 10.10)

Table 10.10 Impact of multiple changed hypothyroid symptoms on health status summary score

Totalled changed hypothyroid symptoms	Median physical component summary score	χ^2 (p) df = 3	Median mental component summary score	χ^2 (p) df = 3
None (n=1259)	51.8	392.3 (<0.001)	54.2	255.6 (<0.001)
1-2 (n=973)	44.9		51.5	
3-4 (n=387)	40.6		48.2	
5 or more (n=198)	37.5		42.7	

Summary of chapter 10

In this chapter, symptom expression and health status of the cohort was explored and described. The most prevalent current symptom suggestive of hypothyroidism reported by the cohort was weight gain. Lethargy, poorer memory and weaker muscles were the most prevalent changed symptoms reported by the cohort. Fast thinking was the most frequently reported symptom suggestive of overt hyperthyroidism. In terms of intensity of current and changed symptoms the cohort reported a higher prevalence of mild intensity symptoms than severe intensity symptoms.

At the individual symptom level, median physical component summary score was significantly lower in those reporting presence of 16 current symptoms and 17 changed symptoms suggestive of overt thyroid dysfunction. The presence of current fast thinking, changed weight loss or changed dry skin were not associated with lower median physical component summary scores. Mental component summary scores were significantly lower in individuals reporting presence of 15 current and 17 changed symptoms. Those reporting presence of current symptoms weight gain and deep voice did not score significantly lower in terms of median component summary score. Individuals reporting current presence of fast thinking scored significantly higher with respect to median mental component summary score than those reporting absence of fast thinking. The difference between those reporting changed fast thinking compared with those reporting an absence of changed fast thinking however failed to reach significance. In general, mental health status of the cohort was better than physical health status. An inverse relationship between totalled number of symptoms suggestive of overt thyroid dysfunction reported and median

physical and mental component summary scores was observed. Reduced physical and mental component summary scores are associated with presence of current and changed individual symptoms suggestive of overt thyroid dysfunction. Furthermore, physical and mental component summary scores declined as the totalled number of current and changed symptoms suggestive of overt thyroid dysfunction increased.

These results suggest that symptoms suggestive of overt thyroid dysfunction are prevalent in individuals aged 65 years or more and appear to have a significant impact upon health status. Whilst individual symptoms do have a statistically significant influence upon heath status the impact is generally small (<10 units) and unlikely to be clinically meaningful. The results related to multiple symptoms however demonstrate that presence of five or more symptoms leads to clinically important changes in health status.

This chapter explored symptom expression and health status in the study cohort. The next chapter explores and describes the characteristics of the thyroid function groups.

CHAPTER 11 DESCRIPTION OF THE SUBGROUPS

Overview of chapter 11

The current chapter introduces the thyroid function groups and presents the characteristics and demographics of the subgroups. This chapter commences with a description of how the study population was divided into three subgroups according to the results of the thyroid function tests. The characteristics of the subgroups are then presented and findings of comparisons between the euthyroid and subclinical hyperthyroidism groups and the euthyroid and subclinical hypothyroidism groups reported. This chapter concludes with a summary of the main findings.

11.1 Expression of symptoms in accordance with thyroid function category

Using standard reference criteria for classification of thyroid function, patients were divided into three subgroups: group 1 with subclinical hyperthyroidism (n=29), group 2; euthyroid (n=2703) and group 3; subclinical hypothyroidism (n=138).

11.2 Categorisation and description of the subgroups

The euthyroid group were significantly younger than the subclinical hyperthyroidism group (mean age 76.83 versus 79.06 years respectively; $p<0.02$) and the subclinical hypothyroidism group (mean age 76.83 versus 77.70 years respectively; $p<0.05$). There was no significant difference in mean age of the subclinical hyperthyroidism group compared with the subclinical hypothyroidism group (79.06 versus 77.70 years respectively; $p<0.21$). In terms of socioeconomic status, the subclinical hyperthyroidism group was the most affluent with a mean IMD score of 22.16 and the subclinical hypothyroid group the least affluent (mean IMD score 21.72) no significant difference existed between these groups when compared with the euthyroid group (Table11.1).

The median serum thyrotrophin concentration was 5.39mIU/L in the subclinical hypothyroidism group, 0.15 mIU/L in the subclinical hyperthyroidism group and in the euthyroid group 1.78mIU/L. The lower limit of reporting serum thyrotrophin concentration was 0.02mIU/L, therefore concentrations below this threshold were undetectable. For analysis purposes, all five individuals with an undetectable thyrotrophin concentration were allocated a value of 0.02 mIU/L. Serum thyrotrophin concentration ranged from 0.02-0.29mIU/L in the subclinical hyperthyroidism group,

0.30- 4.50 mIU/L euthyroid and 4.53-19.30 mIU/L subclinical hypothyroidism. Serum free thyroxine concentration ranged from 9.1-30.10pmol/L in the euthyroid group, 12.60-21.20pmol/L in the subclinical hyperthyroidismgroup and 10.50–17.90pmol/L subclinical hypothyroidism group.

Table 11.1 Euthyroid versus subclinical thyroid dysfunction; comparison of demographic and clinical variables

Variable	Euthyroid n=2703	Subclinical hyperthyroid n =29	(Euth vs SChyper) (p) df = 1	Subclinical hypothyroid n=138	(Euth vs SChypo) (p) df = 1
Male n (%, 95% CI)	1414 (52.3)	10 (34.5)	χ^2 3.7 (0.06)	61 (44.2)	$\chi^2$3.5 (0.06)
Female n (%, 95% CI)	1289 (47.7)	19 (65.5)		77 (55.8)	
Age	n=2703	n=29		n=138	
Mean,95% CI (SD)	76.8,76.6-77.0 (4.9)	79.1,77.6-81.1 (5.5)	(0.02)#	77.7,76.8-78.6 (5.3)	(0.05)#
Median, 95%CI (IQR)	76.0,75.8-76.3 (7.50)	79.6,74.9-82.3 (9.80)	Z-2.26 (0.02)*	76.2,75.5-77.7 (7.30)	Z-1.84 (0.07)*
IMD score	n=2702	n=29		n=138	
Mean, 95% CI (SD)	21.7,21.2-22.3 (15.2)	22.2,17.3-27.0 (13.3)	(0.88)#	20.4,18.3-22.5 (12.5)	(0.23)#
Median 95%CI (IQR)	17.2,17.4-18.3 (18.7)	17.8,14.3-23.4 (14.8)	Z-0.65 (0.52)*	18.1,15.5-19.3 (18.4)	Z-0.12 (0.90)*
TSH	n=2703	n=29		n=138	
Mean,95% CI (SD)	1.94, 1.91-1.97 (0.90)	0.14, 0.1-0.18 (0.10)	(<0.001)#	6.28, 5.87-6.69 (2.48)	(<0.001)#
Median, 95%CI (IQR)	1.80,1.75-1.82 (1.24)	0.2,0.06-0.21 (0.20)	Z-9.28 (<0.001)*	5.4,5.20-5.63 (1.49)	Z-9.84 (<0.001)*
FT4	n=2703	n=29		n=138	
Mean,95% CI (SD)	15.1,15.0-15.2 (2.04)	16.3,15.6-17.0 (1.94)	(<0.001)#	13.6,13.4-13.9 (1.74)	(<0.001)#
Median,95%CI (IQR)	15.0,14.8-15.0 (2.5)	16.0,15.5-17.2 (2.3)	Z-3.45 (<0.001)*	13.5,13.2-13.9 (2.40)	Z-7.90 (<0.001)*

* associated with the Mann Whitney U test, # associated with the t test

Comparison of lifestyle characteristics reported by the subgroups revealed that a significantly greater proportion of the subclinical hypothyroidism group had a family history of thyroid dysfunction compared with euthyroid group (21.7% versus 14.2% respectively, χ^2 6.03, df 1, p<0.01). The subclinical hypothyroidism group was also significantly different to the euthyroid group in terms of alcohol intake (56.2% versus 65.5% respectively, χ^2 4.91, df 1, p 0.03) and use of iodine supplementation (χ^2 4.15, df 1, p 0.042**).** No significant difference existed between the euthyroid and subclinical hyperthyroidism groups with respect to any of the self reported lifestyle characteristics (Table 11.2).

Table 11.2 Euthyroid versus subclinical thyroid dysfunction; comparison of self-reported lifestyle characteristics and family history of thyroid dysfunction

Lifestyle characteristics and family history of TD	**Euthyroid n (%, 95% CI)**	**Subclinical hyperthyroid n (%, 95% CI)**	**χ^2 (p value) df = 1 (Euth vs SChyper)**	**Subclinical hypothyroid n (%, 95% CI)**	**χ^2 (p value) df = 1 (Euth vs SChypo)**
Alcohol intake	1753 (65.5,63.0-66.6)	14 (50.0,31.4-65.6)	2.92 (0.09)	77 (56.2,47.2-63.8)	4.91 (0.03)
Current smoker	165 (6.1,5.3-7.1)	2 (7.1,1.9-22.0)	(0.69)*	8 (5.8,3.0-11.0)	0.02 (0.90)
Kelp/iodine supplementation	175 (6.6,5.6-7.5)	1 (3.7,0.6-17.2)	(1.0)*	3 (2.2,0.7-6.2)	4.15 (0.042)
Family history of TD	384 (14.2,12.9-15.6)	7 (24.1,12.2-42.1)	(0.10)*	30 (21.7,15.7-29.3)	6.03 (0.01)

*associated with the Fisher exact test

In terms of the frequency of prescription medication, there were no significant differences between these with euthyroid compared with the subclinical hyperthyroidism or subclinical hypothyroidism groups. Beta-adrenergic blockers were the most frequently prescribed concomitant medication with 24% of the subclinical hyperthyroid group, 13.9% of the euthyroid group and 10.1% of the subclinical hypothyroid group receiving this treatment (Table 11.3).

Table11.3 Euthyroid versus subclinical thyroid dysfunction; comparison of medication prescribed by the GP

Prescribed medication	**Euthyroid n (%,95% CI)**	**Subclinical hyperthyroid n (%,95% CI)**	**(Euth vs SChyper) χ^2 (p value) df = 1**	**Subclinical hypothyroid n (%,95% CI)**	**(Euth vs SChypo) χ^2 (p value) df = 1**
Amiodarone	11 (0.40,0.2-0.7)	0 (0-11.7)	(1.00)*	0 (0-2.7)	(1.00)*
Antidepressant	145 (5.40,4.6-6.3)	0 (0-11.7)	(0.40)*	6 (4.3,2.0-9.2)	0.27 (0.60)
Anxiolytic	56 (2.10,1.6-2.7)	0 (0-11.7)	(1.00)*	1 (0.7,0.1-4.0)	(0.53)*
Beta-adrenergic blocker	376 (13.90,12.7-15.3)	7 (24.1,12.2-42.1)	(0.17)*	14 (10.1-6.1-16.3)	1.57 (0.21)
Lithium	4 (0.10,0.1-0.4)	0	(1.00)*	0 (0.2-2.7)	(1.00)*
Major tranquiliser	12 (0.40,0.3-0.8)	1 (3.4,0.6-17.2)	(0.13)*	0 (0.2-2.7)	(1.00)*
Morphine or other opioid	25 (0.90,0.6-1.4)	0 (0-11.7)	(1.00)*	0 (0.2-2.7)	(0.63)*
Glucocorticoids	136 (5.0, 4.3-5.9)	1 (3.4, 0.6-17.2)	(1.00)*	8 (5.8, 3.0-11.0)	0.16 (0.69)

*associated with the Fishers exact test

There were no significant differences between the euthyroid and subclinical hyperthyroidism groups with respect to prevalence of co-morbidity. However, a significant difference between the euthyroid and subclinical hypothyroidism groups was observed with respect to the prevalence of pulmonary disease. A significantly greater proportion of the euthyroid subjects had a diagnosis of pulmonary disease compared with the individuals with subclinical hypothyroidism (12.9% versus 3.6 respectively; $p<0.001$. These two groups were otherwise similar with respect to all other co-morbidities (Table 11.4).

Table 11.4 Euthyroid versus subclinical thyroid dysfunction; comparison of co-morbidity

Medical history	Euthyroid n (%,95% CI)	Subclinical hyperthyroid n (%,95% CI)	(Euth vs SChyper) χ^2 (p value) df = 1	Subclinical hypothyroid n (%,95% CI)	(Euth vs SChypo χ^2 (p value) df = 1
Anaemia	13 (0.50,0.3-0.8)	0 (0-11.7)	(1.00)	0 (0.9-2.7)	(1.00)
Anxiety present	163 (6.00,5.2-7.0)	0 (0-11.7)	(0.41)*	9 (6.50,3.5-11.9)	0.07 (0.81)
Atrial Fibrillation	195 (7.20,6.3-8.3)	1 (3.40,0.6-17.2)	(0.72)*	6 (4.30,2.0-9.2)	1.64 (0.20)
Cancer	280 (10.40,9.3-11.6)	2 (6.90,1.9-22.0)	(0.76)	18 (13.00,8.4-19.7)	0.97 (0.33)
Dementia	18 (0.70,6.9-8.9)	1 (3.40,0.6-17.2)	(0.18)	0 (0.9-2.7)	(1.00)
Depression	211 (7.80,6.9-8.9)	0 (0-11.7)	(0.61)	13 (9.40,5.6-15.5)	0.47 (0.49)
Diabetes	315 (11.70,10.5-12.9)	4 (13.80,5.5-30.6)	(0.77)	17 (12.30,7.8-18.8)	0.06 (0.81)
Goitre	5 (0.20,0.1-0.4)	0 (0-11.7)	(1.00)	0 (0.9-2.7)	(1.00)
Heart failure	123 (4.60,3.8-5.4)	0 (0-11.7)	(0.64)	3 (2.20,0.7-6.2)	1.75 (0.19)
Hip Replacement	66 (2.40,1.9-3.1)	0 (0-11.7)	(1.00)	0 (0.9-2.7)	(0.08)
Hypertension	1379 (51.0,49.7-52.9)	14 (48.30,31.4-65.6)	(0.85)	77 (55.80,47.5-63.8)	1.20 (0.27)
Ischemic heart disease	339 (12.50,11.3-13.8)	1 (3.40,0.6-17.2)	(0.25)	23 (16.70,11.4-23.8)	2.01 (0.16)
Irregular heart rhythm	95 (3.50,2.9-4.3)	1 (3.40,0.6-17.2)	(1.00)	1 (0.70,0.1-4.0)	(0.09)
Knee Replacement	80 (3.00,2.4-3.7)	2 (6.90,1.9-22.0)	(0.22)	7 (5.10,2.5-10.1)	(0.20)
Neurological disease	26 (1.00,0.7-1.4)	0 (0-11.7)	(1.00)	0 (0.9-2.7)	(0.64)
Osteoporosis	51 (1.90,2.7-4.1)	0 (0-11.7)	(1.00)	2 (1.40,0.4-5.1)	(1.00)
Peripheral vascular disease	90 (3.30,2.7-4.11)	2 (6.90,1.9-22.0)	(0.16)	6 (4.30,2.0-9.2)	(0.47)
Pituitary disease	8 (0.30,0.2-0.6)	0 (0-11.7)	(1.00)	0 (0.9-2.7)	(1.00)
Pulmonary disease	348 (12.90,11.7-14.2)	2 (6.90)	(0.57)	5 (3.60,1.6-8.2)	10.23 (0.001)
Renal disease	497 (18.40-17.0-19.9)	5 (17.20,7.6-34.5)	(1.00)	23 (16.70,11.4-6.2)	0.260 (0.61)
Rheumatoid Arthritis	66 (2.40,1.9-3.1)	0 (0-11.7)	(1.00)	3 (2.20,0.7-6.2)	(1.00)
Stroke	148 (5.50,4.7-6.4)	3 (10.30,3.6-26.4)	(0.21)	6 (4.30,2.0-9.2)	0.33 (0.57)

11.3 Health status in the thyroid function groups

The euthyroid and subclinical hyperthyroidism groups were similar with respect to both mental and physical component scores. Likewise, the euthyroid and subclinical hypothyroidism groups were similar in terms of median mental and physical component summary scores (Table 11.5).

Table 11.5 Euthyroid versus subclinical thyroid dysfunction; comparison of mental and physical health status summary scores

Median component summary score	Euthyroid n=2653	Subclinical hyperthyroid n=27	Euth vs Schyper Z score* (p value)	Subclinical hypothyroid n=137	Euth vs ScHypo Z Score* (p value)
Median physical component summary score, 95% CI (IQR)	46.5, 45.8-47.4 (16.52)	45.8,35.6-54.5 (21.77)	-0.72 (0.47)	47.0,44.5-49.3 (13.32)	-0.17 (0.87)
Median mental component summary score, 95% CI (IQR)	51.8,51.5-52.3 (11.46)	49.2,44.6-54.1 (9.95)	-1.66 (0.09)	53.1,51.5-54.9 (8.32)	-1.15 (0.25)

* associated with the Mann Whitney U test

Summary of chapter 11

The subclinical hyperthyroidism group was significantly older than the euthyroid group (79.0 versus 76.8 years respectively, $p<0.017$). These groups were nevertheless similar with respect to gender, socioeconomic status, lifestyle characteristics, prescription medication, co-morbidities and physical and mental health status.

The subclinical hypothyroidism and euthyroid groups were significantly different in terms of age, alcohol intake, family history of thyroid dysfunction and prevalence of pulmonary disease. Similarly, the subclinical hypothyroidism group were older than the group with euthyroid (77.7 versus 76.8 years respectively, $p<0.049$). Additionally, a larger proportion of the subclinical hypothyroidism group self reported having a family history of thyroid dysfunction. The euthyroid group had a significantly greater proportion of individuals self reporting regular alcohol intake (65.5% versus 56.2%, $p<0.03$) and a greater prevalence of pulmonary disease (12.9% versus 10.2% respectively, $p <0.001$). These groups were, however, similar with respect to gender, socioeconomic status, lifestyle characteristics, prescription medication and physical and mental health status.

The findings from comparisons of physical and mental component summary scores across the thyroid function groups in the current chapter suggest that neither subclinical hyperthyroidism or subclinical hypothyroidism are associated with reduced health status. In combination with the previous results demonstrating a significant difference in physical and mental component summary scores between groups reporting presence and absence of individual symptoms, these findings suggest that it is the presence of individual symptoms rather than subclinical thyroid dysfunction itself that is responsible for impaired health status.

This chapter introduced the thyroid function subgroups and described lifestyle, co-morbidity, concomitant medication and perceived health status in euthyroid subjects and individuals with subclinical hyperthyroidism and subclinical hypothyroidism. In the next chapter, symptom expression in the thyroid function groups is further explored.

CHAPTER 12 SYMPTOMS IN THE SUBGROUPS

Overview of chapter 12

The aim of this chapter is to present the findings of univariate and multivariate analyses exploring the relationship between thyroid function category and expression of symptoms. Results of the univariate analyses are tabulated and summarised to clarify which individual symptoms and combinations of symptoms are potentially important predictors of thyroid function and were included in the multivariate analysis.

Binary logistic regression models constructed to identify those symptoms or combinations of symptoms that are independent predictors of subclinical thyroid dysfunction while controlling for lifestyle characteristics, demographics, concomitant medication and medical history are then presented.

12.1 Prevalence of hypothyroid symptoms

To enable characterisation of symptoms reported in the euthyroid and subclinical hypothyroidism groups, the prevalence of individual hypothyroid symptoms reported by each group was calculated. The chi squared test of independence was used to compare the prevalence of current and changed individual symptoms between the euthyroid and subclinical hypothyroidism groups. Where appropriate the Fishers exact test was used. A Bonferroni adjusted alpha value of $p<0.004$ was used to control for type I error for each comparison between euthyroid and subclinical hypothyroidism groups.

At the individual symptoms level there were no significant differences between the euthyroid and subclinical hypothyroidism groups with respect to any of the twelve current symptoms suggestive of hypothyroidism. Likewise there were no significant differences in the prevalence of changed symptoms reported by these two groups (Table 12.1).

Table 12.1 Euthyroid versus subclinical hypothyroidism; comparison of the prevalence of individual current and changed hypothyroid symptoms

	Current symptoms reported			Changed symptoms reported		
Symptom	Euthyroid %, 95% CI, (n)	Subclinical hypothyroid %, 95% CI (n)	χ^2 (p value) df = 1	Euthyroid %, 95% CI, (n)	Subclinical hypothyroid %, 95% CI (n)	χ^2 (p value) df = 1
Lethargy	16.40, 15.0-17.8 (442)	10.90, 6.7-17.3 (15)	2.83 (0.09)	18.70, 17.3-20.2 (505)	16.10, 10.9-23.1 (22)	0.62 (0.43)
Weak muscles	14.30, 13.0-15.7 (386)	14.50, 9.6-21.3 (20)	0.04 (0.95)	16.40, 15.0-17.8 (442)	13.90, 9.1-20.6 (19)	0.61 (0.44)
Poor memory	9.70, 8.6-10.9 (262)	8.00, 4.5-13.7 (11)	0.45 (0.50)	16.50, 15.2-18.0 (446)	15.90, 10.8-23.0 (22)	0.03 (0.86)
Hoarse voice	6.00, 5.2-7.0 (163)	8.00, 4.5-13.8 (11)	0.90 (0.34)	4.80, 4.1-5.7 (128)	6.50, 3.5-11.9 (9)	0.83 (0.36)
Deep voice	6.40, 5.5-7.4 (172)	9.50, 5.6-15.6 (13)	2.07 (0.15)	2.00, 1.5-2.6 (54)	1.40, 0.4-5.1 (2)	(1.00)*
Dry skin	32.20, 30.4-34.0 (868)	33.30, 26.0-41.6 (46)	0.08 (0.78)	13.10, 11.8-14.4 (352)	9.50, 5.6-15.6 (13)	1.48 (0.23)
Puffy eyes	13.30, 12.1-14.7 (360)	15.90, 10.8-23.0 (22)	0.76 (0.38)	6.00, 5.2-7.0 (162)	5.80, 3.0-11.0 (8)	0.12 (0.91)
Muscle cramps	15.10, 13.8-16.5 (408)	15.20, 10.2-22.1 (21)	0.01 (0.97)	13.10, 11.9-14.4 (354)	13.80, 9.0-20.5 (19)	0.05 (0.83)
Constipation	13.20, 11.9-14.5 (355)	14.50, 9.6 -21.3 (20)	0.20 (0.65)	6.70, 5.8-7.7 (181)	8.00, 4.5-13.8 (11)	0.35 (0.56)
Sensitivity to cold	34.80, 33.0-36.7 (925)	37.20, 29.6-45.6 (51)	0.33 (0.57)	12.80, 11.6-14.1 (345)	10.90, 6.7-17.2 (15)	0.45 (0.50)
Slow thinking	7.90, 6.9-8.9 (212)	11.60, 7.3-18.9 (16)	2.48 (0.12)	11.70, 10.6-13.0 (316)	13.80, 9.0-20.5 (19)	0.53 (0.47)
Weight gain	48.50, 46.7-50.4 (1310)	53.60, 45.3-61.7 (74)	1.36 (0.24)	15.90, 14.6-17.3 (429)	20.30, 14.4-27.8 (28)	1.88 (0.17)

Bonferroni adjustment p<0.004 * associated with the Fishers exact test

12.2 Intensity of hypothyroid symptoms reported by subgroups

Comparisons between the groups with respect to the reported intensity of current and changed symptoms were also undertaken. Again, a Bonferroni adjusted alpha value of $p<0.004$ was applied to control for type I error for each comparison between the euthyroid and subclinical hypothyroidism groups. No significant differences in prevalence of mild intensity current or changed symptoms suggestive of hypothyroidism existed between the euthyroidism and subclinical hypothyroidism groups (Table 12.2).

Table 12.2 Euthyroid versus subclinical hypothyroidism; comparison of the prevalence of individual current and changed mild intensity hypothyroid symptoms

	Current mild intensity symptoms			Changed mild intensity symptoms		
Symptom	Euthyroid %, 95%CI (n)	Subclinical hypothyroid %, 95%CI (n)	χ^2 (p value) df 1	Euthyroid %, 95%CI (n)	Subclinical hypothyroid %, 95%CI (n)	χ^2 (p value) df 1
Lethargy	13.90, 12.6-15.2 (364)	10.30, 6.2-16.5 (14)	1.4 (0.23)	17.00 15.6-18.5 (449)	16.10, 10.9-20.1 (22)	0.08 (0.77)
Weak muscles	13.30, 12.0-14.6 (354)	14.50, 9.6-21.3 (20)	0.17 (0.68)	15.80 14.4-17.2 (422)	13.2, 8.5-20.0 (18)	0.63 (0.43)
Poor memory	9.00, 8.0-10.2 (242)	8.00, 4.5-13.7 (11)	0.18 (0.67)	16.00, 14.7-17.5 (430)	15.9, 10.8-23.0 (22)	0.001 (0.98)
Hoarse voice	5.80, 5.0-6.70 (156)	8.00, 4.5-13.7 (11)	1.17 (0.28)	4.50, 3.8-5.4 (121)	6.5, 3.5-11.9 (9)	1.15 (0.28)
Deep voice	6.20, 5.4-7.2 (168)	9.5, 5.6-15.6 (13)	2.29 (0.13)	1.90, 1.5-2.5 (52)	1.4, 0.4-5.1 (2)	0.17 (0.68)
Dry skin	28.50, 26.8-30.3 (730)	31.30, 24.1-39.6 (42)	0.49 (0.48)	12.10, 10.9-13.4 (322)	9.5, 5.6-15.6 (13)	0.83 (0.36)
Puffy eyes	12.90, 11.7-14.2 (346)	14.1, 9.2-20.9 (19)	0.16 (0.69)	5.70, 4.9-6.7 (154)	5.1, 2.5-10.2 (7)	0.09 (0.76)
Muscle cramps	13.10 11.8-14.4 (344)	15.2, 10.2-22.1 (21)	0.54 (0.46)	12.20, 11.0-13.5 (326)	13.1, 8.5-19.8 (18)	0.11 (0.75)
Constipation	10.20 9.1-11.5 (267)	13.9, 9.1-20.6 (19)	1.83 (0.18)	5.90, 5.0-6.8 (156)	8.0, 4.5-13.8 (11)	1.10 (0.29)
Sensitivity to cold	31.60 29.8-33.4 (798)	34.4, 26.8-42.8 (45)	0.45 (0.50)	12.10, 10.9-13.4 (322)	10.9, 6.7-17.2 (15)	0.18 (0.67)
Slow thinking	7.40 6.5-8.5 (200)	10.9, 6.7-17.3 (15)	2.28 (0.13)	11.40, 10.3-12.7 (307)	13.1, 8.5-19.8 (18)	0.37 (0.54)
Weight gain	45.00 43.1-47.0 (1137)	49.6, 41.1-58.2 (65)	1.03 (0.31)	15.20, 13.9-16.6 (408)	20.3, 14.4-27.8 (28)	2.58 (0.11)

Bonferroni adjusted p value < 0.004. * associated with the Fishers exact test

Similarly, there were no significant differences observed between the euthyroid and subclinical hypothyroidism groups with respect to the prevalence of severe current or changed symptoms suggestive of hypothyroidism (Table 12.3)

Table 12.3 Euthyroid versus subclinical hypothyroidism; comparison of the prevalence of individual current and changed severe intensity hypothyroid symptoms

	Current severe intensity symptom			**Changed severe intensity symptom**		
Symptom	Euthyroid %, 95% CI (n)	Subclinical hypothyroid %, 95% CI (n)	χ^2 (p) df = 1	Euthyroid %, 95% CI (n)	Subclinical hypothyroid %, 95% CI (n)	χ^2 (p) df = 1
Lethargy	3.30, 2.7-4.1 (78)	0.80, 0.1-4.5 (1)	(0.18)*	2.50, 1.9-3.2 (56)	0 (0-3.2)	(0.11)*
Weak muscles	1.40, 1.0-1.9 (32)	0 (0-3.2)	(0.40)*	0.90, 0.6-1.4 (20)	0.80 (1)	(1.00)*
Poor memory	0.80, 0.5-1.3 (20)	0 (0-2.9)	(0.62)*	0.70, 0.4-1.1 (16)	0 (0-3.2)	(1.00)*
Hoarse voice	0.30, 0.1-0.6 (7)	0 (0.3.0)	(1.00)*	0.30, 0.1-0.6 (7)	0 (0-2.9)	(1.00)*
Deep voice	0.20, 0.1-0.4 (4)	0 (0.3.2)	(1.00)*	0.10, 0.1-0.3 (2)	0 (0.27)	(1.00)*
Dry skin	7.00, 6.0-8.2 (138)	4.20, 2.6-10.2 (4)	1.16 (0.28)	1.30, 0.9-1.8 (30)	0 (0-30)	(0.40)*
Puffy eyes	0.60, 0.4-1.0 (14)	2.50, 0.9-7.2 (3)	(0.05)*	0.30, 0.2-0.6 (8)	0.80, 0.1-4.2 (1)	(0.37)*
Muscle cramps	2.70, 2.1-3.5 (64)	0 (0-3.2)	(0.07)*	1.20, 0.8-1.7 (28)	0.80, 0.1-4.6 (1)	(1.00)*
Constipation	3.60, 2.9-4.4 (88)	0.80, 1.0-4.6 (1)	(0.15)*	1.00, 0.7-1.5 (25)	0 (0-3.0)	(0.63)*
Sensitivity to cold	6.80, 5.8-81 (127)	6.50, 3.0-13.5 (6)	0.01 (0.91)*	1.00, 0.6-1.5 (23)	0 (0-3.0)	(0.63*
Slow thinking	0.50, 0.3-0.8 (12)	0.80, 0.1-4.5 (1)	(0.47)*	0.40, 0.2-0.7 (9)	0.80, 0.1-4.6 (1)	(0.39)*
Weight gain	11.10, 9.6-12.7 (173)	14.70, 8.4-24.4 (11)	0.93 (0.34)	0.90, 0.6-1.4 (21)	0 (0.3.4)	(0.62)*

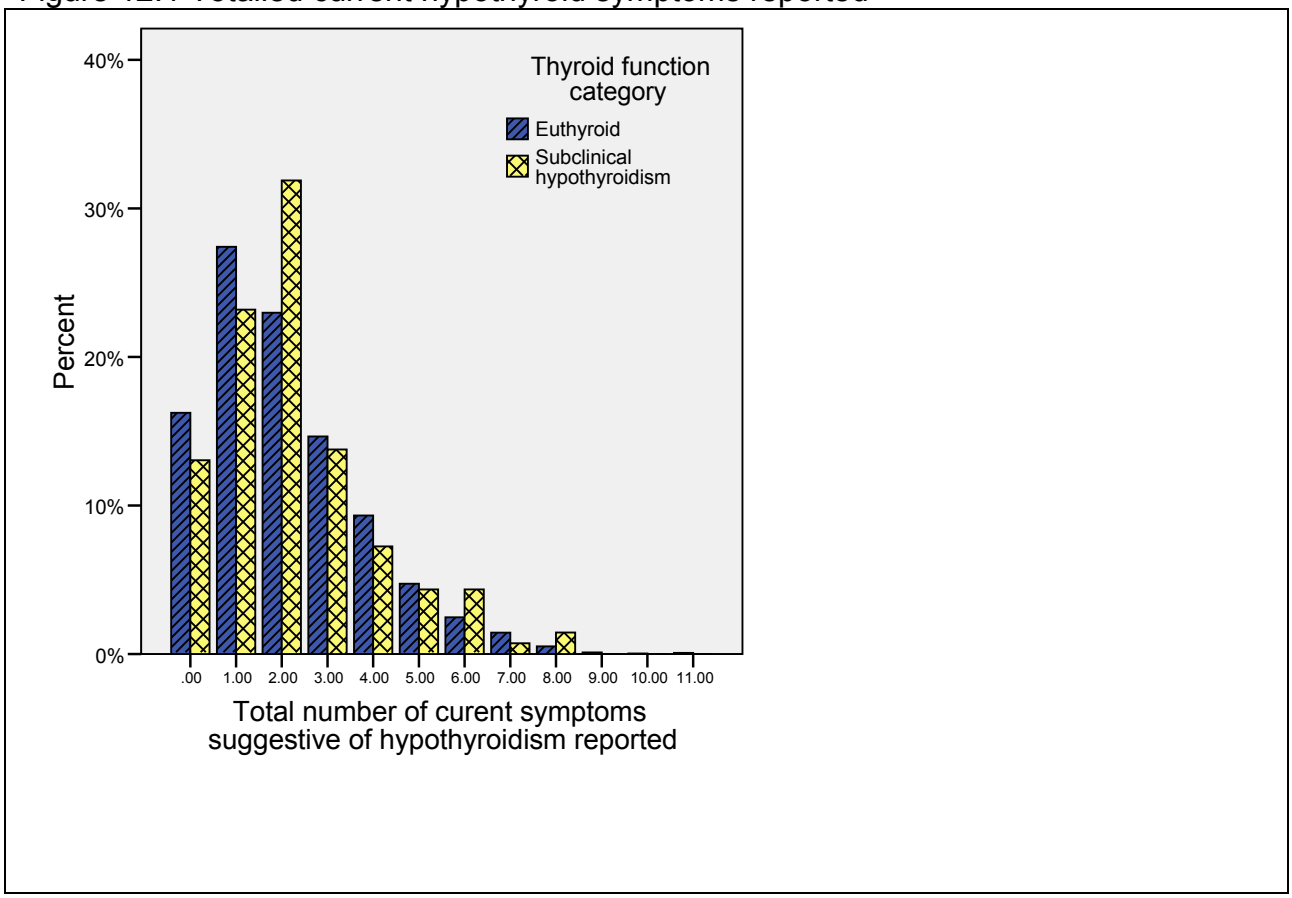
Bonferroni adjusted p value < 0.004. * associated with the Fishers exact test

12.3 Totalled number of hypothyroid symptoms

Whilst few individual symptoms exhibited differing prevalence in the subclinical hypothyroidism and euthyroid groups, it is possible that subclinical dysfunction manifests in a multiple symptom presentation. To enable further exploration of the relationship between symptoms and category of thyroid function, the cohort was divided into groups in accordance with totalled number of hypothyroid symptoms reported. The proportion of each thyroid function group reporting hypothyroid symptoms was plotted against the totalled number of symptoms reported.

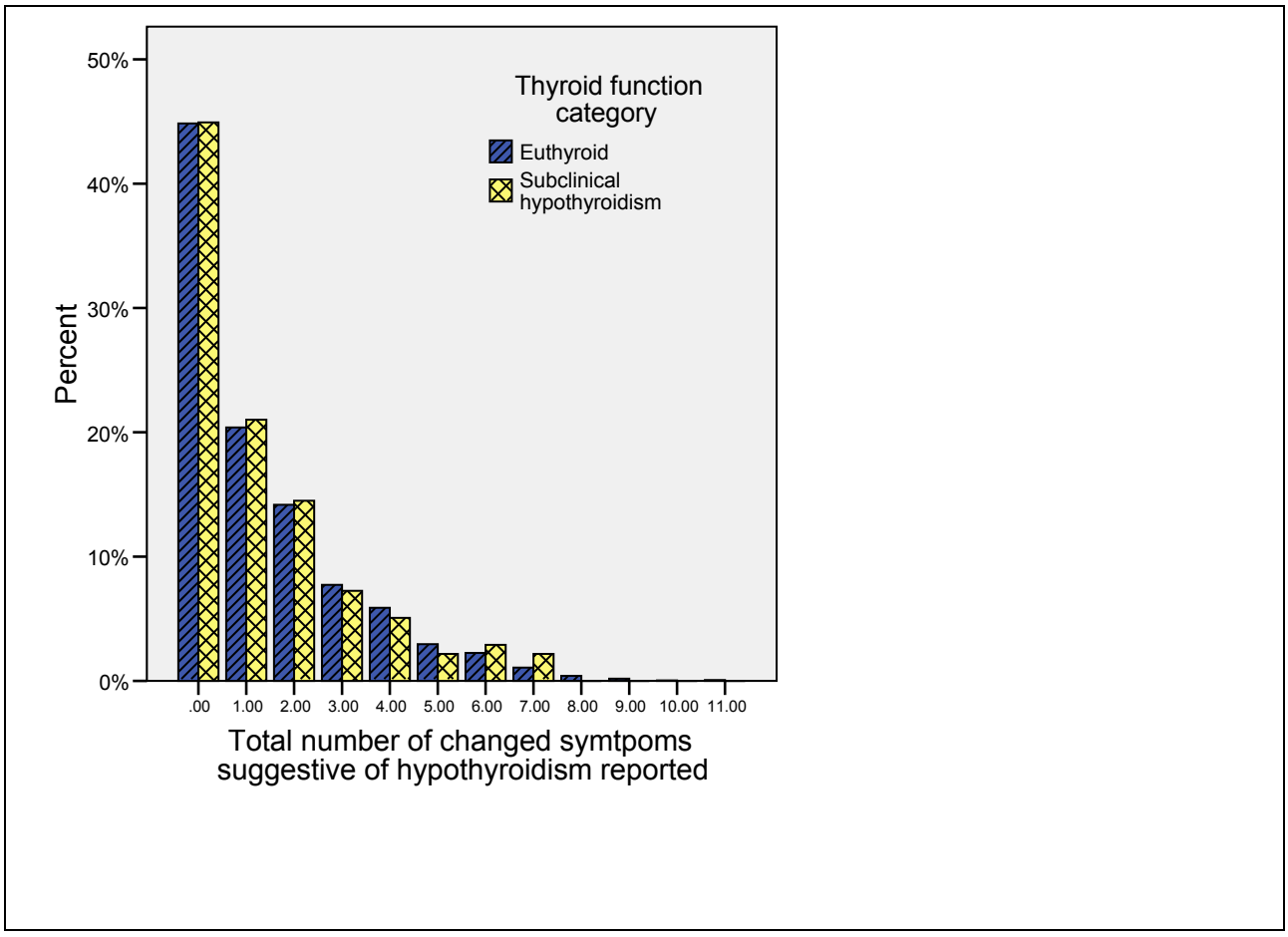
No clear trends between totalled numbers of current hypothyroid symptoms and thyroid function group were observed (Figure 12.1).

Figure 12.1 Totalled current hypothyroid symptoms reported



Similarly, no clear relationship between thyroid function category and total number of changed hypothyroid symptoms reported was observed (Figure 12.2).

Figure 12.2 Totalled changed hypothyroid symptoms reported



The chi squared test for independence was used to compare the proportions of each thyroid function group with respect to the category of total number of hypothyroid symptoms reported. No association between thyroid function and category of total number of current or changed hypothyroid symptoms was observed (Table 12.4).

Table 12.4 Euthyroid versus subclinical hypothyroidism; comparison of the prevelance of multiple hypothyroid symptoms

Category	**Current hypothyroid symptoms**			**Changed hypothyroid symptoms**		
Totalled symptoms	**Euthyroid n (%)**	**Subclinical hypothyroid n (%)**	**χ^2 (p value) df = 3**	**Euthyroid n (%)**	**Subclinical hypothyroid n (%)**	**χ^2 (p value) df = 3**
None	439 (16.20)	18 (13.00)	2.19 (0.54)	1212 (44.80)	62 (44.90)	0.22 (0.98)
1-2	1362 (50.40)	76 (55.10)		934 (34.60)	49 (35.50)	
3-4	648 (24.00)	29 (21.00)		368 (13.60)	17 (12.30)	
5 or more	254 (9.40)	15 (10.90)		189 (7.00)	10 (7.20)	

12.3.1 Totalled number of mild hypothyroid symptoms reported

Since no clear trends between totalled number of current or changed hypothyroid symptoms and thyroid function group were observed, bar charts were not employed to further describe data related to intensity of symptoms.

With respect to hypothyroid symptoms, no significant differences in totalled number of current or changed mild intensity symptoms were observed between the euthyroid and subclinical hypothyroidism groups (Table 12.5).

Table 12.5 Euthyroid versus subclinical hypothyroidism; comparison of the prevelance of multiple mild intensity hypothyroid symptoms

	Current mild intensity symptoms			**Changed mild intensity symptoms**		
Totalled symptoms	Euthyroid % (n)	Subclinical hypothyroid % (n)	χ^2 (p value) df = 3	Euthyroid % (n)	Subclinical hypothyroid % (n)	χ^2 (p value) df = 3
None	17.80 (481)	15.20 (21)	1.42 (0.70)	45.50 (1229)	44.90 (62)	0.86 (0.84)
1-2	50.20 (1357)	48.60 (67)		35.50 (960)	37.00 (51)	
3-4	25.00 (675)	27.50 (38)		13.00 (351)	10.90 (15)	
5 or more	7.00 (190)	8.70 (12)		6.00 (163)	7.20 (10)	

12.3.2 Totalled number of severe hypothyroid symptoms

The relationship between totalled number of severe intensity hypothyroid symptoms and thyroid function group was also examined. No significant differences between thyroid function groups were observed with respect to symptoms of severe intensity (Table 12.6).

Table 12.6 Euthyroid versus subclinical hypothyroidism; comparison of the prevelance of multiple severe intensity hypothyroid symptoms

	Current severe intensity symptoms			**Changed severe hypothyroid symptoms**		
Totalled symptoms	Euthyroid % (n)	Subclinical hypothyroid % (n)	χ^2 (p value) df = 1	Euthyroid % (n)	Subclinical hypothyroid % (n)	χ^2 (p value) df = 1
None	79.40 (2145)	82.60 (114)	0.85 (0.36)	93.50 (2526)	97.10 (134)	2.93 (0.09)
1-2	20.60 (558)	17.40 (24)		6.50 (177)	2.90 (4)	

12.4 Combination of current symptoms suggestive of overt hypothyroidism

To evaluate the potential clinical importance of combinations of current symptoms, each possible pair of symptoms was determined. The purpose of this was two-fold, firstly to enable calculation and comparison of prevalence of symptom pairs across the thyroid function groups and, secondly, to allow examination of interactions between symptoms.

12.4.1 Combinations of current symptoms suggestive of overt hypothyroidism

Prevalence of each pair of current symptoms suggestive of overt hypothyroidism was compared between the euthyroid and subclinical hypothyroidism groups (Table 12.7-12.8). At the Bonferroni adjusted alpha level ($p<0.0014$) no statically significant differences were observed between these groups for any of the 66 possible symptom pairs. At the more conventional significance level of 5%, however, a significant difference between groups existed with respect to the prevalence of two pairs of symptoms. The combination of weak muscles with slow thinking was significantly more prevalent in the subclinical hypothyroidism group than the euthyroid group (6.5% versus 2.9% respectively; $p<0.036$). Additionally dry skin with slow thinking was significantly more prevalent in those with subclinical hypothyroidism (7.2% versus 3.7% respectively, $p<0.038$).

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Table 12.7 Euthyroid versus subclinical hypothyroidism; comparison of the prevalence of 66 possible pairs of current hypothyroid symptoms

	Weak muscles % n		**Poor memory % n**		**Hoarse voice % n**		**Deep voice % n**		**Dry skin % n**		**Puffy eyes % n**	
	Euth	SC Hypo	Euth	SC Hypo	Euth	SC Hypo	Euth	SC Hypo	Euth	SC Hypo	Euth	SC Hypo
Lethargy	7.2 194	3.6 5	3.6 96	3.6 5	1.9 51	2.9 4	1.2 32	1.4 2	7.2 194	5.8 8	3.0 81	1.4 2
Weak muscles			3.2 86	3.6 5	1.9 5.1	2.2 3	1.0 28	1.4 2	7.4 200	8.0 11	3.1 83	1.4 2
Poor memory					1.3 36	0.7 1	0.8 22	1.4 2	4.4 118	4.3 6	2.4 66	1.4 2
Hoarse voice							1.4 38	2.2 3	2.8 77	2.2 3	1.6 42	1.4 2
Deep voice									2.4 65	0.7 1	1.5 40	2.9 4
Dry skin											5.7 155	5.8 8
Puffy eyes												

Bonferroni adjusted alpha level of <0.0014

Table 12.8 Euthyroid versus subclinical hypothyroidism; comparison of the prevalence of 66 possible pairs of current hypothyroid symptoms continued

	Muscle cramps %/n		Constipation %/n		Sensitivity to cold %/n		Slow thinking %/n		Weight gain %/n	
	Euth	**SC Hypo**	**Euth**	**SC Hypo**	**Euth**	**SC Hypo**	**Euth**	**SC Hypo**	**Euth**	**SC Hypo**
Lethargy	4.5 122	2.9 4	3.6 98	4.3 6	7.3 198	6.5 9	3.1 84	3.6 5	9.5 257	7.2 10
Weak muscles	4.7 128	3.6 5	3.7 100	4.3 6	7.0 190	8.0 11	2.9* 78	6.5* 9	7.2 195	5.8 8
Poor memory	2.2 59	0.7 1	2.6 70	4.3 6	4.8 130	3.6 5	4.3 117	5.8 8	4.5 121	3.6 5
Hoarse voice	2.0 55	1.4 2	1.3 36	2.9 4	2.6 70	3.6 5	1.3 35	0.7 1	3.1 85	2.2 3
Deep voice	1.4 37	1.4 2	0.7 20	2.2 3	2.3 64	2.2 3	0.6 17	1.4 2	3.8 104	5.8 8
Dry skin	7.3 197	6.5 9	5.8 157	6.5 9	13.8 373	18.1 25	3.7# 101	7.2# 10	16.1 434	15.9 22
Puffy eyes	3.2 86	5.8 8	2.2 60	4.3 6	5.5 150	6.5 9	1.8 49	2.2 3	7.2 194	8.7 12
Muscle cramps			3.7 99	2.2 3	7.0 189	8.7 12	1.6 42	2.9 4	8.1 219	10.1 14
Constipation					6.2 167	7.4 10	2.0 54	4.3 6	6.2 167	7.2 10
Sensitivity to cold							4.1 111	7.2 10	15.0 405	15.9 22
Slow thinking									3.7 99	6.5 9
Weight gain										

*Weak muscles with slow thinking p<0.036, #Dry skin with slow thinking p<0.03, Bonferroni adjusted alpha level of <0.0014

In terms of interactions between hypothyroid symptoms, a significant interaction between the symptoms deep voice and dry skin was observed (p<0.04) (Table 12.9). The odds ratio associated with presence of deep voice was 2.44 and statistically significant (p<0.01). The OR for presence of dry skin however was 1.22 and not satistically significant (p<0.29). The interaction term however, produced an OR 0.11 and a negative and statistically significant co-efficient (-2.19, p<0.04). This model therefore suggests that subclinical hypothyroidism is 0.11 times less likely in the presence of the hypothyroid symptoms deep voice and dry skin than in the presence of either deep voice or dry skin alone. Due to the large numbers of interactions tested, it of of course possible that this is a spurious finding and does not make clinical sense.

Table 12.9 Euthyroid versus subclinical hypothyroidism; Interactions between hypothyroid symptoms

Variable	Co- efficient	p value	OR
Deep Voice (DV)	0.89	<0.01	2.44
Dry Skin (DS)	0.20	0.29	1.22
Interaction term DVDS	-2.19	0.04	0.11
Constant	-3.08	0.00	0.05

12.5 Summary of the univariate analysis related to hypothyroid symptoms

Initial exploratory univariate analyses were undertaken to determine the relationship between individual symptoms suggestive of overt hypothyroidism and thyroid function category and to select variables for inclusion in the multivariate analysis. Due to multiple testing, a Bonferroni adjusted alpha level (p<0.004) was applied. At the Bonferroni significance level, no differences were observed between the euthyroid and subclinical hypothyroidism groups with respect to the prevalence of any of the 12 current or

changed individual symptoms suggestive of overt hypothyroidism. Further exploratory analysis to determine whether combinations of two symptoms were associated with subclinical hypothyroidism or to identify interactions between symptoms also failed to demonstrate any differences between the thyroid function groups at the Bonferroni adjusted alpha level.

To further enable selection of appropriate symptoms for inclusion in multivariate logistic analysis, it was necessary to apply a more conventional statistical significance level.
At the 5% level, no significant differences between the euthyroid and subclinical hypothyroidism groups were observed with respect to prevalence of individual current hypothyroid symptoms. A significant difference was, however, observed between the euthyroid and subclinical hypothyroidism groups with respect to two combinations of symptoms. A significantly greater proportion of the subclinical hypothyroidism group reported presence of the combination; weak muscles with slow thinking (6.5% versus 2.9% respectively; $p<0.036$) and dry skin with slow thinking (7.2% versus 3.7% respectively; $p<0.038$) compared with the euthyroid group.

A significant interaction between the hypothyroid symptoms deep voice and dry skin was also observed ($p<0.04$).

Comparison of totalled number of symptoms reported by thyroid function groups failed to demonstrate any differences between groups with respect to current or changed symptoms suggestive of overt hypothyroidism. Likewise, no clear relationship existed

between category of thyroid function and total number mild or severe intensity current or changed hypothyroid symptoms reported.

Further exploration of combinations of more than two hypothyroid symptoms was not performed due to the low frequency of reported pairs of hypothyroid symptoms and similarities between euthyroid and subclinical hypothyroidism groups with respect to the prevalence of symptom pairs. Similarly, further examination of interactions between more than two hypothyroid symptoms was not undertaken because results are difficult to interpret and apply in a clinical setting and are therefore of limited clinical utility.

Likewise, additional exploration of changed hypothyroid symptoms with respect to prevalence of pairs of symptoms and interactions was not conducted. The main reason for not undertaking this analysis again was the low frequency of changed hypothyroid symptoms reported. Additionally, since this data relies upon patient recall of the time of onset of symptoms within the previous 12 months it is likely to be less convenient, accurate and meaningful in a clinical setting than data on current symptoms.

Overall, these findings suggest that no single symptom is associated with subclinical hypothyroidism. Two possible combinations of symptoms and a pair of interacting symptoms suggestive of overt hypothyroidism may however be important indicators of subclinical hypothyroidism (Table 12.10).

Table 12.10 Hypothyroid symptoms for the multivariate analysis

Symptoms suggestion of overt hypothyroidism	
Significant individual symptoms	None
Significant combinations of two symptoms	Weak muscles with slow thinking
	Dry skin with slow thinking
Significant interaction between symptoms Interaction term and composite symptoms	Deep voice with dry skin Deep voice Dry skin

Binary logistic regression was performed to construct a model to determine which symptoms best predict subclinical hypothyroidism. The symptoms listed in table 12.10 and the additional explanatory variables age, gender, IMD 2004 score, prescription medication and medical history were used to construct this model.

12.6 Predictors of subclinical hypothyroidism

The final *subclinical hypothyroidism model* was statistically significant ($p<0.001$) indicating an ability to distinguish between groups with euthyroidism and subclinical hypothyroidism. The final model correctly predict 95.1% of cases. However, this was similar to the baseline model (block 0) which was also able to correctly predict 95.1% of cases without consideration of any independent explanatory variables and assuming that subclinical hypothyroidism was not present. The final *subclinical hypothyroidism model* was able to explain 20% (Nagelkerke R square) of the variance in the dependent variable. Two variables made a unique statistically significant contribution to the final model which suggested that not having a history of pulmonary disease and presence of the symptom combination weak muscles with slow thinking were associated with subclinical hypothyroidism. In terms of the symptom combination weak muscles with

slow thinking, those reporting presence of this symptom pair were almost three times as likely as those not reporting presence of this symptom combination to have subclinical hypothyroidism (OR 2.46; 95% CI 1.20-5.05) (Table 12.11).

Table 12.11 Subclinical hypothyroidism model (n=2872)

Variable	Co-efficient	p-value	OR	Lower 95 % CI for OR	Upper 95 % CI for OR
Pulmonary disease	-1.37	0.003	0.26	0.10	0.63
Current weak muscles with slow thinking	0.90	0.014	2.46	1.20	5.05
Constant	-2.92				

12.7 Summary of the main findings related to hypothyroid symptoms

The adjusted (multivariate) analysis demonstrated an association between subclinical hypothyroidism and the symptom pair weak muscles with slow thinking. These associations however are weak, with the model being able to explain only 20% of the variance in the dependent variable. Furthermore, whilst the final logistic regression model was able to correctly classify 95% of cases suggesting an ability to distinguish between cases of euthyroid subjects and individuals with subclinical hypothyroidism, the model was only able correctly classify euthyroid subjects.

12.8 Prevalence of hyperthyroid symptoms

To enable characterisation of symptoms in the subclinical hyperthyroidism and euthyroid groups, the prevalence of individual symptoms reported by each group was calculated. The chi squared test of independence was used to compare the prevalence of current and changed individual hyperthyroid symptoms between the euthyroid and subclinical hyperthyroidism groups. A Bonferroni adjusted alpha value of $p<0.005$ was used to control for type I error.

At the individual symptom level there were no significant differences between the euthyroid and subclinical hyperthyroidism groups with respect to any of the nine current symptoms suggestive of overt hyperthyroidism. Likewise, there were no significant differences in the prevalence of changed hyperthyroid symptoms reported by these two groups (Table 12.12).

Table 12.12 Euthyroid versus subclinical hyperthyroidism; comparison of the prevalence of individual hyperthyroid symptoms

	Current symptoms			Changed symptoms		
Symptom	Euthyroid %,95% CI (n)	Subclinical hyperthyroid %,95% CI (n)	χ^2 (p) df =1	Euthyroid %,95% CI (n)	Subclinical hyperthyroid %,95% CI (n)	χ^2 (p) df =1
Excessive perspiration	3.1,2.5-3.8 (84)	3.4,0.6-17.2 (1)	(0.60)*	2.1,1.6-2.7 (57)	6.9,1.9-22.0 (2)	(060)*
Trembling hands	4.3,3.6-5.1 (115)	3.4,0.6-17.2 (1)	(1.00)*	4.9,4.2- 5.8 (133)	0	(1.00)*
Frequent palpitation	6.0,5.2-7.0 (163)	6.9,1.9-22.0 (2)	(0.69)*	4.4,3.7-5.3 (119)	10.3,3.6-26.4 (3)	(0.69)*
Sensitivity to heat	10.7,9.6-11.9 (284)	13.8,5.5-30.4 (4)	(0.54)*	1.9,1.5-2.5 (52)	6.9,1.9-22.0 (2)	(0.54)*
Fast thinking	22.7,21.1-24.3 (612)	31.0,17.3-49.2 (9)	1.14 (0.27)	0.5,0.3-0.8 (13)	3.4,0.2-17.2 (1)	1.14 (0.29)
Weight loss	7.4,7.0-9.1 (200)	3.4,0.6-17.2 (1)	(0.72)*	13.3,12.1-14.7 (360)	20.7,9.8-38.4 (6)	(0.70)*
Lethargy	16.4,15.0-17.8 (442)	10.3,3.6-26.4 (3)	(0.61)*	18.7,17.3-20.2 (505)	17.2,7.6-34.5 (5)	(0.61)*
Weak muscles	14.3,13.0-15.7 (386)	6.9,1.9-22.0 (2)	(0.42)*	16.4,15.0-17.8 (442)	13.8,5.5-30.6 (4)	(0.42)*
Poor memory	9.7,8.6-10.9 (262)	0	(0.11)*	16.5,15.2-18.0 (446)	17.2,7.6-34.5 (5)	(0.11)*

Bonferroni adjusted p value <0.005, * associated with the Fishers exact test

12.9 Intensity of hyperthyroid symptoms

Comparisons between the groups with respect to the reported intensity of current and changed hyperthyroid symptoms were also undertaken. Again, Bonferroni adjusted alpha values of $p<0.005$ were used to control for type one error for each comparison between the euthyroid and subclinical hyperthyroidism groups. No significant differences in the prevalence of mild intensity current or changed hyperthyroid symptoms existed between the euthyroid and subclinical hyperthyroidism groups (Table 12.13).

Table 12.13 Euthyroid versus subclinical hyperthyroidism; comparison of the prevalence of individual mild intensity hyperthyroid symptoms

	Current mild intensity symptoms			**Changed mild intensity symptoms**		
Symptom	Euthyroid %,95% CI (n)	Subclinical hyperthyroid %,95% CI (n)	χ^2 (p) df = 1	Euthyroid %,95% CI (n)	Subclinical hyperthyroid %,95% CI (n)	χ^2 (p) df = 1
Excessive perspiration	2.6,2.0-3.2 (69)	0,0.12.1	0.74 (0.39)	2.0,1.5-2.6 (53)	6.9,1.9-22.0 (2)	3.52 (0.06)
Trembling hands	3.2,2.6-3.9 (85)	3.4,0.6-17.2 (1)	0.007 (0.94)	4.6,3.8-5.4 (122)	0,0-11.7 (0)	1.38 (0.24)
Frequent palpitation	5.2, 4.4-6.1 (138)	3.4,0.6-17.2 (1)	0.14 (0.70)	4.2,3.5-5.0 (113)	10.3,3.6-26.4 (3)	2.64 (0.10)
Sensitivity to heat	9.8,8.8-11.0 (259)	10.7,3.7-27.2 (3)	0.24 (0.88)	1.6,1.2-2.2 (43)	3.4,0.6-17.2 (1)	0.67 (0.41)
Fast thinking	21.0,19.5-22.6 (555)	28.6,15.3-47.0 (8)	0.95 (0.33)	0.4,0.2-0.7 (10)	3.4, 0.6-17.2 (1)	6.75 (0.01)
Weight loss	6.9,6.0-7.9 (184)	3.4,0.6-17.2 (1)	2.53 (0.47)	12.8,11.6-14.1 (343)	20.7,9.8-38.4 (6)	1.60 (0.21)
Lethargy	13.9,12.2-13.5 (364)	10.3,7.1,2.0-22.6 (2)	0.55 (0.30)	17.0,15.6-18.5 (449)	14.3,5.7-31.5 (4)	0.15 (0.70)
Weak muscles	13.3,12.0-14.5 (354)	3.6,0.6-17.7 (3)	2.28 (0.13)	15.8,14.4-17.2 (422)	10.7,3.6-26.4 (3)	0.54 (0.47)
Poor memory	9.0,8.0-10.2 (242)	0,0-11.7 (0)	2.87 (0.09)	16.0,14.7-17.5 (430)	13.8,5.5-30.6 (5)	0.03 (0.86)

Bonferroni adjusted p value <0.005

The euthyroid and subclinical hyperthyroidism groups were similar with respect to the prevalence of severe intensity hyperthyroid symptoms reported (Table 12.14).

Table 12.14 Euthyroid versus subclinical hyperthyroidism; comparison of the prevalence of individual severe intensity hyperthyroid symptoms

	Current severe intensity symptoms			Changed severe intensity symptoms		
Symptom	Euthyroid %,95% CI (n)	Subclinical hyperthyroid %,95% CI (n)	χ^2 (p) df = 1	Euthyroid %,95% CI (n)	Subclinical hyperthyroid %,95% CI (n)	χ^2 (p value) df = 1
Excessive perspiration	0.6, 0.3-0.9 (15)	3.4,0.6-17.2 (1)	(0.16)*	0.2,0.1-0.4 (4)	0,0-12.1 (0)	(1.00)*
Trembling hands	1.1,0.8-1.6 (30)	0,0-12.1 (0)	(1.00)*	0.4,0.2-0.8 (11)	0,0-12.1 (0)	(1.00)*
Frequent palpitation	1.0,0.7-1.4 (25)	3.6,0.6-17.7 (1)	(0.25)*	0.2,0.1-0.5 (6)	0,0-12.1 (0)	(1.00)*
Sensitivity to heat	1.0,0.7-1.5 (25)	3.8,0.7-18.9 (1)	(0.25)*	0.3,0.2-0.6 (9)	3.6,0.6-17.7 (1)	(0.10)*
Fast thinking	2.7,2.1-3.4 (57)	4.8,0.8-22.7 (1)	(0.44)*	0.1,0-0.3 (3)	0,0-12.1 (0)	(1.00)*
Weight loss	0.6,0.4-1.0 (16)	0, 0-12.1 (0)	(1.00)*	0.7,0.5-1.2 (17)	0,0-12.1 (0)	(1.00)*
Lethargy	3.3,2.7-4.1 (78)	3.7,0.7-18.3 (1)	(0.60)*	2.5,1.9-3.2 (56)	4.0,0.7-19.5 (1)	(0.47)*
Weak muscles	1.4,1.0-1.9 (32)	3.6,0.6-17.7 (1)	(0.33)*	0.9,0.6-1.4 (20)	3.8,0.7-18.9 (1)	(0.21)*
Poor memory	0.8, 0.5-1.3 (20)	0,0-17.0 (0)	(1.00)*	0.7,0.4-1.1 (16)	0,0-12.1 (0)	(1.00)*

Bonferroni adjusted pvalue <0.005, * associated with the Fishers exact test

Whilst few individual symptoms exhibited different prevalence in the subclinical hyperthyroidism and euthyroid groups, it is possible that subclinical hyperthyroidism manifests with multiple symptom presentation. To enable further exploration of the relationship between symptoms and category of thyroid function, the cohort was divided into groups in accordance with totalled number of hyperthyroid symptoms reported. The proportion of each thyroid function group reporting hyperthyroid symptoms was plotted against the totalled number of symptoms reported.

Figure 12.3 Totalled current hyperthyroid symptoms

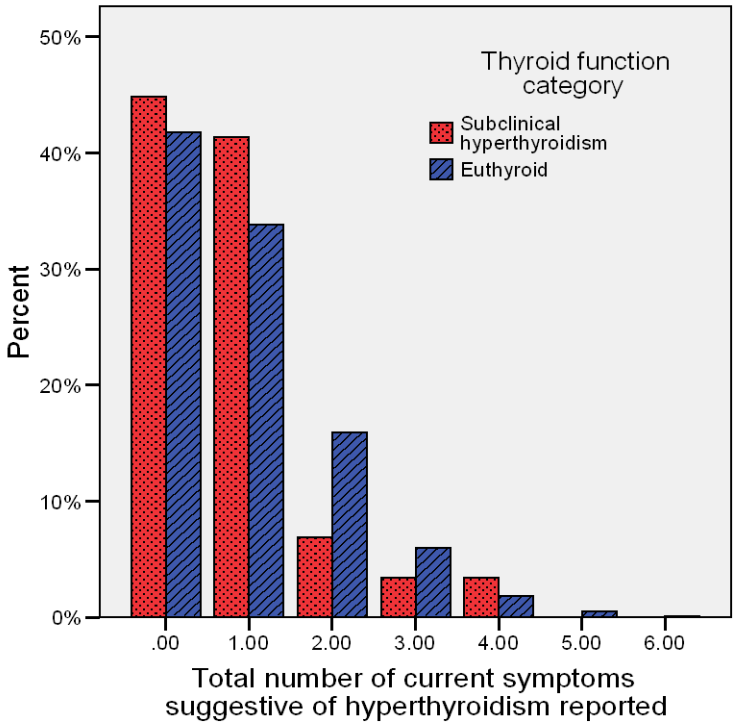
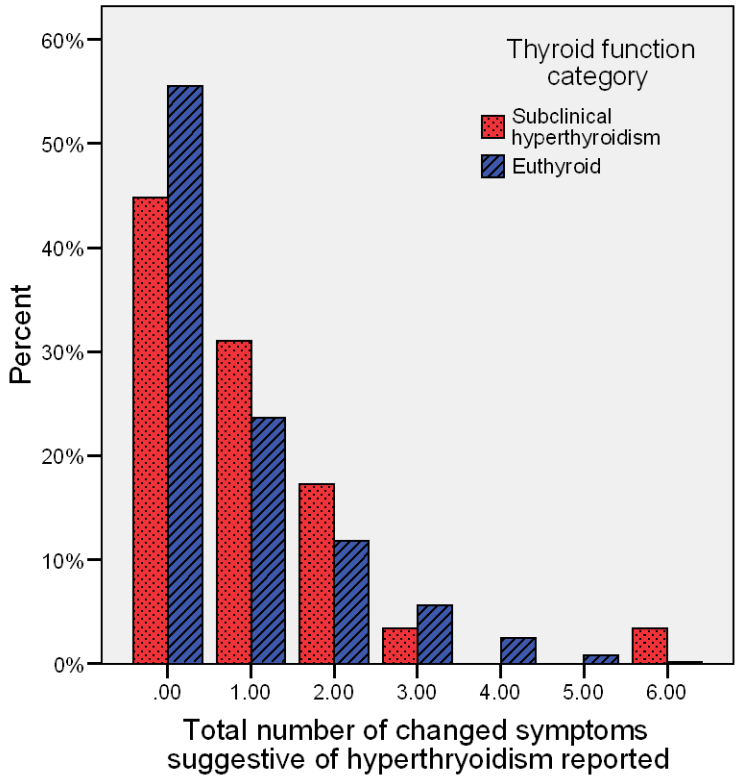


Figure 12.4 Totalled changed hyperthyroid symptoms



The chi squared test for independence suggested that there was no association between category of thyroid function and totalled number of current or changed symptoms suggestive of overt hyperthyroidism (Table 12.15).

Table 12.15 Euthyroid versus subclinical hyperthyroidism; comparison of the prevalence of multiple hyperthyroid symptoms

	Current multiple symptoms			**Changed multiple symptoms**		
Totalled number of symptoms	Euthyroid % (95% CI)	Subclinical hyperthyroid % (95% CI)	χ^2 (p) df = 3	Euthyroid % (95% CI)	Subclinical hyperthyroid % (95% CI)	χ^2 (p) df = 3
None	1130 (41.90)	13 (44.80)		1502 (55.70)	13 (46.40)	
1 symptom	914 (33.90)	12 (41.40)	1.85 (0.40)	639 (23.70)	9 (32.10)	1.27 (0.53)
2 or more	656 (24.30)	4 (13.80)		558 (20.70)	6 (21.40)	

12.10 Totalled number of mild intensity hyperthyroid symptoms

The chi squared test for independence was used to compare the proportions of the euthyroid and subclinical hyperthyroidism groups with respect to total number of mild and severe intensity hyperthyroid symptoms reported. No significant differences in totalled number of current or changed mild intensity symptoms suggestive of hyperthyroidism existed between the euthyroid and subclinical hyperthyroidism groups (Table 12.16).

Table 12.16 Euthyroid versus subclinical hyperthyroidism; comparison of the prevalence of multiple mild intensity hyperthyroid symptoms

	Current mild intensity symptoms			**Changed mild intensity symptoms**		
Totalled number of symptoms	Euthyroid % (n)	Subclinical hyperthyroid % (n)	χ^2 (p) df = 1	Euthyroid % (n)	Subclinical hyperthyroid % (n)	χ^2 (p) df = 1
None	45.00 (1215)	51.70 (15)	0.53 (0.47)	56.50 (1528)	44.80 (13)	1.60 (0.20)
1-2	55.00 (1487)	48.30 (14)		43.50 (1175)	55.20 (16)	

The relationship between total number of severe intensity symptoms and thyroid function group was also examined. There were no significant differences observed between the euthyroid and subclinical hyperthyroidism groups with respect to prevalence of hyperthyroid symptoms of severe intensity (Table 12.17).

Table 12.17 Euthyroid versus subclinical hyperthyroidism; comparison of the prevalence of multiple severe intensity hyperthyroid symptoms

	Current severe intensity symptoms			**Severe changed symptoms**		
Totalled number of Symptoms	Euthyroid % (n)	Subclinical hyperthyroid % (n)	Fisher exact p value df = 1	Euthyroid % (n)	Subclinical hyperthyroid % (n)	Fisher exact (p) df = 1
None	91.2 (2464)	86.2 (25)	0.321	95.7(2587)	96.6 (28)	1.00
1-2	8.8 (239)	13.8 (4)		4.3 (116)	3.4 (1)	

12.11 Combination of current hyperthyroid symptoms

To evaluate the potential clinical importance of combinations of current hyperthyroid symptoms, each possible combination of two symptoms was defined.

12.12 Combinations of current hyperthyroid symptoms

The prevalence of each pair of symptoms suggestive of overt hyperthyroidism was compared between the euthyroid and subclinical hyperthyroidism groups using the Chi squared test for independence.

At a Bonferroni adjusted alpha level of $p<0.0014$, no significant differences were observed between the euthyroid and subclinical hyperthyroidism groups with respect to the prevalence of any of the 36 possible pairs of symptoms.

At a significance level of 5%, however, a significant difference between the euthyroid and subclinical hyperthyroidism groups existed with respect to the combination of symptoms sensitivity to heat with fast thinking. A significantly greater proportion of individuals with subclinical hyperthyroidism than euthyroid reported presence of this symptom combination (10.3% versus 2.7% respectively; $p<0.045$) (Table12.18)

No interactions between symptoms suggestive of hyperthyroidism were identified.

Table 12.18 Euthyroid versus subclinical hyperthyroidism; comparison of the prevalence of 36 pairs of current hyperthyroid symptoms

	Trembling hands % n		**Frequent palpitations % n**		**Sensitivity to heat % n**		**Fast thinking % n**		**Weight loss % n**		**Lethargy % n**		**Weak muscles % n**		**Poor memory % n**	
	Euth	SC Hyper	Euth	SC Hyper	Euth	SC Hyper	Euth	SC Hyper	Euth	SC Hyper	Euth	SC Hyper	Euth	SC Hyper	Euth	SC Hyper
Excessive perspiration	0.1 4	0	0.4 12	0	1.4 37	0	0.8 22	0	0.1 1	0	1.0 26	0	1.0 27	0	0.4 12	0
Trembling hands			0.5 14	0	10.5 284	4.0 13.8	22.6 612	31.0 9	7.4 200	1 3.4	16.4 442	10.3 3	15.1 408	13.8 4	9.7 262	0
Frequent palpitation					0.9 24	3.4 1	1.2 33	3.4 1	0.5 14	0	2.1 57	3.4 1	1.8 48	0	1.0 27	0
Sensitivity to heat							2.7* 73	10.3* 3	0.1 4	0	2.1 58	3.4 1	1.6 43	3.4 1	0.8 22	0
Fast thinking									2.0 53	0	2.8 75	3.4 1	2.4 64	3.4 1	0.7 18	0
Weight loss											1.3 36	0	1.8 48	0	0.9 23	0
Lethargy													7.2 194	3.4 1	3.6 96	0
Weak muscles															3.2 86	0
Poor memory																

* Sensitivity to heat with fast thinking p<0.045

Further exploration of combinations of three or more symptoms was not warranted because few significant differences in the prevalence of individual symptoms existed between the euthyroid and subclinical hyperthyroidism groups. Similarly, further examination of changed hyperthyroid symptoms was not undertaken due to the low frequency of changed symptoms reported.

12.13 Summary of univariate analysis of hyperthyroid symptoms

Initially, exploratory univariate analyses were undertaken to determine the relationship between individual symptoms suggestive of overt hyperthyroidism and thyroid function category and to select variables for inclusion in the multivariate analysis. Due to multiple testing, a Bonferroni adjusted alpha level ($p<0.005$) was applied. At this level no significant differences were observed between the euthyroid and subclinical hyperthyroidism groups with respect to reported prevalence of any of the nine current or changed individual hyperthyroid symptoms. Further exploratory analysis to determine whether combinations of two symptoms were associated with subclinical hyperthyroidism or to identify interactions between symptoms also failed to demonstrate any differences between the thyroid function groups at the Bonferroni adjusted alpha level.

To further enable selection of appropriate and potentially important hyperthyroid symptoms for inclusion in the multivariate logistic regression analysis it was therefore necessary to apply a less conservative and more conventional significance level of 5%.

At the 5% level, no differences between the euthyroid and subclinical hyperthyroid groups were observed with respect to the prevalence of individual current hyperthyroid symptoms. At a significance level of 5%, however, a significant difference between the euthyroid and subclinical hyperthyroidism groups existed with respect to the combination of symptoms sensitivity to heat with fast thinking. A significantly greater proportion of individuals with subclinical hyperthyroidism than euthyroidism reported presence of this symptom combination (10.3% versus 2.7% respectively; $p<0.045$).

Investigation of potential interactions between symptoms suggestive of hyperthyroidism failed to demonstrate any significant interactions between pairs of symptoms.

Overall, these findings suggest that no single symptom is associated with subclinical hyperthyroidism. However, in terms of combinations of symptoms, one possible combination of two symptoms suggestive of overt hyperthyroidism may be an important indicator of subclinical hyperthyroidism (Table 12.19).

Table 12.19 Hyperthyroid symptoms for the multivariate analysis

Symptoms suggestion of overt hyperthyroidism	
Significant individual symptoms	None
Significant combinations of two symptoms	Sensitivity to heat with fast thinking
Significant interaction between symptoms	None

12.14 Predictors of subclinical hyperthyroidism

Binary logistic regression was performed to construct a model to determine which symptoms best predict subclinical hyperthyroidism. The subclinical hyperthyroidism model included the symptoms listed in Table 12.19 and the additional explanatory variables age, gender, IMD 2004 score, prescription medication and medical history.

The final *subclinical hyperthyroidism model* was statistically significant, indicating an ability to distinguish between euthyroid subject and individuals with subclinical hyperthyroidism ($p<0.016$). Whilst this model was able to correctly classify 99% of cases, it failed to demonstrate any improvement upon the baseline model (block 0) which was also able to correctly classify 99% of cases without consideration of any of the independent explanatory variables and under the assumption that the event of interest; subclinical hyperthyroidism was not present (Table 12.20). Furthermore, the final *subclinical hyperthyroidism model* was only able to explain 28% (Nagelkerke R square) of the variance. Two variables made a unique statistically significant contribution to the model which suggested that age, and the symptom combination sensitivity to heat with fast thinking were associated with subclinical hyperthyroidism. The model indicated that with each year increase in age subclinical hyperthyroidism was 1.08 times more likely than euthyroidism. Furthermore, the final *subclinical hyperthyroidism model* suggested that individuals reporting presence of sensitivity to

heat with fast thinking were over four times more likely to have subclinical hyperthyroidism than those not reporting presence of this pair of symptoms (OR 4.69; 95% CI 1.37-16.01).

Table 12.20 Subclinical hyperthyroidism model

Variable	Co-efficient	p-value	OR	Lower 95% CI for OR	Upper 95% CI for OR
Age	0.077	0.032	1.08	1.01	1.16
Current sensitivity to heat with fast thinking	1.55	0.014	4.69	1.37	16.01
Constant	-10.60				

12.15 Summary of multivariate analyses of hyperthyroid symptoms

At the less stringent significance level of 5%, significant differences between the thyroid function groups were observed, therefore enabling selected of potentially important symptoms for inclusion in the multivariate analyses.

In terms of symptoms suggestive of overt hyperthyroidism the symptom pair sensitivity to heat with fast thinking was significantly more prevalent in the subclinical hyperthyroidism group than the euthyroid group (2.7 % versus 10.3% respectively, $p<0.045$). Likewise, the adjusted (multivariate) analysis demonstrated an association between subclinical hyperthyroidism and sensitivity to heat with fast thinking.

However, these associations are weak since the model was not able to explain more than 28% of the variance in the dependent variable. Furthermore, whilst the final logistic regression models were able to correctly classify over 95% of cases suggesting an ability to distinguish between cases of with subclinical hyperthyroidism and euthyroid subjects, the model did not correctly classify any of the cases with subclinical hyperthyroidism.

Summary of chapter 12

The results of the univariate analysis suggest that there is no association between category of thyroid function and individual symptoms or combinations of symptoms suggestive of overt thyroid dysfunction.

To enable selection of individual symptoms and combinations of symptoms for inclusion in the multivariate analyses it was necessary to relax the Bonferroni adjusted alpha level used to control for type 1 error. At a less stringent significance level of 5%, significant differences between the thyroid function groups were observed, therefore enabling selection of potentially important symptoms for inclusion in the multivariate analyses.

The results of the univariate and adjusted (multivariate) analysis were consistent and demonstrated an association between subclinical hyperthyroidism and sensitivity to heat with fast thinking and subclinical hypothyroidism with weak muscles and slow thinking. However, these associations were weak and neither model was able to explain more than 28% of the variance in the dependent variable. Furthermore, whilst the final logistic regression models were able to correctly classify over 95% of cases, suggesting an ability to distinguish between euthyroid subjects and individuals with subclinical thyroid dysfunction, neither model correctly classified any of the cases with subclinical thyroid dysfunction (sensitivity 0, specificity 100%).

The final subclinical hyperthyroid model suggested that a subject reporting presence of sensitivity to heat with fast thinking is 4.5 times more likely to have subclinical hyperthyroidism than to have normal euthyroid function. The final subclinical hypothyroidism model suggested that an individual reporting presence of weak muscles with slow thinking is twice as likely to have subclinical hypothyroidism as

normal thyroid function. From a clinical perspective, these findings do not aid GPs in distinguishing between an elderly individual who is more likely to have subclinical thyroid dysfunction and who would benefit from further investigation of thyroid function from an individual less likely to have subclinical disease. The clinical utility of these findings is further restricted by the fact that these symptom pairs are not exclusive to individuals with subclinical thyroid dysfunction and may also be reported by euthyroid subjects. Additionally, the difference in the prevalence of these symptom pairs between euthyroid subjects and individuals with subclinical thyroid function, although statistically significant, is relatively small and unlikely to be clinically useful at the individual patient level. Sensitivity to heat with fast thinking was reported by 2.7% of the euthyroid group compared with 10.3% of the subclinical hyperthyroidism group and weak muscles with slow thinking was reported by 2.9% of the euthyroid group and 6.5% of the subclinical hypothyroidism group. Since the Bonferroni corrected alpha level was substituted for a more conventional significance level of 5%, these may be spurious findings and as such should be interpreted with caution.

An alternative explanation for failure to identify an association between symptoms and thyroid function category is that important determinants of subclinical thyroid dysfunction have not been measured within the current study. Indeed, it has been suggested that the clinical profile of subclinical thyroid dysfunction has changed since the advent of more sensitive serum thyrotrophin assays. As such, it is possible that thyroid dysfunction is being identified earlier and those symptoms previously considered indicative of thyroid abnormalities reflect longer standing thyroid dysfunction and are no longer relevant.

In this chapter, symptom expression in the thyroid function subgroups was explored and described. In the next chapter, symptom expression in incident cases of subclinical thyroid dysfunction occurring during the interval period is examined and compared with cases of persistent thyroid dysfunction.

CHAPTER 13 SYMPTOMS IN THE INCIDENT CASES

Overview of chapter 13

It is possible that incident cases experience a greater symptom burden than those with persistent subclinical thyroid dysfunction who may be more accustomed to and/or tolerant of symptoms. This chapter aims to characterise symptoms in individuals that developed subclinical thyroid dysfunction during the interval period between baseline and follow-up thyroid function screening. Symptom expression in subgroups of the study population with incident and persistent thyroid function are compared.

Although not reported in this chapter, for completeness the prevalence of symptoms reported by cases with persistent euthyroid and persistent subclinical thyroid dysfunction were explored. These data are reported in Appendix 6 and 7.

Thyroid function category remained unchanged between baseline follow-up for 94.6% (n=2715) of the cohort with 91.9% (n=2638) being categorised as having persistent euthyroidism and 2.7% with persistent subclinical thyroid dysfunction. During the interval period, thyroid function category changed from euthyroid to subclinical thyroid dysfunction in 90 (3.1%) individuals (incident cases) and in 65 individuals (2.3%) thyroid function reverted to euthyroid status from subclinical thyroid dysfunction. (Table 13.1)

Table 13.1 Description of longitudinal thyroid function groups

Group	Type of change between baseline and follow-up	n (%)
1	Persistent Euthyroidism (PEuth)	2638 (91.9)
2	Persistent Subclinical Thyroid Dysfunction (PSCTD)	77 (2.7)
3	Incident Subclinical Thyroid Dysfunction (NSCTD)	90 (3.1)
4	Reverted to Euthyroidism (RevEuth)	65 (2.3)
	Total	2870 (100.0)

The proportion of the incident and persistent subclinical thyroid dysfunction groups reporting presence of each individual symptom was compared using the χ^2 test for independence or the Fisher's exact test where appropriate. Given the fact that multiple comparisons were being made between groups, a Bonferroni adjusted alpha value of $p<0.003$ was used to control for type I error. The results are presented in Table 13.1-13.2. In the tables, NSCTD is indicative of incident/new cases of subclinical thyroid dysfunction and PSCTD relates to persistent cases of subclinical thyroid dysfunction.

Table 13.2 Incident subclinical thyroid dysfunction versus persistent subclinical thyroid dysfunction; comparison of the prevalence of current symptoms

Changed symptom	NSCTD %,95%CI (n)	PSCTD %,95%CI (n)	χ^2 (p) df=1
Excessive perspiration	3.3,1.1-9.3 (3)	3.9, 1.3-10.8 (3)	(1.0)*
Trembling hands	3.4,1.1-9.3 (3)	2.6,0.7-9.0 (2)	(1.0)*
Frequent palpitations	5.6,2.4-12.4 (5)	3.9,1.3-10.8 (3)	(0.73)*
Sensitivity to heat	14.4,8.6-23.2 (13)	9.2,4.5-17.6 (7)	1.07 (0.30)
Fast thinking	27.8,19.6-37.8 (25)	23.4,15.3-34.0 (18)	0.42 (0.52)
Weight loss	2.2,0.6-7.7 (2)	5.2,2.0-12.6 (4)	(0.42)*
Lethargy	14.6,8.6-23.2 (13)	6.5,2.8-14.3 (5)	2.81 (0.09)
Weak muscles	14.4,8.6-23.2 (13)	11.7, 6.3-20.7 (9)	0.28 (0.60)
Poor memory	8.9,4.6-16.6 (8)	3.9, 1.3-10.8 (3)	1.68 (0.10)
Hoarse voice	5.5,2.4-12.4 (5)	11.7,6.3-20.7 (9)	1.97 (0.16)
Deep voice	12.4,7.0-20.6 (11)	6.5,2.8-14.4 (5)	1.63 (0.20)
Dry skin	35.6,26.4-45.9 (32)	31.2, 21.9-42.2 (24)	0.36 (0.55)
Puffy eyes	15.6,7.8-21.9 (12)	20.0,15.3-34.0 (18)	0.55 (0.46)
Muscle cramps	20.0,13.0-29.4 (18)	9.1, 4.5-17.6 (7)	3.88 (0.05)
Constipation	15.6,9.5-24.4 (14)	11.7,6.3-20.7 (9)	0.52 (0.47)
Sensitivity to cold	37.8,28.5-48.1 (34)	34.2, 24.4-44.9 (26)	0.23 (0.63)
Slow thinking	13.3,7.8-21.9 (12)	5.2, 2.0-12.6 (4)	3.17 (0.08)
Weight gain	54.4,44.2-64.3 (49)	48.1,37.3-59.0 (37)	0.68 (0.41)

Bonferroni adjusted alpha level $p<0.003$ *associated with the Fisher Exact test

Table 13.3 Incident subclinical thyroid dysfunction versus persistent subclinical thyroid dysfunction; comparison of the prevalence of changed symptoms

Changed symptom	NSCTD %,95%CI (n)	PSCTD %,95%CI (n)	χ^2 (p) df=1
Excessive perspiration	1.1, 0.2-6.0 (1)	2.6,0.7-9.0 (2)	(0.59)*
Trembling hands	3.31.1-9.3 (3)	5.2,2.0-12.6 (4)	(0.71)*
Frequent palpitations	7.8,3.8-15.2 (7)	2.5,0.7-9.0 (2)	(0.18)*
Sensitivity to heat	4.4,1.7-10.9 (4)	3.9,1.3-10.8 (3)	(1.00)*
Fast thinking	0,0-4.1 (0)	2.6, 0.7-9.0(2)	(0.21)*
Weight loss	11.1,6.1-19.3 (10)	11.7,6.3-20.7 (9)	0.01 (0.91)
Lethargy	14.6,8.6-23.2 (13)	18.2,11.2-28.2 (14)	0.39 (0.53)
Weak muscles	12.4,7.0-20.6 (11)	15.6,9.1-25.3 (12)	0.36 (0.55)
Poor memory	16.7,10.4-25.7 (15)	15.6,9.1-25.3 (12)	0.36 (0.55)
Hoarse voice	6.7,3.1-13.8 (6)	9.2,4.5-17.6 (7)	0.37 (0.54)
Deep voice	0, 0.4.1 (0)	3.9,1.3-10.8 (3)	(0.10)*
Dry skin	10.0,5.4-17.9 (9)	9.2,4.5-17.6 (7)	0.03 (0.86)
Puffy eyes	7.8, 3.8-15.2 (7)	5.2,2.0-12.6 (4)	0.45 (0.502)
Muscle cramps	14.4,8.6-23.2 (13)	13.0,7.2-22.3 (10)	0.07 (0.79)
Constipation	6.7,3.1-13.8 (6)	9.1,4.5-17.6 (7)	0.32 (0.79)
Sensitivity to cold	13.3,7.8-21.9 (12)	10.4,5.4-19.2 (8)	0.34 (0.56)
Slow thinking	14.4,8.6-23.2 (13)	10.4,5.4-19.2 (8)	0.62 (0.43)
Weight gain	24.4,16.7-34.2 (22)	15.6,11.2-28.2 (12)	2.0 (0.16)

Bonferroni alpha level p <0.003. *associated with the Fisher Exact test

To enable further exploration of the totalled number of symptoms reported by the incident and persistent subclinical thyroid function groups, individuals in each subgroup were further categorised in accordance with the total number of symptoms reported. The Chi squared test for independence was used to compare the proportions in each of the totalled symptom categories between the incident and persistent subclinical thyroid dysfunction subgroups.

The incident and persistent subclinical thyroid dysfunction groups were similar with respect to the total number of current symptoms suggestive of hypothyroidism. A significant difference in total number of changed hypothyroid symptoms was however observed with the persistent subclinical thyroid dysfunction group reporting a greater prevalence of 1-2 symptoms than the incident subclinical thyroid dysfunction group (46.8% versus 27.8% respectively, $p<0.036$) (Table 13.4).

Table 13.4 Incident subclinical thyroid dysfunction versus persistent subclinical thyroid dysfunction; comparison of the prevelance of multiple hypothyroid symptoms

	Current hypothyroid symptoms			Changed hypothyroid symptoms		
Totalled number of symptoms	NSCTD n=90	PSCTD n=77	χ^2 (p) df = 2	NSCTD n=90	PSCTD n=77	χ^2 (p) df = 2
None	10 (11.10)	12 (15.60)		43 (47.80)	29 (37.70)	
1-2	49 (54.40)	47 (61.00)	2.68 (0.26)	25 (27.80)	36 (46.80)	6.68 (0.04)
3 or more	31 (34.40)	18 (23.40)		22 (24.40)	12 (15.60)	

Since only four individuals with persistent subclinical thyroid dysfunction reported presence of three or more symptoms, amalgamation of individuals reporting two or more symptoms was necessary to enable analysis. No significant difference between the thyroid function groups was observed (Table 13.5).

Table 13.5 Incident subclinical thyroid dysfunction versus persistent subclinical thyroid dysfunction; comparison of the prevalence of multiple hyperthyroid symptoms

	Current hyperthyroid symptoms			Changed hyperthyroid symptom		
Totalled number of symptoms	NSCTD n=90	PSCTD n=77	χ^2 (p) df = 2	NSCTD n=90	PSCTD n=77	χ^2 (p) df = 2
None	36 (40.0	38 (49.4)	2.60 (0.27)	52 (57.8)	39 (50.6)	0.85 (0.65)
1	36 (40.0)	30 (39.0)		23 (25.6)	23 (29.9)	
2 or more	18 (20.0)	9 (11.7)		15 (16.7)	15 (19.5)	

Figures 13.1 - 13.2 Incident subclinical thyroid dysfunction versus persistent subclinical thyroid dysfunction; comparison of the prevalence of multiple hypothyroid symptoms

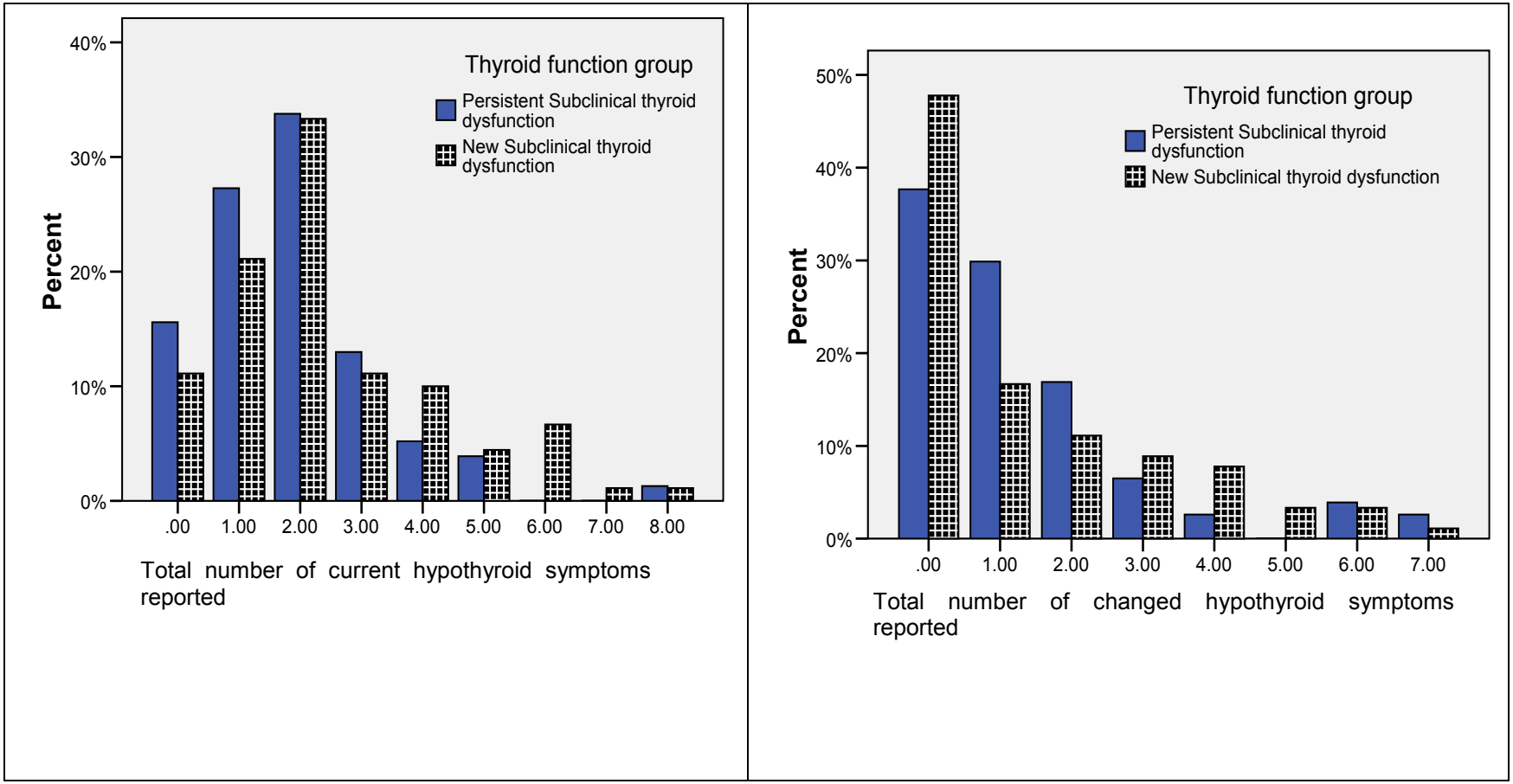
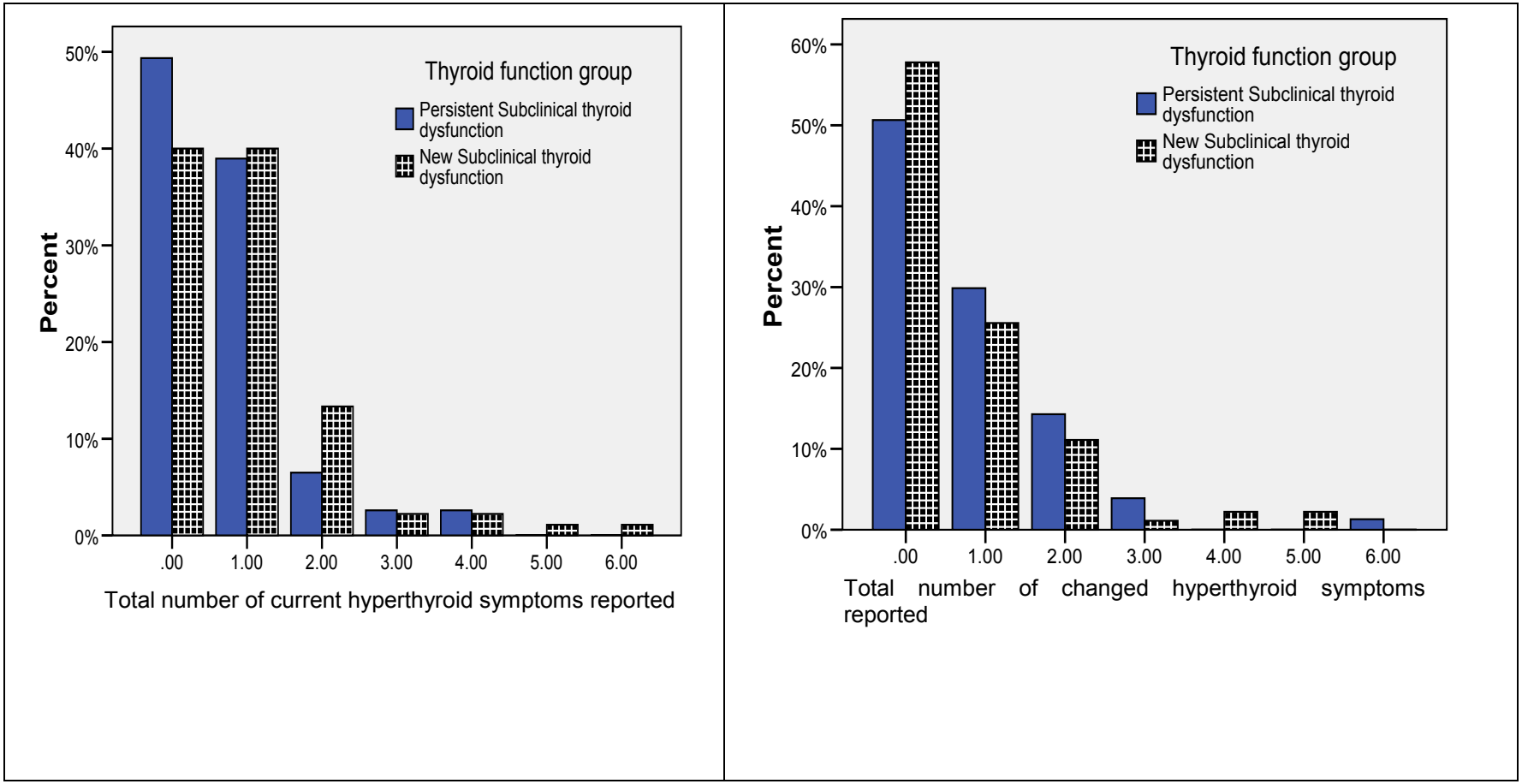


Figure 13.3 - 13.4 Incident subclinical thyroid dysfunction versus persistent subclinical thyroid dysfunction; comparison of the prevalence of multiple hyperthyroid symptoms



Summary of chapter 13

In this chapter, the prevalence of symptoms reported by individuals with incident subclinical thyroid dysfunction was compared with individuals with persistent subclinical thyroid dysfunction. No significant differences between the incident and persistent subclinical thyroid dysfunction groups existed with respect to the prevalence of 18 individual current or changed symptoms suggestive of overt hyperthyroidism or hypothyroidism. Similarly, no clear relationship between the thyroid function subgroups and total number of symptoms was observed.

A significant difference in total number of changed hypothyroid symptoms was observed which could warrant further analysis. However, since there were no other significant differences observed between the groups with respect to totalled number of changed hypothyroid symptoms this finding is likely to be spurious. In general, these results corroborate the findings presented in Chapter 12 and, as such, further demonstrate that subclinical thyroid dysfunction in this population is not associated with symptoms suggestive of overt thyroid dysfunction.

In conclusion, incident cases of subclinical thyroid dysfunction do not experience a greater symptom burden than those with persistent subclinical thyroid dysfunction. These findings further demonstrate that the presence of symptoms either alone or in combination with previous thyroid function test results are of limited clinical utility and do not aid decision making with regard to management of subclinical thyroid dysfunction.

This chapter explored and compared prevalence of symptoms in individuals with incident subclinical thyroid dysfunction with individuals with persistent subclinical thyroid dysfunction. The next chapter explores the relationship between symptoms and serum thyrotrophin concentration.

CHAPTER 14 SYMPTOMS AND SERUM THYROTROPHIN CONCENTRATION

Overview of chapter 14

It is possible that symptoms are manifested at specific concentrations of serum thyrotrophin. This chapter will therefore examine the relationship between symptoms and serum thyrotrophin concentration.

Univariate analyses were undertaken to explore the relationship between serum thyrotrophin concentration and individual symptoms, combinations of symptoms and interactions between symptoms and to enable selection of variables for inclusion in the multivariate analyses. In this chapter, the results of the univariate analyses are summarised and the findings of the multiple linear regression analysis (forward stepwise) performed to establish models for predicting serum thyrotrophin concentration are presented and discussed. The full findings of the univariate analyses are presented in Appendix 8.

14.1 Summary and justification for selection of symptoms

At the Bonferroni adjusted alpha level, no significant differences in serum thyrotrophin concentration were observed between groups with respect to individual symptoms or pairs of symptoms. The significance level was therefore relaxed to 5% to enable selection of symptoms for inclusion in the multiple linear regression analysis.

At the 5% significance level, the groups were significantly different with respect to one of the 18 individual symptoms and nine of the 98 possible symptom pairs. Four interacting pairs of symptoms were also identified. These interaction variables alongside the corresponding composite symptoms were selected for inclusion in the multivariate analysis (Table 14.1).

Table 14.1 Summary and justification for selection of symptoms for inclusion in the TSH model

Type of symptom	Symptom/ pair of symptoms	Symptom present[#]	Symptom absent[#]	Z score* p value
Hyperthyroid pair	Excessive perspiration with trembling hands	3.13	1.82	Z-2.010 p<0.044
Hyperthyroid pair	Frequent palpitations with sensitivity to heat	1.38	1.83	Z-2.370 p<0.018
Hyperthyroid pair	Frequent palpitations with weak muscles	1.45	1.83	Z-2.067 p<0.039
Hypothyroid individual	Weight gain	1.89	1.78	Z-2.906 p<0.004
Hypothyroid pair	Lethargy with constipation	1.83	1.55	Z-2.513 p<0.012
Hypothyroid pair	Poor memory with deep voice	1.32	1.83	Z-2.181 p<0.029
Hypothyroid pair	Hoarse voice with puffy eyes	1.39	1.82	Z-1.998 p<0.046
Hypothyroid pair	Puffy eyes with weight gain	2.00	1.81	Z-2.070 p<0.038
Hypothyroid pair	Sensitivity to cold with weight gain	1.91	1.81	Z-2.322 p< 0.020
Either hypo or hyper pair	Lethargy with poor memory	1.72	1.82	Z-2.262 p<0.024
Type of interaction	Interaction term and p value	Interacting symptoms		
Hypothyroid	Muscle cramps and sensitivity to cold p<0.043	Muscle cramps Sensitivity to cold		
Hypothyroid	Hoarse voice and weight gain p<0.012	Hoarse voice Weight gain		
Hypothyroid	Hoarse voice and constipation p<0.002	Hoarse voice Constipation		
Hypothyroid	Hoarse voice and puffy eyes p<0.038	Hoarse voice Puffy eyes		

* associated with the Mann Whitney test, [#] median TSH concentration - mIU/L

14.3 Multiple linear regression to predict thyrotrophin concentration

Eight independent variables made a unique and statistically significant contribution to the final *TSH model.* The final model was able to explain only 16% (R Squared) of the variance in serum thyrotrophin concentration and indicated that presence of current symptoms, weight gain, hoarse voice with constipation and excessive perspiration with trembling hands were associated with an increase of 0.167 units, 1.160 units and 1.348 units in serum thyrotrophin concentration respectively. Furthermore, the model suggested age was associated with serum thyrotrophin concentration with each year increase being associated with a 0.012 unit increase in serum thyrotrophin concentration. Four variables were independently associated with a decrease in serum thyrotrophin with history of irregular heart rhythm other than AF being associated with a 0.292 unit decrease in serum thyrotrophin. The symptom combination of hoarse voice with puffy eyes, hoarse voice with weight gain and lethargy with constipation were associated with a decrease of 0.448 units, 0.336 units and 0.381 units of serum thyrotrophin respectively (Table 14.2)

Table 14.2 TSH model - predictors of serum TSH concentration

Variable	Co-efficient	Standard error	t	p value
Constant	1.115	0.420	2.6574	0.008
Hoarse voice with constipation	1.160	0.258	4.486	0.001
Hoarse voice with puffy eyes	-0.448	0.228	-1.965	0.050
Weight gain	0.167	0.055	3.048	0.002
Lethargy with constipation	-0.381	1.46	-2.067	0.009
Age	0.012	0.005	2.308	0.021
Excessive perspiration with trembling hands	1.348	0.627	2.150	0.032
Other Irregular heart rhythm	-0.292	0.147	-1.984	0.047
Hoarse voice with weight gain	-0.336	0.171	-1.965	0.049

Standardised residuals: > ± 2.5 =2%; >± 2.0 = 4%

Exploration of the distribution of the standardised residuals for outliers indicated that only 4% of the standardised residuals were more than 2 standard deviations away from the mean (i.e. larger than 2.0 and smaller than -2.0). However, more than 1% were greater than 2.5 standard deviations away from the mean (> ± 2.5 =2%) suggesting that for these cases the model fits rather poorly.

Summary of chapter 14

Only six of the 19 symptoms identified in the univariate analysis contributed to the final serum thyrotrophin model. It is possible of course that the findings of the univariate analysis were spurious and multiple testing is responsible for inclusion of symptoms in the adjusted analysis that are not associated with serum thyrotrophin.

Multiple linear regression analysis suggested that six symptoms are independently associated with serum thyrotrophin concentration. The observed relationships between higher serum thyrotrophin concentration and the symptoms hoarse voice with constipation and weight gain were consistent with the biochemical profile of overt hypothyroidism. Furthermore, these relationships were consistent with the classification of these symptoms as those suggestive of hypothyroidism. In contrast, the association between excessive perspiration with trembling hands and lower concentrations of serum thyrotrophin was not consistent with either the symptom classification or the biochemical profile of overt hyperthyroidism. Similarly, the associations between serum thyrotrophin concentration and the symptoms hoarse voice with puffy eyes, lethargy with constipation and hoarse voice with weight gain did not concur with the biochemical profile or symptom classification of overt hypothyroidism. The final TSH model also suggested that age and irregular heart rhythm other than AF were independently associated with serum thyrotrophin concentration. Age was associated with a higher serum thyrotrophin concentration and history of irregular heart rhythm other than AF with lower serum thyrotrophin concentration. Whilst a statistically significant association between serum thyrotrophin concentration and a number of symptoms has been identified, these findings are unlikely to be clinically significant given that presence of symptoms is

associated with small (range 0.16-1.34 units) changes in serum thyrotrophin concentration. Furthermore, given that most of these results are contradictory and no significant differences between the groups were observed after adjustment for multiple testing it is likely that all significant findings are spurious.

CHAPTER 15 SYMPTOMS AND SERUM THYROXINE CONCENTRATION

Overview of chapter 15

In the previous chapter, the relationship between symptoms and serum thyrotrophin concentration was examined. The analyses did not demonstrate a strong association between serum concentration of thyrotrophin and symptom expression. It is possible that symptoms are expressed at specific concentrations of serum thyroxine. In the current chapter, the relationship between serum thyroxine concentration and symptoms is explored. The full results of the univariate analyses are presented in Appendix 9.

15.1 Summary of the univariate analysis and symptoms selection

Since no significant differences in serum free thyroxine concentration were observed at the Bonferroni adjusted alpha level of $p<0.0005$, relaxation of the significance level to 5% was necessary to enable symptom selection.

This resulted in selection of three individual symptoms, 14 symptom pairs and six symptom interaction terms with associated composite symptoms for inclusion in the multivariate linear regression model (Table 15.1).

Table 15.1 Summary and justification for selection of symptoms for inclusion in the FT4 model

Type of symptom	Symptom/ pair of symptoms	Symptom present#	Symptom absent#	Z score* p value
Hyperthyroid	Weight loss	15.30	14.80	Z-3.778 p<0.001
Hypothyroid	Weight gain	14.80	15.00,	Z-3.494, p<0.001
Either	Lethargy	15.30	14.80	Z-3.906, p<0.001
Hyperthyroid pair	Excessive perspiration with heat sensitivity	14.00	14.90	Z-2.245, p<0.025
Hyperthyroid pair	Frequent palpitation with weight loss	16.75	14.90	Z-2.922, p<0.003
Hyperthyroid pair	Frequent palpitation with poor memory	15.60	14.90	Z-2.070, p<0.038
Hyperthyroid pair	Fast thinking with weight loss	15.60	14.90	Z-2.357, p<0.018
Hypothyroid pair	Lethargy with dry skin	15.20	14.80	Z-2.398, p<0.016
Hypothyroid pair	Lethargy with sensitivity to cold	15.30	14.90	Z-3.054, p<0.020
Hypothyroid pair	Lethargy with muscle cramp	15.50	14.90	Z-3.714, p <0.001
Hypothyroid pair	Lethargy with slow thinking	15.30	14.90	Z-2.248, p <0.025
Hypothyroid pair	Dry skin with puffy eyes	14.50	14.90	Z 2.120, p <0.034
Hypothyroid pair	Dry skin with constipation	14.60	14.90	Z-3.037, p <0.002
Hypothyroid pair	Puffy eyes with weight gain	14.70	14.90	Z-2.025, p<0.043
Hypothyroid pair	Constipation with weight gain	14.40	14.90	Z- 3.307, p< 0.001
Either	Lethargy with weak muscles	15.30	14.90	Z-2.770, p<0.006
Either	Lethargy with poor memory	15.30	14.90	Z -2.222, p<0.020
Interaction type	**Interaction term**	**Interacting symptoms**		
Hypothyroid	Fast thinking * lethargy, p<0.015	Fast thinking/Lethargy		
Hypothyroid	Deep voice * muscle cramp, p<0.044	Deep voice/Muscle cramp		
Hypothyroid	Dry skin * constipation, p <0.017	Dry skin/Constipation		
Hypothyroid	Lethargy * muscle cramp, p <0.004	Lethargy/Muscle cramp		
Hypothyroid	Lethargy * weight gain, p <0.038	Lethargy/Weight gain		
Hypothyroid	Hoarse voice*constipation,p<0.048	Hoarse voice/Constipation		

* associated with the Mann Whitney test, # median FT4 concentration, pmol/l

15.2 Multiple linear regression to predict free thyroxine

Twelve independent variables made a unique statistically significant contribution to *FT4 model.* This model was able to explain 37% (R Squared) of the variance in free thyroxine and indicated that each one unit decrease in IMD score 2004 was associated with an increase of 0.008 units in serum FT4. Gender was also associated with serum concentration of free thyroxine with female gender being associated with a 0.196 unit decrease in free FT4 concentration. The presence of the current symptoms weight loss and lethargy were associated with 0.3112 unit and 0.687 unit increases in FT4 concentration respectively. Similarly, the symptom combinations lethargy with muscle cramps and frequent palpitation with weight loss were associated with an increase in serum thyroxine concentration of 0.495 units and 1.257 units respectively. Alcohol and smoking status were also associated with serum thyroxine concentration with regular alcohol intake and current smoking being associated with a decrease in serum FT4 of 0.219 and 0.382 units respectively (Table 15.2). One individual symptom and three symptom pairs were associated with decreased serum FT4 concentration. Presence of the symptom weight gain was associated with a 0.165 unit decrease in serum thyroxine concentration and presence of the symptom pairs dry skin with constipation, hoarse voice with constipation and lethargy with weight gain were associated with a 0.523, 0.759 and 0.495 unit decrease in serum FT4 concentration respectively. Female gender was associated with a 0.196 unit increase in serum FT4 concentration and each unit increase in IMD score 2004 was associated with a 0.08 unit decrease in serum FT4 concentration (Table 15.2).

Table 15.2 FT4 model - predictors of serum TF4 concentration

Variable	Co-efficient	Standard error	t	p=value
Constant	15.307	0.163	93.807	0.000
Lethargy	0.687	0.171	4.015	0.000
Weight gain	-0.165	0.086	-1.911	0.056
Alcohol	0.219	0.084	2.613	0.009
Dry skin with constipation	-0.523	0.170	-3.078	0.002
IMD score 2004	-0.08	0.003	-3.166	0.002
Frequent palpitations with weight loss	1.257	0.565	2.225	0.026
Gender	-0.196	0.079	-2.479	0.013
Smoking	0.382	0.163	2.346	0.019
Hoarse voice with constipation	-0.759	0.340	-2.233	0.026
Lethargy with muscle cramps	0.495	0.216	2.294	0.022
Lethargy with weight gain	-0.433	0.213	-2.034	0.042
Weight loss	0.312	0.159	1.968	0.049

Standardised residuals: > ± 2.5 =2%; >± 2.0 = 5%

Exploration of the distribution of the standardised residuals for outliers indicated that 5% of cases were more than two standard deviations away from the mean (i.e. larger than 2.0 and smaller than -2.0 standard deviations). Furthermore, this model was a poor fit for more than 1% of the cases (>±2.5 =2%) that were greater than 2.5 standard deviations away from the mean (i.e. larger than 2.5 and smaller than -2.5 standard deviations).

Summary of chapter 15

Given that some findings of the univariate analyses are discordant with the biochemical profile of overt hypothyroidism or overt hyperthryroidsm and the corresponding symptom classification, it is reasonable to suggest that all findings are spurious. Multiple linear regression analysis demonstrated that the symptoms weight gain, weight loss, lethargy and the symptom pairs lethargy with weight gain, lethargy with muscles cramps, frequent palpitations with weight loss, hoarse voice with constipation and dry skin with constipation were independently associated with serum free thyroxine concentration. Again, however, the relationship between the symptom pair lethargy with muscle cramps and lower concentrations of FT4 was discordant with the biochemical profile of overt hypothyroidism and the corresponding symptom classification. The most consistent finding was the association between serum FT4 concentration and the symptoms lethargy and weight change. The association of weight gain with lower concentrations of FT4 is consistent with the biochemical profile and symptom classification of overt hypothyroidism. Similarly, the association between weight loss and higher serum FT4 concentration is in agreement with the biochemical definition and symptom classification of overt hyperthyroidism. The symptom combination lethargy with weight gain is also independently associated with FT4 concentration with presence of weight modifying the relationship between lethargy and serum free thyroxine. Whilst statistically significant, these findings are unlikely to be clinically relevant due to the presence of symptoms being associated with such small (between 0.08 and 1.257 units) changes in serum thyroxine concentration.

CHAPTER 16 DISCUSSION

16.1 Statement of principal findings from the literature review

The literature review comprised evidence from a recent systematic review by Biondi et al which compiled data published between 1970 and April 2007[92] supplemented by subsequently published articles retrieved from electronic searches. The literature review demonstrated that whilst there is a wealth of research related to investigation of the pathophysiological consequences of subclinical thyroid dysfunction the findings are inconsistent. Furthermore, there is a lack of good quality data to confirm or refute expression of symptoms and other pathophysiological consequences associated with overt thyroid dysfunction other than AF in community dwelling individuals with subclinical thyroid dysfunction.

16.2 Statement of principal findings of the cross-sectional study

In terms of symptoms, the large cross-sectional survey provides comprehensive data on the prevalence of self reported symptoms suggestive of overt thyroid dysfunction and perceived health status in an unselected, community dwelling elderly cohort with and without subclinical thyroid dysfunction. The results indicate that symptoms suggestive of overt thyroid dysfunction are not associated with subclinical hypothyroidism or subclinical hyperthyroidism. Additionally, the findings demonstrate that subclinical thyroid dysfunction is not associated with impaired health status in this population. As expected, perceived health status is independently associated with presence of individual symptoms. The current study provides further evidence to demonstrate that

subclinical hypothyroidism and subclinical hyperthyroidism are not clinically relevant or important in this population in terms of symptom burden, and as such, routine screening and/or treatment of subclinical thyroid dysfunction is not justified in this population.

16.3 Discussion of the results of the literature review

In general, the literature review contributed little additional, robust and generalisable data to further substantiate or significantly alter the conclusions made by Biondi et al. [91] Subsequent data do nevertheless, provide good evidence to refute an association between subclinical hypothyroidism and increased risk of coronary heart disease, heart failure or cardiovascular mortality. [138,139] With respect to subclinical hyperthyroidism, subsequent data corroborate the findings of Biondi et al and provide good evidence for an increased risk of AF in older individuals with severe subclinical hyperthyroidism characterised by serum thyrotrophin concentrations of less than 0.1mIU/L. [151] However, risk estimates for AF in subclinical hyperthyroidism are still to be established. Whether treatment for subclinical thyroid dysfunction is more beneficial or preferential than treatment for AF likewise requires further investigation. There is also consistent data to support the hypothesis that reduced bone mineral density can be induced by endogenous subclinical hyperthyroidism, [5,167,168] although these data require confirmation in larger, population based studies.

In terms of symptoms, the literature review identified evidence suggesting that individuals with subclinical thyroid dysfunction experience symptoms suggestive of overt thyroid dysfunction. [24,37,171] However, these data are derived from small studies of patient populations and findings have not been corroborated in larger, population based

cohorts. On the whole, few studies evaluate symptoms and findings related to symptom prevalence are limited by small sample sizes, different outcome measures and heterogeneity of populations studied. Furthermore, in studies where physical examination was required for evaluation of signs and symptoms, the examiners were not always blind to the subjects' thyroid function status meaning that observer bias cannot be entirely ruled out. With respect to perceived health status, data are again generally derived from small studies within highly selected populations and therefore data are not widely generalisable. An additional methodological issue with these studies is that participants are often aware of their thyroid function category, meaning that results may be subject to response bias.

With respect to perceived health status, whilst data derived from smaller studies demonstrate impaired mental and physical health status in individuals with subclinical thyroid dysfunction, these findings are limited by the cross-sectional design meaning that cause and effect can not be established. Few studies investigate both symptom expression and perceived health status in relation to subclinical thyroid dysfunction therefore it is difficult to comment upon whether symptoms or thyroid dysfunction are responsible for impaired health status. [15,176,188]

Multiple reasons for the inconsistencies in study findings have been proposed. In general, studies differ with respect to the assays used to measure serum thyrotrophin concentration and the reference criteria against which subclinical thyroid dysfunction is defined. [91] Other possible explanations for the discrepancies in study findings are differences in inclusion/exclusion criteria employed with regard to individuals with known thyroid disease. Furthermore, heterogeneity of underlying cause and duration of

subclinical hypothyroidism may lead to disparate findings. Similarly, differential definition of outcome measures and identification of and adjustment for confounders may contribute to the conflicting results.

16.4 Discussion of results of the cross-sectional study

16.4.1 Representativeness

Compared with the general population of England and Wales and the West Midlands, the study cohort had a larger proportion of 75-84 year olds and a higher prevalence of AF and hypertension. [205, 207] These disparities are however likely to be artefacts of the study methodology since the inclusion criteria for the original cohort established in 2002 stipulated 65 years of age and above. Similarly, screening for AF and hypertension in the original study may be responsible for a higher prevalence of these conditions in the study cohort compared with the general populations of the West Midlands and England.[205]

In addition, the cohort was dissimilar to these populations in terms deprivation score, being more deprived than the general population of England and Wales and less deprived than the population of the West Midlands. Given that this thesis aimed to explore the association between thyroid function category and symptom expression at the individual patient level, these dissimilarities are unlikely to impact upon the validity of primary findings. As such, there is no foreseeable reason why these findings should not be extrapolated to other similarly aged populations. Iodine status of the population is often cited as a reason for caution with respect to extrapolation of findings to other

populations. [169] The current study was conducted in an iodine sufficient area however with respect to symptoms this is unlikely to be of significant clinical note.

16.4.2 Symptoms in the thyroid function groups

The euthyroid and subclinical hypothyroidism groups were similar with respect to gender, socioeconomic status, lifestyle characteristics, prescription medication and physical and mental health status. A greater proportion of the euthyroid group self reported regular alcohol intake and had a history of pulmonary disease compared with the subclinical hypothyroidism group. This finding is potentially spurious due to the fact that multiple testing was conducted, although the use of a Bonferroni corrected alpha level was designed to minimise the effects of multiple statistical testing. The groups with subclinical hypothyroidism and subclinical hyperthyroidism were significantly older than the euthyroid group. As expected, symptoms suggestive of overt thyroid dysfunction were relatively prevalent in this elderly cohort. In agreement with other community based studies evaluating symptoms, the results of the univariate analysis suggest that there is no association between subclinical thyroid dysfunction and any individual symptom or total number of symptoms suggestive of overt thyroid dysfunction in an elderly community dwelling population. [179, 189] In agreement with other studies, the hyperthyroid symtoms excessive perspiration, palpitation, sensitivity to heat [171,184] and the hypothyroid symptoms hoarse voice, dry skin and weight gain were more prevalent in individuals with subclinical thyroid dysfunction than in euthryoid subjects. [24,37] In the current study however these differences failed to reach statistical significance.

In terms of combinations of symptoms, at the conventional significance level of 5%, an association between subclinical hyperthyroidism and presence of sensitivity to heat with fast thinking was noted. Similarly, an association between subclinical hypothyroidism and weak muscles with slow thinking and dry skin with slow thinking was observed. Although a statistically significant difference in the prevalence of these symptom pairs existed between the euthyroid and subclinical thyroid function groups, the differences were small and therefore unlikely to be clinically useful at the individual patient level. Sensitivity to heat with fast thinking was reported by 2.7% of the euthyroid group compared with 10.3% of the subclinical hyperthyroidism group. Weak muscles with slow thinking were reported by 2.9% of the euthyroidism group and 6.5% of the subclinical hypothyroidism group. Additionally, these findings are likely to be spurious and as such should be interpreted with caution.

The results of the univariate and adjusted (multivariate) analyses were consistent with respect to the association between subclinical hyperthyroidism and sensitivity to heat with fast thinking, and, similarly, with respect to the association between subclinical hypothyroidism and presence of weak muscles with slow thinking. The association between subclinical hypothyroidism and dry skin with slow thinking however did not remain in the adjusted analysis. The findings further suggest that subclinical hyperthyroidism is 4.5 times more likely in an elderly individual presenting with sensitivity to heat and fast thinking than in an elderly individual without these symptoms. Likewise the odds of an elderly individual having subclinical hypothyroidism increases two-fold if the patient presents with weak muscles and slow thinking. Again however, the clinical utility and diagnostic value of these observations at the individual patient level is limited.

Furthermore, these associations were weak with neither logistic regression model being able to explain more than 28% of the variance in the dependent variables. Additionally, whilst both models had a specificity of 100% and were able to correctly classify all euthyroid cases (true negatives), neither model was able to correctly classify any cases of subclinical hyperthyroidism or subclinical hypothyroidism (true positives). These findings support previous observations in community based populations [182,189] and in older individuals [179] and further demonstrate that symptoms are poor predictors of subclinical thyroid dysfunction in an elderly population.

The availability of historical data provided an opportunity for further subgroup analysis and allowed exploration of symptom expression in new cases of subclinical thyroid dysfunction compared with persistent cases of subclinical thyroid dysfunction. The results demonstrated a similar symptom burden in individuals with incident subclinical thyroid dysfunction compared with individuals with persistent subclinical thyroid dysfunction. These findings further demonstrate that the presence of symptoms either alone or in combination with a previous thyroid function test results are of limited clinical utility and do not aid decision making with regard to management of subclinical thyroid dysfunction. These data are however limited because the date of onset of subclinical thryoid dysfunction is unknown and may have occurred at any point during the five year interval period.

16.4.3 Perceived health status and symptoms

Perceived health status was examined with respect to presence and absence of individual symptoms and in relation to category of thyroid function. Physical and mental

component summary scores were explored at an individual symptom level in order to identify those symptoms with the greatest impact upon health status. The results demonstrate a statistically significant difference between groups reporting presence and absence of the majority of current and changed individual symptoms with respect to both physical and mental component summary scores. Furthermore, in accordance with another community based study, the current study observed a decrease in median physical and mental component summary score as the total number of reported current or changed symptoms increased. [180] The group reporting the highest total number of symptoms described significantly lower levels of physical and mental health compared with the groups reporting fewer symptoms. Furthermore, similar levels of mental and physical health were described by the euthryoid and subclinical hypothyroidism and subclinical hyperthyroidism groups. The findings of the current study therefore do not support an association between subclinial thyroid dysfunction and impaired health status. [24, 181] In contrast, the current study findings suggest that reduced health status is independently associated with the presence of symptoms suggestive of overt thyroid dysfunction.

16.4.4 Symptoms and biochemical parameters of thyroid function

Multiple linear regression analysis demonstrated an association between serum TSH and weight gain and also the symptom pair hoarse voice with constipation. Both were associated with higher serum TSH which is consistent with the biochemical profile and symptom classification of overt hypothyroidism. Serum TSH was also associated with hoarse voice with puffy eyes, lethargy with constipation and hoarse voice with weight

gain. However, these associations were not consistent with the biochemical profile or symptom classification of overt hypothyroidism. Similarly, presence of the symptom combination excessive perspiration with trembling hands was associated with higher serum TSH which is contrary to the biochemical profile and symptom classification of overt hyperthyroidism. Given that many findings are contradictory it is reasonable to suggest that all findings are spurious.

In agreement with other studies, multiple linear regression analysis also demonstrated an association between higher serum thyrotrophin concentrations and advancing age and lower serum thyrotrophin levels and irregular heart rhythm other than AF. [151] Serum TF4 concentration was associated with five symptom combinations, three individual symptoms, smoking and alcohol status, gender and deprivation score. The relationship between higher FT4 concentration and weight loss and frequent palpitation with weight loss was consistent with the biochemical profile and symptom classification of overt hyperthyroidism. Equally, the association between lower serum TF4 concentration and the symptoms weight gain, hoarse voice with constipation and dry skin with constipation was in agreement with the symptom classification of overt hypothyroidism. Lethargy and lethargy with muscle cramps which are symptoms that have been observed in both overt hyperthyroidism and in overt hypothyroidism were associated with higher FT4 concentration whereas lethargy with weight gain was associated with lower FT4 concentration. This suggests that presence of weight gain modifies the relationship between lethargy and FT4 concentration. A higher FT4 concentration was associated with being of female gender and less affluent. Smoking and regularly consuming alcohol was associated with lower FT4 concentrations. These associations were weak though,

with neither the TSH or FT4 regression model explaining more than 37% of the variance. It is possible of course, that important determinants of serum TSH and FT4 were not assessed in the current study. The most consistent finding was the association between serum FT4 and the symptoms lethargy and weight change. With respect to the relationship between serum TSH and symptoms suggestive of overt thyroid dysfunction the results were less consistent. Although statistically significant differences in the distribution of serum FT4 and TSH concentration were observed, the differences were small and are unlikely to be clinically meaningful. These data further support the earlier results demonstrating that symptoms are not associated with subclinical hyperthyroidism or subclinical hypothyroidism.

16.5 Comparison with other published works

Several investigators support the use of multiple symptoms or symptom scores as diagnostic aids for the identification of individuals in whom subsequent testing would be most appropriate. [37,38,39] Symptom scores were not investigated in the current study because the prevalance of more than two symptoms was low and no clear relationship existed between category of thyroid function and total number of current or changed symptoms suggestive of overt thyroid dysfunction reported. Furthermore, derivation of a symptom score often requires allocation of arbitrary values to individual symptoms and is frequently difficult to calculate and interpret. Symptom scores are therefore of limited clinical utility and are unlikely to be convenient or feasible in the primary care setting.

Community based studies generally have failed to demonstrate differences between thyroid function groups with respect to total number of symptoms. [180] One exception to this is the Colorado symptoms study in which individuals with subclinical hypothyroidism reported a significantly higher mean percentage of symptoms compared with euthyroid individuals. [56] The possible explanations for these disparate findings include the heterogeneity in the populations studied in terms of age, study inclusion criteria, assays and reference criteria for definition of serum TSH. The possibility that concomitant medication was responsible for the presence of symptoms could also cannot be entirely ruled out because data related to medication use in this population was not recorded or controlled for in the analysis.

Few previous studies of symptoms or perceived health status have been conducted in community based populations. [180,189] The majority of studies demonstrating an association between subclinical thyroid dysfunction and symptoms or impaired health

status have been conducted in the hospital setting. In the outpatient environment, symptoms and impaired health status are likely to be more frequently observed than in non health seeking community dwelling populations and are likely to be affected by reporting times.

Differences in perceived health status between thyroid function groups have been previously demonstrated. However, in general, the participants have been aware of their thyroid function category at the time of questionnaire completion. [176] It is possible that medicalisation or labelling of abnormal biochemical profiles as subclinical thyroid dysfunction is responsible for impaired health status in these individuals. A key feature of the current study is that all participants were blind to their thyroid function categorisation at the time of completion of the symptom and health status questionnaires. In accordance with Bell et al, the current study failed to demonstrate any differences in perceived health status between thyroid function groups, thereby demonstrating that subclinical thyroid function is not associated with impaired health status. [180]

Two investigators have explored the relationship between thyroid function category and symptoms and thyroid function category and perceived health status. [24,176] However, only one additionally evaluated the relationship between perceived health status and presentation of symptoms. Similar to the findings of the current study, the investigators suggested that deterioration in perceived health status was associated with the presence of symptoms. In contrast to the current study, however, this relationship was not independent of category of thyroid function.

16.6 Strengths

The strengths of this research are the large number of unselected elderly individuals studied and the simultaneous and detailed evaluation of thyroid function, self reported symptoms and perceived health status, concomitant disease, medical history and lifestyle characteristics. Additionally, current data is not subject to response bias because all participants were unaware of their thyroid function status at the point of completion of the symptoms and health status questionnaire. Another strength of this study is that all participants self completed the study questionnaire therefore researcher bias can be entirely ruled out.

16.7 Weaknesses and study limitations

An alternative explanation for not identifying an association between symptoms and thyroid function category is that important determinants of subclinical thyroid dysfunction have not been measured within the current study. Indeed, it has been suggested that the clinical profile of subclinical thyroid dysfunction has changed since the advent of more sensitive serum thyrotrophin and free thyroxine assays. As such, it is possible that thyroid dysfunction is being identified earlier and those symptoms previously considered indicative of thyroid abnormalities reflect longer standing thyroid dysfunction and are no longer relevant. Equally, since the final logistic regression models only explained between 20-28% of the variance it is possible that important determinants of thyroid dysfunction were not measured in the current study. Evidence based development of the symptoms questionnaire was employed to ensure that the most relevant and sensitive symptoms were selected and included. It is therefore unlikely that known determinants

were not measured. It is of course possible that there is no “one size fits all” with respect to presentation of symptoms in subclinical thyroid dysfunction. Expression of symptoms may be unique to the individual based upon sensitivity to alterations in thyroid parameters outside of the reference range and the duration of subclinical thyroid dysfunction. Investigation of the prevalence of 18 individual symptoms reflecting a variety of metabolic processes involving a range of organ systems nevertheless failed to establish an association between subclinical thyroid dysfunction and any symptoms that the literature suggests indicate overt thyroid dysfunction.

Cross-sectional study designs that categorise thyroid function based upon measurement at one point in time face the possibility of detecting a transient abnormality in thyrotrophin concentration due to a non thyroidal illness. Thus, it is conceivable that individuals with transient changes in serum thyrotrophin were misclassified as having subclinical thyroid dysfunction. Due to the large sample size, however, misclassification of thyroid function category is unlikely to be of significance in this study. Furthermore, the prevalence of subclinical thyroid dysfunction was similar to that observed in similar community dwelling elderly populations in iodine sufficient areas. The thyroid function groups were similar with respect to prevalence of prescription medication and medical history with the exception of pulmonary disease which was significantly greater in the euthyroid group than the subclinical hyperthyroidism group. The adjusted analysis however controlled for these potential confounders. Similarly, due to the cross-sectional nature of this study, the impact of duration of subclinical thyroid dysfunction on expression of symptoms is unknown and is another limitation of this study. It is possible that incident cases experience a greater symptom burden than those with persistent

subclinical thyroid dysfunction who may be more accustomed to and/or tolerant of symptoms. In the current study, exploration of symptom expression in individuals that developed subclinical thyroid dysfunction (incident cases) during the interval period was possible due to the availability of historical thyroid function test results. The results demonstrated a similar symptom burden in individuals with incident subclinical thyroid dysfunction compared with individuals with persistent subclinical thyroid dysfunction.

Furthermore, data related to symptoms were self reported and therefore it is not possible to entirely rule out acquiescence and social desirability bias. This of course is inevitable due to the subjective nature of the outcome measures. Participants did however self complete the study questionnaires at home before attending the research clinic therefore their answers were not influenced by the research nurse. Additionally, in an attempt to reduce bias, the position of symptom suggestive of thyroid dysfunction was varied through out the symptom questionnaire. However, since the original format of the Colorado survey was maintained, the neutral option remained in a central position for each questionnaire item. Participants' responses were not influenced by category of thyroid function since they were unaware of thyroid function categorisation at the time of questionnaire completion. Furthermore, the analysis predominantly focused upon current symptoms as this data is likely to be more accurately reported than data related to symptoms that have changed during the previous 12 months.

A final limitation of the study is the relatively small number of individuals identified with subclinical hyperthyroidism (n=29). This is an artefact of the low prevalence of subclinical hyperthyroidism in the general population. Due to the large sample of euthyroid individuals included in the univariate analysis, all outcomes related to

subclinical hyperthyroidism have large confidence intervals. The precise nature of the outcomes related to the euthyroid subjects (due to the large sample size) in the same way offsets this. The estimates of the logistic regression analysis should be interpreted more cautiously since these are based upon 29 cases and 25 predictor variables and generally at least 10 times as many cases as predictor variables are recommended for stable and reproducible results.

CHAPTER 17 CONCLUSIONS

This thesis aimed to characterise symptoms and further clarify the pathophysiological consequences of subclinical thyroid dysfunction in community dwelling individuals aged 65 years of more. In fulfilment of the aim of this thesis there were four objectives. This chapter will demonstrate how each of these objectives has been met.

The first objective of this thesis was:

To further clarify the pathophysiological consequences of subclinical thyroid dysfunction in community dwelling individuals aged 65 years of more.

In fulfilment of this objective, a systematic literature review was undertaken. The findings of the review of existing evidence pertaining to the pathophysiological consequences of subclinical hypothyroidism and subclinical hyperthyroidism are presented in chapters 3 and 4 respectively. Current evidence related to expression of symptoms in individuals with subclinical hypothyroidism and subclinical hyperthyroidism is reported in chapters 5 and 6 respectively.

The second objective of the thesis was:

To determine the relationship between symptoms and subclinical thyroid dysfunction in an elderly community dwelling population.

This objective was successfully completed by means of a cross-sectional survey designed to evaluate biochemical parameters of thyroid function (enabling classification of thyroid function) and self reported symptoms suggestive of overt thyroid dysfunction in

a large elderly, community dwelling cohort. The methodology for this survey is detailed in chapter 8 and the results in chapters 9-12.

The third objective of the thesis was:

To establish the impact of symptoms and the effect of subclinical thyroid dysfunction upon perceived health status in this population.

This objective was also met by means of the cross-sectional survey which allowed collection of data related to perceived health status alongside data relating to symptoms. The full methodology is described in chapter 8 and the results are presented in chapters 10-11.

The final objective of this thesis was:

To explore the relationship between symptoms and serum concentration of serum thyrotrophin and free thyroxine in this population.

To address this objective, it was necessary to compare the distribution of the biochemical thyroid function parameters, serum thyrotrophin and free thyroxine in individuals reporting presence of symptoms with subjects reporting absence of symptoms. The methodology for this is detailed in chapter 8 and the results are presented in chapters 14 and 15 respectively.

17.1 Summary of the main findings of the thesis

This thesis examined a large body of research related to the pathophysiological consequences of subclinical thyroid dysfunction and demonstrated that there is a lack of robust data to confirm or refute that subclinical thyroid dysfunction is associated with similar adverse pathophysiological consequences or physical signs and symptoms to overt thyroid dysfunction. The findings of the cross-sectional study provide further evidence to suggest that subclinical thyroid dysfunction is not clinically relevant or important in elderly individuals in terms of impaired health status and symptom burden. Although symptoms suggestive of overt thyroid dysfunction were relatively prevalent in this elderly cohort and statistically significant differences in the prevalence of symptoms and in the distribution of serum thyrotrophin and thyroxine were observed, these differences were small and unlikely to be clinically meaningful at the individual patient level. The clinical utility of these observations is therefore limited and does not aid clinical decision making with regard to management of subclinical thyroid dysfunction in elderly individuals. Whilst this study suggests that elderly individuals with and without subclinical thyroid dysfunction have symptoms traditionally associated with overt thyroid dysfunction, the question as to whether these symptoms maybe reversible with treatment for thyroid dysfunction remains unanswered. Since symptoms are likely to be a consequence of 'healthy' ageing however, interventions which aim to restore euthyroid function are unlikely to resolve symptoms or greatly impact health status. Other non thyroidal causes and/or solutions should be sought to help improve general health status.

17.2 Recommendations

Based upon the findings of the literature review and cross-sectional study, repeated thyroid function testing and/or intervention in elderly individuals on the basis of symptoms suggestive of overt thyroid dysfunction alone can not be justified. Caution is therefore recommended when requesting repeat thyroid function tests or initiating treatment for an elderly individual based upon only the presence of symptoms suggestive of overt thyroid dysfunction.

17.3 Further work

The results of this study further challenge the traditional picture of thyroid dysfunction in older individuals. To confirm or refute the pathophysiology and profile of symptoms associated with overt and subclinical thyroid dysfunction in this population; further population based, longitudinal work, employing repeated measures of thyroid function and symptoms over an extended follow-up period (i.e middle to older age) are required. Then depending upon the outcome of the longitudinal work, a randomised controlled trial of treatment in subclinical thyroid dysfunction may be required to further clarify the benefits of treatment and aid clinical decision making with respect to primary care management of subclinical thyroid dysfunction.

APPENDICES

Appendix 1 Electronic search strategies

No:	Search limits
1	Humans
2	Adult 19-44 years
3	Middle aged 45-64 years
4	Middle aged +aged:45+years
5	Aged: 65+years
6	80+over: 80+ years

No:	Individual search terms	MeSH term
1	Subclinical hypothyroidism	Subclinical- all fields, hypothyroidism- MeSH
2	Atrial fibrillation	Atrial fibrillation
3	Cardiovascular risk	Cardiovascular and risk
4	Cardiovascular disease	Cardiovascular diseases
5	Cardiac status	Heart
6	Cardiac function	Heart and physiology (Subheading)
7	Cardiac morphology	Heart (anatomy and histology-Subheading)
8	Bone fracture	Fractures, bone
9	Bone	Bone and bones
10	Osteoporosis	Osteoporosis
11	Cognitive function	Physiology(cognitive - all fields)
12	Dementia	Dementia
13	Anxiety	Anxiety
14	Neuropsychiatric	All fields
15	Neuromuscular	All fields
16	Adverse consequences	All fields
17	Clinical manifestation	All fields
18	Clinical importance	All fields
19	Progression	
20	Symptoms	
21	Quality of life	
22	Health status	
23	1&2	
24	1&3	
25	1&4	
26	1&5	
27	1&6	
28	1&7	
29	1&8	

30	1&9	
31	1&10	
32	1&11	
33	1&12	
34	1&13	
35	1&14	
36	1&15	
37	1&16	
38	1&17	
39	1&18	
40	1&19	
41	1&20	
42	1&21	
43	1&22	
44	Subclinical hyperthyroidism	Subclinical – all fields, hyperthyroidism - MeSH
45	44&1	
46	44&2	
47	44&3	
48	44&4	
49	44&5	
50	44&6	
51	44&7	
52	44&8	
53	44&9	
54	44&10	
55	44&11	
56	44&12	
57	44&13	
58	44&14	
59	44&15	
60	44&16	
61	44&17	
62	44&18	
63	44&19	
64	44&20	
65	44&21	
66	44&22	

BETS II

Birmingham Elderly Thyroid Study Follow-up

Appendix 2 SF-8 Health Survey

This survey asks for your views about your health. This information will help you to keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. For each of the following questions, please circle the option which best describes your answer, for example

Fair

Q1. Overall, how would you rate your health during the past 4 weeks?					
Excellent	Very good	Good	Fair	Poor	Very poor
Q2. During the past 4 weeks, how much did physical health problems limit your usual physical activities (such as walking or climbing the stairs)?					
Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities	
Q3. During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?					
Not at all	A little bit	Some	Quite a lot	Could not do daily work	
Q4. How much bodily pain have you had during the past 4 weeks?					
None	Very mild	Mild	Moderate	Severe	Very severe
Q5. During the past 4 weeks, how much energy did you have?					
Very much	Quite a lot	Some	A little	None	
Q6. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family and friends?					
Not at all	Very little	Somewhat	Quite a lot	Could not do social activities	
Q7. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?					
Not at all	Slightly	Moderately	Quite a lot	Extremely	
Q8. During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work or other daily activities?					
Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities	

Appendix.3 Symptoms questionnaire

This questionnaire is designed to help us understand more about the type of symptoms people in your age group experience. We are sending this questionnaire to people with and without thyroid disease.

Each question has two parts:

- **Part A asks you to think about yourself compared to others in your age group**
- **Part B asks you to think about whether you have experienced any change over the previous 12 months.**

Please read each item and circle the response which best answers the question for you, for example Dry

Q1 Voice	A) Is your voice generally (compared with others in your age group)……	Very hoarse	Hoarse	Average	Clear	Very clear
	B) Is this different from 12 months ago?	Much more hoarse now	More hoarse	Unchanged	More clear now	Much more clear now

Q2 Tone of voice	A) Is the tone of your voice (compared with others in your age group)……	Very high	High	Average	Deep	Very deep
	B) Is this different from 12 months ago?	Much higher now	Higher now	Unchanged	Deeper now	Much deeper now

Q3 Skin	A) Is your skin (compared with others in your age group)……	Very dry	Dry	Average	Oily	Very oily
	B) Is this different from 12 months ago?	Much more dry now	More dry now	Unchanged	More oily now	Much more oily now

Q4 Eyes	A) Is the area around your eyes (compared with others in your age group)……	Very puffy	Puffy	Average	Sunken	Very sunken
	B) Is this different from 12 months ago?	Much more puffy now	More puffy now	Unchanged	More sunken now	Much more sunken now

Q5 Weight	A) For your height is your current weight……	Very high	A little high	Average	A little low	Very low
	B) Is this different from 12 months ago?	Much heavier now	Heavier now	Unchanged	Lighter now	Much lighter now

Q6 Activity	A) Are you generally (compared with others in your age group)…..	Much more active than others	More active than others	Average	Less active than others	Much less active than others

	B) Is this different from 12 months ago?	Much more active now	More active now	Unchanged	Less active now	Much less active now

Q7 Muscles	A) Are your muscles generally (compared with others in your age group)……	Very weak	Weak	Average	Strong	Very strong
	B) Is this different from 12 months ago?	Much weaker now	Weaker now	Unchanged	Stronger now	Much stronger now

Q8 Muscles 2	A) Do your muscles cramp (compared with others in your age group)……	Very rarely	Rarely	Average amount	Often	Very often
	B) Is this different from 12 months ago?	Cramp much less often now	Cramp less often now	Unchanged	Cramp more often now	Cramp much more often now

Q9 Thinking	A) Is your thinking (compared with others in your age group)……	Very slow	Slow	Average	Fast	Very fast
	B) Is this different from 12 months ago?	Much slower now	Slower now	Unchanged	Faster now	Much faster now

Q10 Temperature	A) Are you generally (compared with others in your age group)……	Very sensitive to cold	Sensitive to cold	Average	Sensitive to heat	Very sensitive to heat
	B) Is this different from 12 months ago?	Much colder now	Colder now	Unchanged	Warmer now	Much warmer now

Q11 Memory	A) Is your memory (compared with others in your age group)……	Very good	Good	Average	Poor	Very poor
	B) Is this different from 12 months ago?	Much better now	Better now	Unchanged	Poorer now	Much poorer now

Q12 Perspiration and sweating	A) When you are NOT in a warm or hot place and NOT exercising do you perspire or sweat……	Excessively or very heavily	Heavily	Average amount	Only slightly	Not at all

	B) Is this different from 12 months ago?	Sweat much more heavily now	Sweat more heavily now	Unchanged	Sweat less now	Sweat much less now

Q13 Trembling or shaky hands	A) Do your hands tremble or shake……	Very obviously	Obviously	Average amount	Slightly but not obviously	Not at all
	B) Is this different from 12 months ago?	Much more obviously now	More obviously now	Unchanged	Less obviously now	Much less obviously now

Q14 Palpitations (heart races, flutters or skips a beat)	A) When you are sitting quietly or lying in bed do you feel that your heart races, flutters or skips a beat……	Very rarely	Rarely	Average amount	Often	Very often
	B) Is this different from 12 months ago?	Much less often now	Less often now	Unchanged	More often now	Much more often now

Q15 Constipation	A) Are you constipated	Very rarely	Rarely	Average amount	Often	Very often
	B) Is this different from 12 months ago?	Much less often now	Less often now	Unchanged	More often now	Much more often now

Please return this questionnaire to your BETS II nurse. If you have any problems completing any of the questions the BETS II nurse will help you during your study appointment.

Thank you for taking time to complete this questionnaire.

Please note:
All information provided will be held in accordance with the Data Protection Act 1998

Appendix 4 Participant Consent Form

For The Attention of

UNIVERSITY OF BIRMINGHAM

Title of Study: **BETS II - Birmingham Elderly Thyroid Study Follow-up**
Are current reference ranges appropriate for identification of thyroid dysfunction in the elderly?

Centre ID: <GP Practice>
Patient Identification Number: <Patient ID>
Patient Initials: <Patient Initials>

Name of Researcher: Dr Lesley Roberts

Please **initial** inside **each** applicable box

1. I confirm that I have read and understand the BETS II information sheet dated 09/11/07 version 3 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree for a blood sample to be taken for the purposes of BETS II. ☐
4. I understand that my medical notes may be looked at by members of the BETS II research team, but understand that strict confidentiality will be maintained. I give permission for these individuals to access my records. ☐
5. I agree for my contact details to be retained on the BETS II Database so that I can be contacted in the future and invited to participate in further research in this area. ☐
6. I agree to take part in the above BETS II study

Name of Patient	Date	Signature
Name of person taking consent	Date	Signature

(White original for researcher site file, yellow copy for the patient; pink copy to be kept in medical notes)

Appendix 5 Changes to assay and reference criteria

This section details the changes in laboratory methodologies for thyroid function testing occurring between the two studies (BETS I and BETS II). In addition, the impact of these changes is reported and the methods used to resolve problems encountered are described and justified. Whilst not of direct relevance to the cross-sectional element of this thesis an appreciation of laboratory changes is essential for the reader to fully understand the inclusion criteria.

Changes in the assay used to measure serum thyrotrophin, FT4 and FT3 occurred between the two studies with the Avida Centaur assay used during BETS I being replaced by the Roche E170. In parallel with this, a change to the standard reference ranges for TSH and the thyroid hormones FT4 and FT3 occurred at the UHB endocrine laboratory during the period between the baseline and follow-up studies. Table A5.1 shows the standard reference ranges for serum thyrotrophin, FT4 and FT3 in use by the laboratory at the two time points. Table A5.2 details the reference criteria upon which classification of thyroid status was based in BETS I and BETS II.

Table A5.1 References criteria used for during BETS I and BETS II

Assay	BETS I reference range	BETS II reference range
Thyrotropin (TSH)	0.4-5.5 mIU/L	0.3-4.5 mIU/L
Free Thyroxine ($FT4_)$	9-20 pmol/L	10-22 pmol/L
Free Triiodothyronine ($FT3_)$	3.5-6.5 pmol/L	3.1-6.8 pmol/L

For the longitudinal study these changes meant that the planned comparison of individuals' TFT results and thyroid status across the two time points was no longer appropriate without prior correction. Reclassification of the BETS I TFT results and subsequent classification was therefore undertaken before data were reviewed. The methodology used for correction and reclassification is fully described. The changes had no impact in terms of the cross-sectional study, however, reclassification of baseline thyroid status inevitably meant that a number of individuals no longer fulfilled the eligibility criteria for the study and were therefore excluded from this nested research.

Table A5.2 reference criteria for classification of thyroid status

Thyroid status	**Thyrotrophin (TSH) mIU/L**		**Free thyroxine (FT4) pmol/L**		**Free Tri- iodothyronine (FT3) pmol/L**	
	BETS I	**BETS II**	**BETS I**	**BETS II**	**BETS I**	**BETS II**
Overt Hyperthyroidism	< 0.4	< 0.3	> 20	> 22	>6.5	>6.8
Subclinical hyperthyroidism	< 0.4	< 0.3	9 – 20	10 - 22	3.5-6.5	3.1-6.8
Euthyroid	0.4 – 5.5	0.3 - 4.5	9 – 20	10 - 22	NA	NA
Subclinical hypothyroidism	>5 5	> 4.5	9 – 20	10 - 22	NA	NA
Overt hypothyroidism	>5 5	> 4.5	< 9	< 10	NA	NA

Correction of baseline TFT results

To enable the comparison of individuals TFT results and thyroid status across the two time points (BETS I and BETS II) as proposed in the longitudinal study protocol, a correction factor was applied to the baseline TFT results. Table A5.3 details the correction factors provided by the regional endocrine laboratory and applied to baseline (BETS I) TFT results.

Table A5.3 Correction factors applied to serum TSH and FT4 measurements

Parameter	Correction factor
TSH correction factor	1.0729 x baseline (Avida centaur) TSH +0.0381
FT4 correction factor	1.1943 x baseline FT4 (Avida Centaur) -2.1128
FT3 correction factor	1.0680 x baseline (Avida Centaur) TSH -0.3866

The Regional Endocrine Laboratory UHB calculated the correction factors necessary to allow comparison of TFT results across the two time points in June 2006. In order to calculate the thyrotrophin correction factor, the thyrotrophin concentrations of 130 samples were measured using the Avida Centaur assay and then measured using the Roche E170 assay. The results obtained were plotted against one another and regression analysis conducted to define a line of best fit. The slope and intercept of the line of best fit were calculated with corresponding 95% confidence intervals (CI). Correlation analysis was used to test the null hypothesis that there was no relationship between the two assays. The findings from assessment of thyrotrophin did not confirm the null hypothesis and review of the confidence intervals for the slope of line of best fit indicated that a multiplication factor equal to the slope of the graph should be applied to

the thyrotrophin measurements obtained using the Avida Centaur assay. In addition review of the 95% CIs for the intercept indicated addition of the value of the intercept was also necessary to enable comparison. These methods were also employed for calculation of the FT4 and FT3 correction factors with 145 samples being measured on each assay for calculation of the FT4 correction factor and 52 samples to obtain the FT3 correction factor (Figures A5.1-A5.3).

Figure A5.1 Serum thyrotrophin concentration (mIU/L)

N= 130; Correlation r=0.9932, t = 96.801, p<0.0001
Roche E170 TSH = 1.0729 x Avida Centaur + 0.0381
Slope se=0.0111 95% CI = 1.0509-1.0948
Intercept se=0.1198 95%CI= -0.1989-0.2752

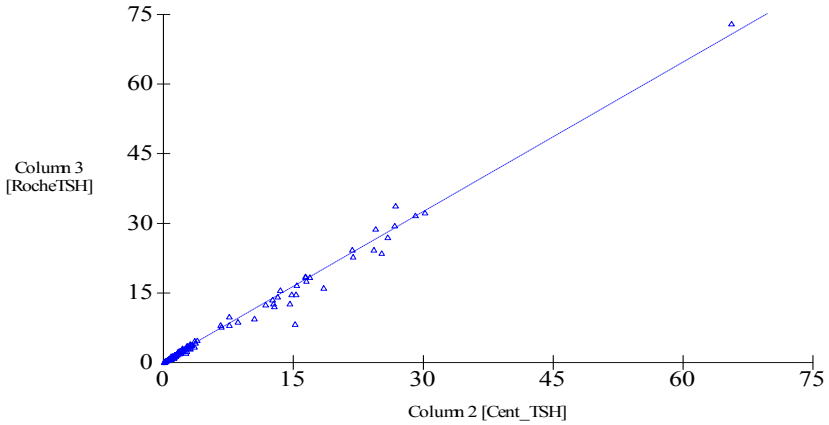


Figure A5.2 Serum free thyroxine concentration (pmol/L)

N=145, r=0.9676, t=45.794, p<0.0001
Roche E170=1.1943 x Avida Centaur -2.1128
Slope se=0.0261 95% CI = 1.1428-1.2459
Intercept se=0.4538 95%CI= -3.0099-1.2158

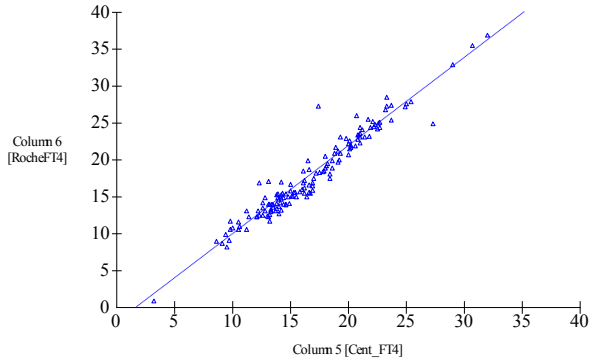
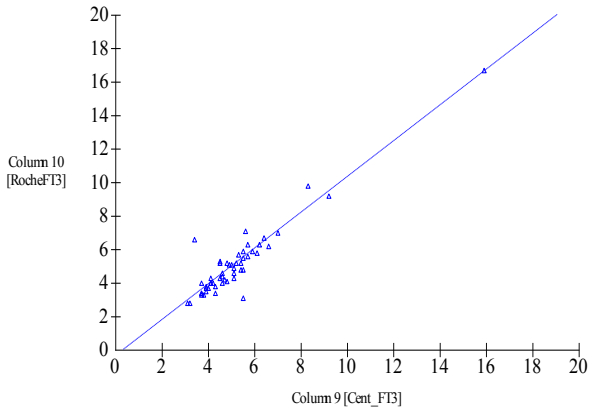


Figure A5.3 Serum free T3 concentration (pmol/L)

N=52; r=0.9407, t=19.614, p<0.0001
Roche E170=1.0680 x Avida Centaur -0.3866
Slope se=0.0545 95% CI = 0.9586-1.1773
Intercept se=0.2990 95%CI= -0.9871-0.2139



Appendix 6 Symptom expression in the incident subclinical thyroid dysfunction and persistently euthyroid subgroups

The proportion of the incident subclinical thyroid dysfunction and persistent euthyroid subgroups reporting presence of each individual symptom was compared using the χ^2 test for independence or the Fisher's exact test where appropriate. Given the fact that multiple comparisons were being made between groups, a Bonferroni adjusted alpha value of $p<0.003$ was used to control for type I error. The results are presented in Tables A6.1-A6.4. In the following tables and bar charts, the acronym NSCTD is used in reference to the incident subclinical thyroid dysfunction subgroup and PEuth is used to denote the persistently euthyroid subgroup.

The prevalence of 18 current symptoms suggestive of overt thyroid dysfunction was similar in the incident subclinical thyroid dysfunction and persistently euthyroid subgroups (Table A6.1). Similarly, there were no significant differences in the prevalence of individual changed symptoms reported by the thyroid function subgroups (Table A6.2).

Table A6.1 Incident subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of current symptoms

Current symptom	NSCTD %, 95% CI (n)	PEuth %, 95%CI (n)	χ^2 (p) df=1
Excessive perspiration	3.3,1.1-9.3 (3)	3.0,2.4-3.7 (7.9)	(0.75)*
Trembling hands	3.4,1.1-9.3 (3)	4.2,3.5-5.1 (112)	(1.00)*
Frequent palpitations	5.6,1.1-9.3 (5)	5.9,5.0-6.8 (155)	0.02 (0.90)
Sensitivity to heat	14.4,2.4-23.2 (13)	10.7,9.4-11.7 (277)	1.27 (0.26)
Fast thinking	27.8,10.9-37.8 (25)	22.7,21.1-24.3 (598)	1.27 (0.26)
Weight loss	2.2,0.6-7.7 (2)	7.5,6.6-8.6 (198)	3.59 (0.06)
Lethargy	14.6,8.6-23.2 (13)	16.5,15.1-17.9 (434)	0.22 (0.64)
Weak muscles	14.4,8.6-23.2 (13)	14.4,12.9-15.6 (375)	0.003 (0.96)
Poor memory	8.9,4.6-16.6 (8)	9.7,8.7-10.9 (257)	0.073 (0.79)
Hoarse voice	5.6,2.4-12.4 (5)	5.8,4.9-6.7 (152)	0.004 (0.95)
Deep voice	12.4,7.0-20.6 (11)	6.3,5.4-7.2 (165)	5.27 (0.02)
Dry skin	35.6,26.4-45.9 (32)	32.2,30.4-33.9 (847)	0.45 (0.50)
Puffy eyes	20.0,13.0-29.4 (18)	13.1,11.8-14.4 (344)	3.64 (0.06)
Muscle cramps	20.0,13.0-29.4 (18)	14.9,13.6-16.3 (392)	1.79 (0.18)
Constipation	15.6,9.5-24.4 (14)	13.0,11.7-14.3 (342)	0.50 (0.48)
Sensitivity to cold	37.8,28.5-48.1 (34)	34.8,32.4-36.0 (902)	0.24 (0.56)
Slow thinking	13.3,7.8-21.9 (12)	7.8,6.8-8.9 (205)	0.34 (0.56)
Weight gain	54.4,44.2-64.3 (49)	48.3,46.3-50.1 (1272)	1.31 (0.25)

Bonferroni alpha level $p<0.003$, * p value associated with the Fisher exact test

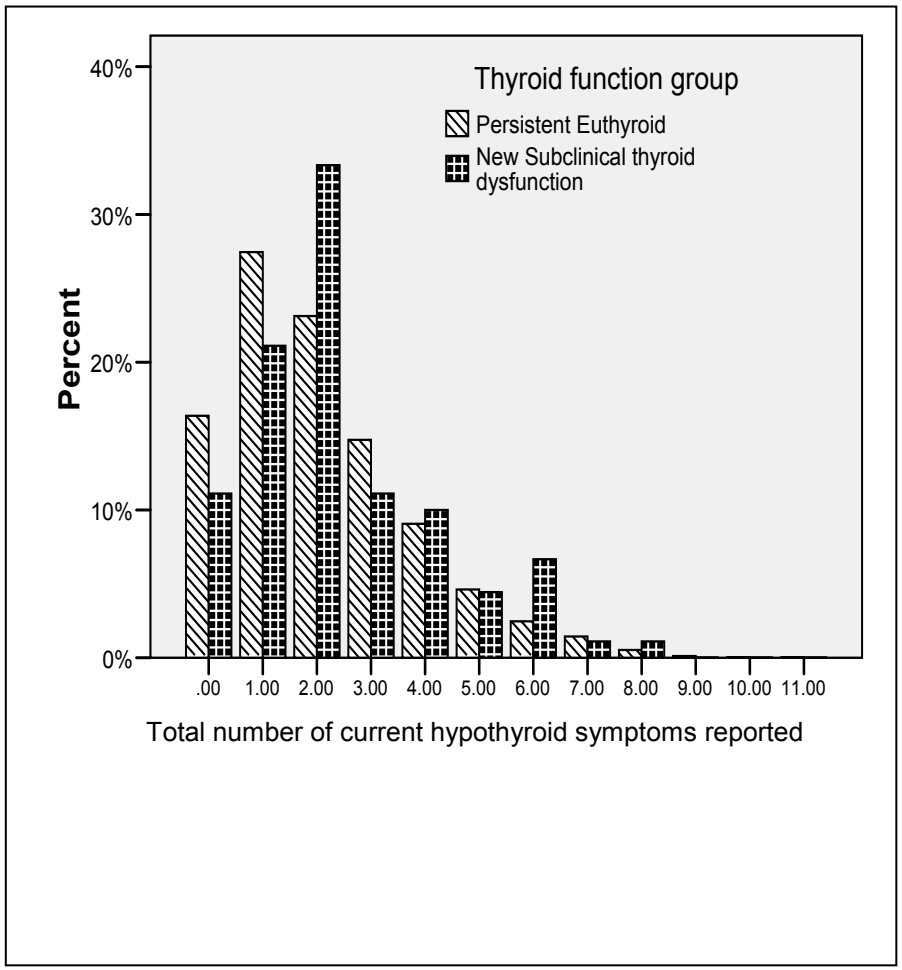
Table A6.2 Incident subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of changed symptoms

Changed symptom	NSCTD %,95%CI (n)	PEuth %,95%CI (n)	χ^2 (p) df=1
Excessive perspiration	1.1,0.2-6.0 (1)	2.1,1.6-2.7 (54)	(1.0)*
Trembling hands	3.3,1.1-9.3 (3)	4.9,4.1-5.8 (129)	(0.80)*
Frequent palpitations	7.8,3.8-15.2 (7)	4.4,3.6-5.2 (115)	(0.12)*
Sensitivity to heat	4.4,1.7-10.9 (4)	1.8,1.4-2.4 (48)	(0.09)*
Fast thinking	0, 0-4.1 (0)	1.8,1.4-2.4 (48)	(0.09)*
Weight loss	11.1,6.1-19.3 (10)	13.3,12.1-14.7 (351)	0.368 (0.544)
Lethargy	14.6,8.6-23.2 (13)	18.7,17.2-20.2 (492)	0.954 (0.329)
Weak muscles	12.4,7.0-20.6 (11)	16.3,14.9-17.7 (429)	0 (0.320)
Poor memory	16.7,10.4-25.7 (15)	16.6,15.2-18.1 (438)	0 (0.991)
Hoarse voice	6.7,3.1-13.8 (6)	4.6,3.9-5.5 (121)	(0.314)*
Deep voice	0, 0.4.1 (0)	2.0,1.5-2.6 (52)	(0.42)*
Dry skin	10.0,5.4-17.9 (9)	13.1,11.8-14.4 (344)	0.727 (0.394)
Puffy eyes	7.8,3.8-15.2 (7)	5.7,4.9-6.6 (150)	0.682 (0.409)
Muscle cramps	14.4,8.6-25.2 (13)	13.0,11.7-14.3 (342)	(1.00)*
Constipation	6.7,3.1-13.8 (6)	6.7,5.8-7.7 (177)	0.33 (0.856)
Sensitivity to cold	13.3,7.8-21.9 (12)	12.7,11.4-13.9 (333)	0.33 (0.856)
Slow thinking	14.4,8.6-23.2 (13)	11.6,10.4-12.9 (306)	0.663 (0.415)
Weight gain	24.4,16.7-34.2 (22)	16.1,14.7-17.5 (424)	4.44 (0.035)

Bonferroni alpha level p <0.003. *p value associated with the Fisher Exact test

No clear relationship between the longitudinal thyroid function subgroups and total number of current or changed, hypothyroid or hyperthyroid symptoms was observed. (Figure A6.1 and Figure A6.2).

Figure A6.1 and A6.2 Incident subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of multiple hypothyroid symptoms



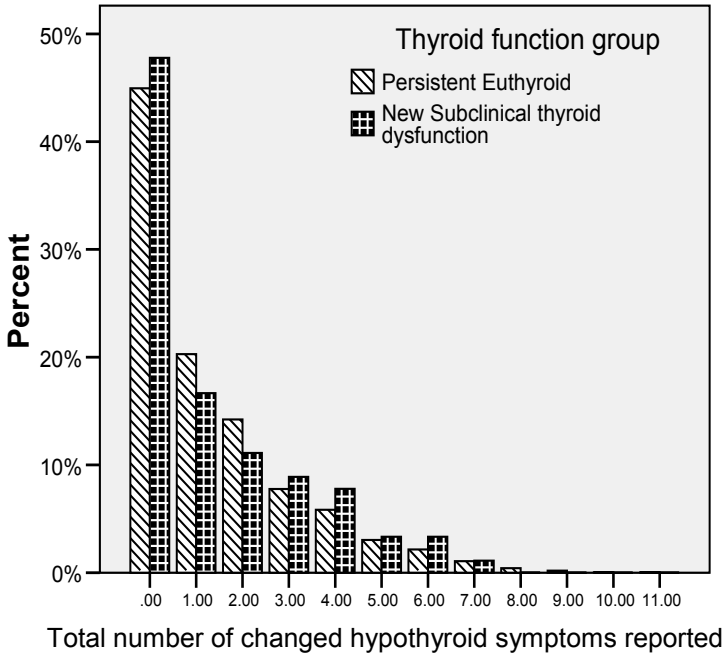
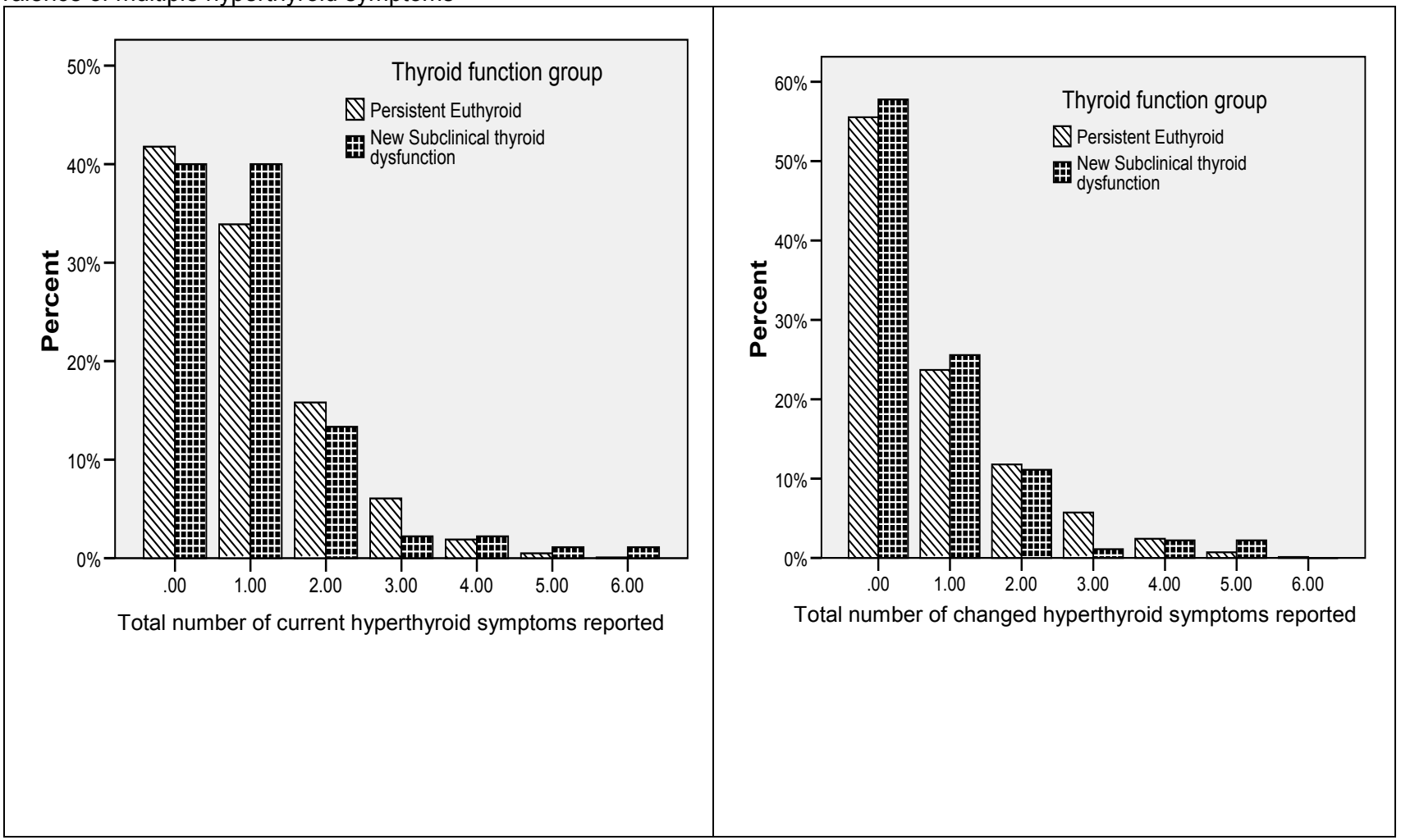


Figure A6.3 and A6.4 Figure A6.1 and A6.2 Incident subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of multiple hyperthyroid symptoms



No significant difference between the longitudinal thyroid function subgroups existed with respect to total number of current or changed symptoms suggestive of hyperthyroidism or hypothyroidism (Table A6.3 and table A6.4).

Table A6.3 Incident subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of multiple hypothyroid symptoms

	Current hypothyroid symptom			**Changed hypothyroid symptom**		
Totalled number of symptoms	NSCTD n=90	PEuth n=2637	χ^2 (p) df = 2	NSCTD n=90	PEuth n=2637	χ^2 (p) df = 2
None	10 (11.1)	432 (16.4)	1.80 (0.41)	43 (47.3)	1186 (45.0)	1.95 (0.38)
1-2	49 (54.4)	1334 (50.6)		25 (27.8)	910 (34.5)	
3 or more	31 (34.4)	871 (33.0)		22 (24.4)	541 (20.5)	

Table A6.4 Incident subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of multiple hyperthyroid symptoms

	Current hyperthyroid symptoms			**Changed hyperthyroid symptom**		
Totalled number of symptoms	NSCTD n=90	PEuth n=2637	χ^2 (p) df = 2	NSCTD n=90	PEuth n=2637	χ^2 (p) df = 2
None	36 (40.0)	1102 (41.8)	0.65 (0.721)	52 (57.8)	1465 (55.5)	1.266 (0.531)
1-2	48 (53.3)	1311 (49.7)		33 (36.7)	936 (35.5)	
3 or more	6 (6.7)	222 (8.5)		5 (5.6)	237 (9.0)	

Appendix 7 Symptom expression in the persistent subclinical thyroid dysfunction and persistently euthyroid subgroups

The proportion of the persistent subclinical thyroid dysfunction and persistent euthyroid subgroups reporting presence of each individual symptom was compared using the χ^2 test for independence or the Fisher's exact test where appropriate. Given the fact that multiple comparisons were being made between groups, a Bonferroni adjusted alpha value of $p<0.003$ was used to control for type 1 error. The results are presented in Tables A7.1-A7.4. In the tables and bar charts the acronym PSCTD is used in reference to the persistent subclinical thyroid dysfunction subgroup and PEuth is used to denote the persistently euthyroid subgroup.

Table A7.1 Persistent subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of current symptoms

Current symptom	PSCTD %,95%CI (n)	PEuth %,95%CI (n)	χ^2 (p) df=1
Excessive perspiration	3.9,1.3-10.8 (3)	3, 2.4-3.7 (79)	(0.51)
Trembling hands	2.6,0.7-9.0 (2)	4.2,3.5-5.1 (112)	(0.77)
Frequent palpitations	3.9,1.3-10.8 (3)	5.9,5.0-6.8 (155)	(0.62)
Sensitivity to heat	9.2,4.5-17.6 (7)	10.7,9.4-11.7 (277)	0.17 (0.68)
Fast thinking	23.4,15.3-34.0 (18)	22.7,21.1-24.3 (598)	0.02 (0.89)
Weight loss	5.2,2.0-12.6 (4)	7.5,6.6-8.6 (198)	0.59 (0.44)
Lethargy	6.5,2.8-14.3 (5)	16.5,15.1-17.9 (434)	5.48 (0.02)
Weak muscles	11.7,6.3-20.7 (9)	14.2,12.9-15.6 (375)	0.40 (0.53)
Poor memory	3.9,1.3-10.8 (3)	9.7,8.7-10.9 (257)	2.96 (0.09)
Hoarse voice	11.7,6.3-20.7 (9)	5.8,4.9-6.7 (152)	(0.05)
Deep voice	6.5,2.8-14.3 (5)	6.3,5.4-7.2 (165)	(0.81)
Dry skin	31.2,21.9-42.2 (24)	32.2,30.4-33.9 (847)	0.04 (0.85)
Puffy eyes	15.6,9.1-25.3 (12)	13.1,11.8-14.4 (344)	0.42 (0.52)
Muscle cramps	9.1,4.5-17.6 (7)	14.9,13.6-16.3 (392)	2.00 (0.16)
Constipation	11.7,6.3-20.7 (9)	13.0,11.7-14.3 (342)	0.11 (0.74)
Sensitivity to cold	34.2,24.3-44.9 (26)	34.8,32.4-36.0 (902)	0.01 (0.92)
Slow thinking	5.2,2.0-12.6 (4)	7.8,6.8-8.9 (205)	0.70 (0.40)
Weight gain	48.1,37.3-59.0 (37)	48.3,46.3-50.1 (1272)	0.002 (0.97)

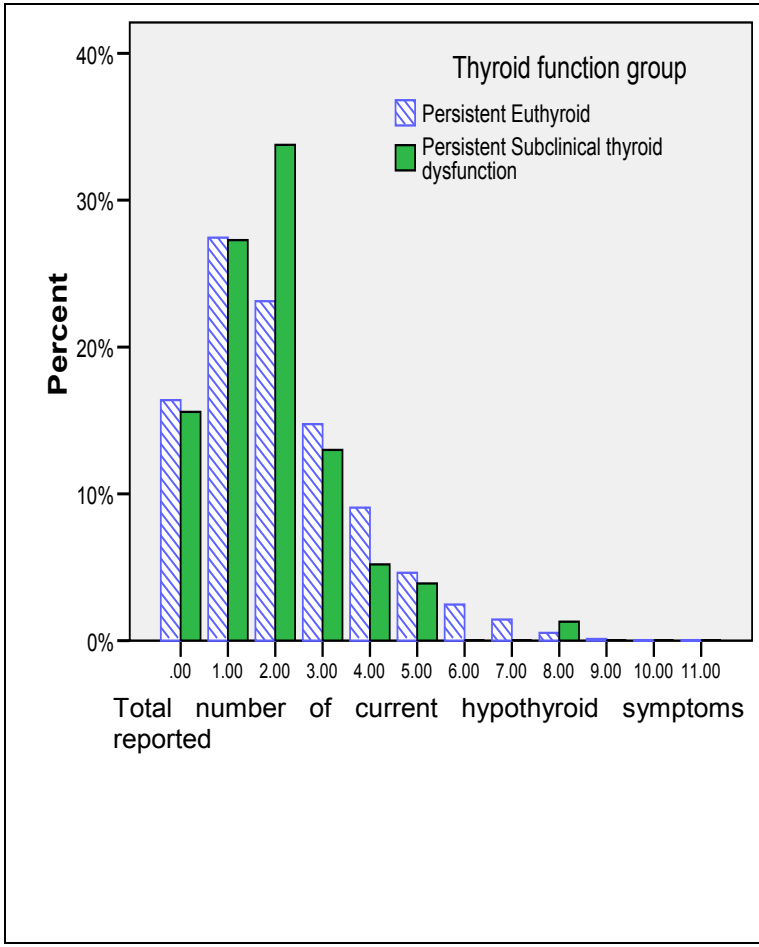
* p value associated with the Fishers Exact test

Table A7.2 Persisent subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of changed symptoms

Changed symptom	PSCTD %,95%CI (n)	PEuth %,95%CI (n)	χ^2 (p) df=1
Excessive perspiration	2.6.0.7-9.0 (2)	2.1, 1.6-2.7 (54)	(0.67)*
Trembling hands	5.2,2.0-12.6 (4)	4.9,4.1-5.8 (129)	(0.79)*
Frequent palpitations	2.6,0.7-9.0 (2)	4.4,3.6-5.2 (115)	(0.77)*
Sensitivity to heat	3.9,1.3-10.8 (3)	1.8,1.4-2.4 (48)	(0.18)*
Fast thinking	2.6,0.7-9.0 (2)	0.5,0.3-0.8 (13)	(0.07)*
Weight loss	11.7,6.3-20.7 (9)	13.3,12.1-14.7 (351)	0.17 (0.68)
Lethargy	18.2,11.2-28.2 (14)	18.7,17.2-20.2 (492)	0.01 (0.91)
Weak muscles	15.6,9.1-25.3 (12)	16.3,14.9-17.7 (429)	0.03 (0.87)
Poor memory	15.6,9.1-25.3 (12)	16.6,15.2-18.1 (438)	0.06 (0.81)
Hoarse voice	9.2,4.5-17.6 (7)	4.6,3.9-5.5 (121)	(0.09)*
Deep voice	3.9 ,1.3-10.8 (3)	2.0,1.5-2.6 (52)	(0.21)*
Dry skin	3.9,1.3-10.8 (3)	13.1,11.8-14.4 (344)	1.00 (0.39)
Puffy eyes	5.2,2.0-12.6 (4)	5.7,4.9-6.6 (150)	(1.00)*
Muscle cramps	13.0,7.2-22.3 (10)	13.0,11.7-14.3 (342)	(1.00)*
Constipation	9.1,4.5-17.6 (7)	6.7,5.8-7.7 (177)	0.65 (0.04)
Sensitivity to cold	10.4,5.4-19.2 (8)	12.7,11.4-13.9 (333)	0.36 (0.55)
Slow thinking	10.4,5.4-19.2 (8)	11.6,10.4-12.9 (306)	0.11 (0.74)
Weight gain	15.6,9.1-25.3 (12)	16.1,14.7-17.5 (424)	0.014 (0.91)

* p value associated with the Fishers Exact test

Figures A7.1 and A7.2 Persisent subclinical thyroid dysfunction versus persistent euthyroidism; comparison of multiple hypothyroid symptoms reported



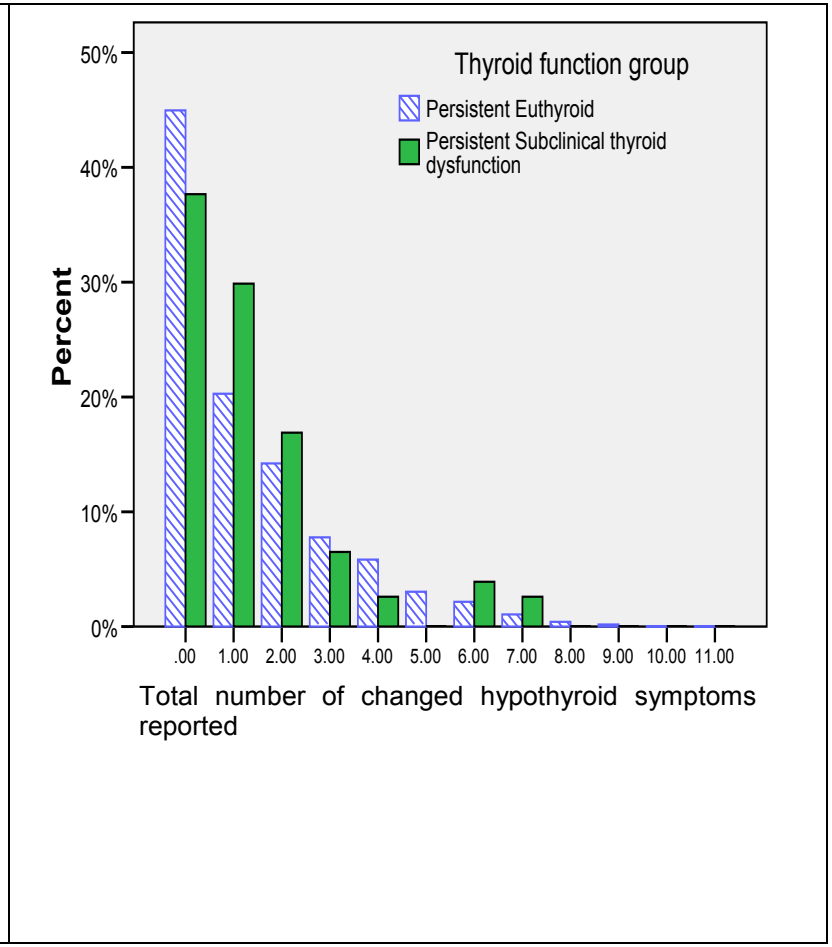
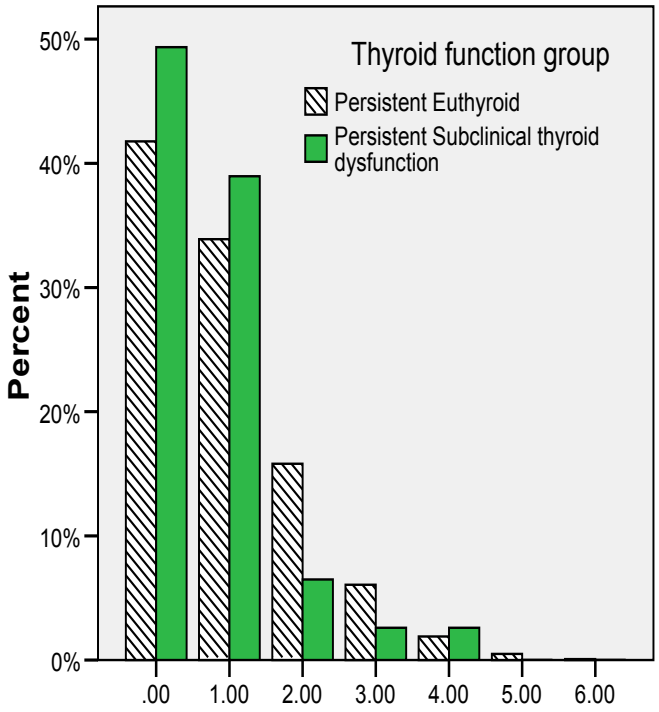


Figure A7.3 and A7.4 Total number of current and changed hyperthyroid symptoms reported



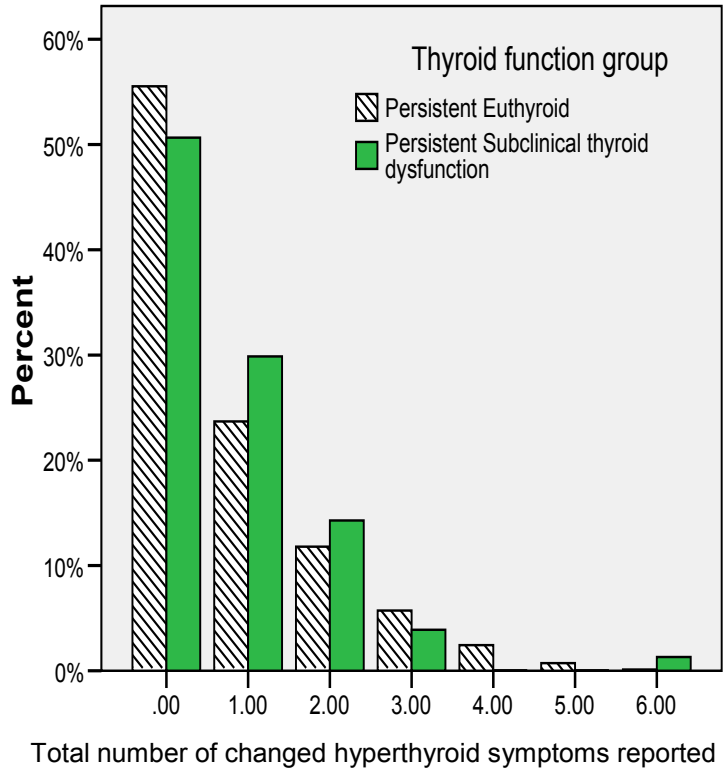


Table A7.3 Persistent subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of multiple hypothyroid symptoms

	Current hypothyroid symptoms			**Changed hypothyroid symptoms**		
Totalled number of symptoms	PEuth n=2637	PSCTD n=77	χ^2 (p) df = 2	PEuth n=2637	PSCTD n=77	χ^2 (p) df = 2
None	432 (16.4)	12 (15.6)	3.76 (0.15)	1186 (45.0)	29 (37.7)	5.01 (0.08)
1-2	1334 (50.6)	47 (61.0)		910 (34.5)	36 (46.8)	
3 or more	871 (33.0)	18 (23.4)		541 (20.5)	12 (15.6)	

These groups were similar also with respect to total number of current and changed symptoms suggestive of overt hypothyroidism and overt hyperthyroidism. (Table A7.3)

Table A7.4 Persistent subclinical thyroid dysfunction versus persistent euthyroidism; comparison of the prevalence of multiple hyperthyroid symptoms

	Current hyperthyroid symptom			**Changed hyperthyroid symptom**		
Totalled number of symptoms	PEuth	PSCTD	χ^2 (p) df = 2	PEuth	PSCTD	χ^2 (p) df = 2
None	1102 (41.8)	38 (49.4)	2.281 (0.320)	1465 (55.5)	39 (50.6)	3.108 (0.21)
1-2 symptom	1311 (49.7)	35 (45.5)		936 (35.5)	34 (44.2)	
3 or more	225 (8.5)	4 (5.2)		237 (9.0)	4 (5.2)	

Appendix 8 Results of univariate exploration of symptoms and serum TSH concentration

The Mann Whitney U test was used to compare median serum thyrotrophin concentration between groups reporting presence and absence of individual symptoms and between those reporting a recent change and no change in intensity of individual symptoms during the preceding 12 months.

At the Bonferroni adjusted alpha level of $p<0.003$ there were no significant differences in median serum thyrotrophin concentration between those reporting presence and absence of symptoms. Since the univariate analysis was explanatory in nature and aimed to identify appropriate symptoms for inclusion in the multivariate analysis the significance level was relaxed to 5% to enable selection of symptoms. At a level of 5% significance, a significant difference existed with respect to the current symptom weight gain. A significantly higher serum thyrotrophin concentration was observed in those reporting presence of current weight gain than in those reporting absence of this symptom (1.89mIU/L versus 1.78mIU/L, $p<0.004$) (Table A8.1).

Table A8.1 Presence versus absence of individual sysmptoms; comparison of serum TSH concentration

		Current symptom			Changed symptom		
	Symptom	Symptom absent Median, 95%CI (n)	Symptom present Median, 95%CI (n)	Z Score (p value)	Symptom absent Median, 95%CI (n)	Symptom present Median, 95%CI (n)	Z Score (p value)
Suggestive of hyperthyroidism	**Excessive perspiration**	1.82,1.78-1.87 (2778)	1.74,1.49-2.04 (90)	- 0.43 (0.67)	1.82,1.78-1.87	1.78,1.43-2.03 (60)	-0.43 (0.67)
	Trembling hands	1.81,1.78-1.86 (2749)	1.81,1.27-1.91 (120)	-1.02 (0.31)	1.82,1.78-1.87 (2719)	1.91,1.70-2.05 (140)	- 0.55 (0.58)
	Frequent palpitations	1.83,1.78-1.88 (2693)	1.72,1.31-175 (171)	0.27 (0.27)	1.82,1.71-1.87 (2728)	1.78,1.56-1.97 (128)	-0.29 (0.77)
	Sensitivity to heat	1.84,1.78-1.89 (2518)	1.84,1.65-1.92 (304)	-0.75 (0.46)	1.83,1.78-1.88 (2798)	1.64,1.36-2.27 (59)	-0.41 (0.68)
	Fast thinking	1.82,1.78-1.88 (2211)	1.82,1.73-1.93 (655)	-0.05 (0.96)	1.82,1.78-1.87(2847)	1.42,0.84-3.46 (15)	-0.87 (0.38)
	Weight loss	1.84,1.79-1.89 (2660)	1.71.1.46-1.51 (206)	-1.75 (0.08)	1.83,1.78-1.88 (2489)	1.80,1.12-1.30 (179)	-0.72 (0.47)
Either form of TD	**Lethargy**	1.83,1.79-1.89 (2408)	1.77,1.69-1.89 (460)	-1.12 (0.26)	1.83, 1.79-1.89 (2330)	1.77,2.12-2.49 (512)	- 1.59 (0.11)
	Weak muscles	1.82,1.78-1.89 (2458)	1.85,1.70-1.94 (408)	-0.31 (0.76)	1.83,1.78-1.87 (2397)	1.82,1.70-1.89 (465)	- 0.82 (0.42)
	Poor memory	1.83,1.78-1.93 (2596)	1.79,1.65-1.90 (273)	-0.99 (0.32)	1.84, 1.79-1.91 (2394)	1.75,1.62-1.83 (473)	- 1.90 (0.06)
Suggestive of hypothyroidism	**Hoarse voice**	1.82,1.78-1.87 (2688)	1.78,1.64-1.97 (177)	-0.08 (0.93)	1.82,1.78-1.87 (2692)	1.82,1.56-2.11 (141)	-0.09 (0.93)
	Deep voice	1.83,1.78-1.88 (2674)	1.73,1.57-1.93 (188)	-1.41 (0.16)	1.82,1.76-1.86 (2789)	1.67, 1.30-2.28 (57)	-0.39 (0.69)
	Dry skin	1.79,1.76-1.85 (1940)	1.88,1.80-1.95 (924)	-1.11 (0.27)	1.83,1.83-1.97 (2495)	1.78, 1.61-2.99 (368)	-1.41 (0.16)
	Puffy eyes	1.81,1.77-1.87 (2475)	1.86,1.77-2.00 (390)	-0.03 (0.98)	1.82,1.78-1.86 (2685)	1.94,1.75-2.40 (173)	-1.39 (0.16)
	Muscle cramps	1.83,1.79-1.89 (2434)	1.76,1.68-1.87 (433)	-0.84 (0.40)	1.83,1.78-1.88 (2488)	1.78,1.65-1.93 (377)	-0.94 (0.35)
	Constipation	1.82,1.78-1.87 (2485)	1.79,1.36-1.57 (373)	-0.31 (0.76)	1.82, 1.78-1.87 (2662)	1.82,0.77-1.67 (194)	-0.13 (0.90)
	Sensitivity to cold	1.82,1.76-1.88 (1837)	1.86,1.78-1.92 (985)	0.27 (0.27)	1.82,1.78-1.88 (2492)	1.83,1.74-1.96 (365)	- 0.14 (0.89)
	Slow thinking	1.82, 1.77-1.86 (2638)	1.90,1.77-1.95 (228)	-0.10 (0.30)	1.83,1.78-1.89 (2525)	1.77,1.65-1.89 (337)	-0.62 (0.54)
	Weight gain	1.76,1.72-1.83 (1470)	1.89,1.82-1.96 (1396)	-2.91 (0.004)	1.83,1.78-1.88 (2525)	1.79, 1.73-1.94 (463)	-0.75 (0.75)

* associated with the Mann Whitney U test

The Kruskal Wallis test was used to compare median serum TSH concentration between participants divided into three groups based upon intensity of reported symptoms (e.g absent, mild or severe). A Bonferroni adjusted alpha value was used to control for type I error. No associations between serum TSH concentration and presence of reported current symptoms suggestive of overt hyperthyroidism and overt hypothyroidism where observed at the Bonferroni adjusted level of significance. (Table A8.2)

Table A8.2 Presence versus absence of individual current mild and severe intensity symptoms; comparison of serum TSH concentration

		Median serum TSH concentration			
	Current symptom	Symptom absent %,95%CI (n)	Mild symptom present %,95%CI (n)	Severe intensity symptom %,95%CI (n)	p value*
Suggestive of hyperthyroidism	**Excessive perspiration**	1.82,1.78-1.87 (2778)	1.72,1.55-2.07 (73)	1.76,1.39-3.13 (17)	0.50
	Trembling hands	1.81,1.78-1.86 (2749)	2.00,1.69-2.39 (90)	1.96,1.36-2.60 (30)	0.22
	Frequent palpitations	1.83,1.78-1.88 (2693)	1.75,1.47-1.94 (145)	1.59,1.36-2.42 (26)	0.27
	Sensitivity to heat	1.84,1.78-1.89 (2518)	1.75,1.63-1.89 (277)	1.98, 1.44-2.66 (27)	0.20
	Fast thinking	1.82,1.78-1.88 (2211)	1.81,1.72-1.93 (595)	1.89,1.48-2.32 (60)	0.95
	Weight loss	1.84,1.79-1.89 (2660)	1.70,1.51-1.73 (190)	1.86,1.33-2.76 (16)	0.46
Either form of TD	**Lethargy**	1.83,1.79-1.89 (2408)	1.78,1.69-1.94(380)	1.74,1.46-1.93 (80)	0.58
	Weak muscles	1.82,1.78-1.89 (2458)	1.85,1.7-1.9 (375)	1.97,1.42-2.60 (33)	0.91
	Poor memory	1.83,1.78-1.93 (2596)	1.79,1.61-1.89 (253)	1.98,1.53-3.16 (20)	0.47
Suggestive of hypothyroidism	**Hoarse voice**	1.82,1.78-1.87 (2688)	1.79,1.64-2.03 (170)	1.77,0.2-3.75 (7)	0.73
	Deep voice	1.83,1.78-1.88 (2674)	1.73,1.57-1.93 (184)	1.69,1.35-2.41 (4)	0.21
	Dry skin	1.79,1.76-1.85 (1940)	1.86,1.78-1.95 (781)	1.92,1.81-2.16 (143)	0.25
	Puffy eyes	1.81,1.77-1.87 (2475)	1.84,1.73-2.00 (373)	2.28, 1.44-3.35 (17)	0.57
	Muscle cramps	1.83,1.79-1.89 (2434)	1.78,1.69-1.90 (368)	1.75,1.50-204 (65)	0.29
	Constipation	1.82,1.78-1.87 (2485)	1.78,1.61-1.94 (288)	1.88,1.64-2.12 (90)	0.56
	Sensitivity to cold	1.82,1.76-1.88 (1837)	1.85,1.77-1.94 (849)	1.88,1.77-2.17 (136)	0.64
	Slow thinking	1.82, 1.77-1.86 (2638)	1.89,1.72-207 (215)	1.96,0.88-3.29 (13)	0.19
	Weight gain	1.76,1.72-1.83 (1470)	1.86,1.78-1.94 (1211)	2.09,1.85-2.33 (185)	0.08

Bonferroni adjusted alpha level, p<0.003 (0.05/18), * associated with Kruskal Wallis test

Likewise the two groups were similar with respect to the prevalence and intensity of changed symptoms suggestive of overt thyroid dysfunction at a Bonferroni adjusted alpha level of p<0.003. (Table A8.3)

Table A8.3 Presence versus absence of individual changed mild and severe intensity sysmptoms; comparison of serum TSH concentration

		Median serum TSH concentration			
	Changed symptom	Symptom absent %,95%CI (n)	Mild symptom present %,95%CI (n)	Severe intensity symptom %,95%CI (n)	p value*
Suggestive of hyperthyroidism	**Excessive perspiration**	1.82,1.78-1.87 (2802)	1.80,1.95-2.04 (56)	1.38,1.22-1.46 (4)	0.70
	Trembling hands	1.82,1.78-1.87(2719)	1.91,1.70-2.05 (129)	1.91,0.86-2.90 (11)	0.36
	Frequent palpitations	1.82,1.71-1.87 (2728)	1.79,1.57-1.99 (122)	1.57,0.86-2.26 (6)	0.79
	Sensitivity to heat	1.83,1.778-1.88 (2798)	1.61,1.30-2.26 (48)	2.66,0.06-3.41 (11)	0.47
	Fast thinking	1.82,1.78-1.87 (2847)	1.45,0.87-3.46 (12)	0.84,0.62-3.92 (3)	0.78
	Weight lose	1.83,1.78-1.88 (2489)	1.80,1.68-1.88 (362)	1.64,1.04-2.33 (17)	0.55
Either form of TD	**Lethargy**	1.83, 1.79-1.89 (2330)	1.77,1.69-1.88 (475)	1.49,1.34-1.86 (57)	0.43
	Weak muscles	1.83,1.78-1.87 (2397)	1.83, 1.70-1.93 (443)	1.68, 0.88-2.55 (22)	0.95
	Poor memory	1.84, 1.79-1.91 (2394)	1.74,1.62-1.83 (457)	1.82,0.86-2.50 (16)	0.49
Suggestive of hypothyroidism	**Hoarse voice**	1.82,1.78-1.87 (2692)	1.84, 1.55-2.08 (134)	1.21,0.88-3.51 (2)	0.95
	Deep voice	1.82,1.76-1.86 (2789)	1.76, 1.38-2.28 (55)	1.39,1.35-1.42 (2)	0.79
	Dry skin	1.83,1.83-1.97 (2495)	1.78,1.60-1.88 (337)	1.78,1.33-2.15 (31)	0.32
	Puffy eyes	1.82,1.78-1.86 (2685)	1.95,1.73-2.41 (164)	1.83,0.86-3.78 (9)	0.21
	Muscle cramps	1.83,1.78-1.88 (2488)	1.83,1.69-1.96 (347)	1.44,1.20-1.76 (30)	1.00
	Constipation	1.82, 1.78-1.87 (2662)	1.94,1.70-2.18 (168)	1.17,1.05-1.88 (26)	0.57
	Sensitivity to cold	1.82,1.78-1.88 (2492)	1.87,1.76-2.03 (339)	1.19,0.79-1.57 (26)	0.57
	Slow thinking	1.83,1.78-1.89 (2525)	1.77,1.64-1.88 (327)	2.02, 0.52- 3.29 (10)	0.67
	Weight gain	1.83,1.78-1.88 (2525)	1.80,1.73-1.93 (327)	1.77,1.05-2.28 (23)	0.83

Bonferroni adjusted alpha level,p<0.003, * associated with Kruskal Wallis test

Serum TSH concentration and combinations of current symptoms

To further investigate the relationship between expression of symptoms and serum thyrotrophin concentration each possible pair of current symptoms was defined. As previously described in Chapter 8 the purpose of this was two-fold, firstly to enable comparison of median serum thyrotrophin concentration between the groups reporting the presence and absence of symptoms and secondly to allow examination and identification of interactions between symptoms. Comparisons between groups were made using the Mann Whitney U Test. A Bonferroni adjusted alpha level was used to control for type I error. Since this analysis was exploratory in nature and aimed to identify appropriate individual symptoms and pairs of symptoms for inclusions in the multivariate analysis the analysis plan allowed for application of a significance level of 5% if necessary.

Serum TSH concentration and symptom interactions

Investigation of interactions between symptoms suggestive of overt hyperthyroidism failed to identify any significant interactions. Examination of interactions between symptoms suggestive of hypothyroidism identified a significant interaction between; hoarse voice with weight gain ($p<0.012$) (Table A8.4), hoarse voice and puffy eyes ($p<0.038$ (Table A8.5), hoarse voice and constipation ($p<0.002$) (Table A8.6) and muscle cramps and sensitivity to the cold ($p<0.043$) (Table A8.7).

TSH and combinations of current hyperthyroid symptoms

At the Bonferroni adjusted alpha level of $p<0.001$ no significant differences in median serum TSH concentration was observed between the groups with respect to the prevalence of any of the 36 possible pairs of current symptoms suggestive of hyperthyroidism (Table A8.8).

At a significance level of 5% however, a significant difference between the groups existed with respect to the prevalence of four symptom pairs; excessive perspiration with trembling hands, frequent palpitation with sensitivity to heat, frequent palpitations with weak muscles and lethargy with poor memory. Serum TSH concentration was significantly lower in those reporting presence of frequent palpitations with sensitivity to heat (1.38mIU/L versus 1.83mIU/L, Z-2.370, $p<0.018$), frequent palpitation with weak muscles (1.45mIU/L versus 1.83mIU/L, Z-2.067, $p<0.039$) and lethargy with poor memory (1.61mIU/L versus 1.83mIU/L, Z-2.262, $p<0.024$) than in those not reporting presence of these symptoms pairs. In contrast serum TSH concentration in those reporting presence of excessive perspiration with trembling hands was significantly higher than median serum concentration in the group reporting an absence of one or both of these symptoms (3.13mIU/L versus 1.82mU/L, Z-2.010, $p<0.010$). (Table A8.8)

Serum TSH and combinations of current hypothyroid symptoms

At the Bonferroni adjusted alpha level of $p<0.0008$, no significant differences in median serum thyrotrophin concentration were observed between the groups with respect to the prevalence of any of the 63 possible pairs of current symptoms suggestive of

hypothyroidism (Table A8.9). At a significance level of 5% however, a significant difference was observed with respect to the prevalence of five symptom pairs, lethargy with constipation, poor memory with deep voice, puffy eyes with weight gain, sensitivity to cold with weight gain and hoarse voice with puffy eyes. Serum TSH concentration was significantly greater in those reporting presence of puffy eyes with weight gain (2.00mIU/L versus 1.81mIU/L, Z- 2.070, $p<0.038$) and sensitivity to cold with weight gain (1.91mIU/L versus 1.81mIU/L, Z-2.322, $p<0.020$) than in those reporting absence of these symptoms. In contrast, serum TSH concentration was significantly lower in those reported presence compared with those reporting absence of hoarse voice with puffy eyes (1.39mIU/L versus 1.83mIU/L, Z-1.998, $p<0.046$), poor memory with deep voice (1.32mIU/L versus 1.83mIU/L, Z-2.181, $p<0.029$) and lethargy with constipation (1.55mIU/L versus 1.83mIU/L, Z- 2.513, $p<0.012$) (Table A8.9).

Table A8.4 TSH interaction model 1- Hoarse voice and weight gain

Model	Co-efficient	Std. Error	t	p value
Constant	2.058	.038	54.707	.000
Hoarse voice	.330	.155	2.137	.033
Weight gain	.141	.054	2.615	.009
Interaction term HVWG	-.548	.217	-2.524	.012

Table A8.5 TSH interaction model 2- Hoarse voice and puffy eyes

Model	Co-efficient	Std. Error	t	p value
Constant	2.118	.029	73.254	.000
Hoarse voice	.187	.126	1.486	.137
Puffy eyes	.052	.081	.643	.520
Interaction term HVPE	-.525	.253	-2.077	.038

Table A8.6 TSH interaction model 3- Hoarse voice and constipation

Model	Co-efficient	Std. Error	t	p value
Constant	2.130	.029	73.795	.000
Hoarse voice	-.136	.123	-1.104	.270
Constipation	-.032	.081	-.399	.690
Interaction term HVC	.827	.264	3.129	.002

Table A8.7 TSH interaction model 4- Muscle cramps and sensitivity to the cold

Model	Co-efficient	Std. Error	t	p value
Constant	2.124	.035	61.324	.000
Muscle cramps	-.148	.101	-1.464	.143
Sensitivity to cold	.028	.061	.467	.640
Interaction term MCSC	.302	.149	2.023	.043

Table A8.8 Presence versus absence of pairs of hyperthyroid symptoms; comparison of serum TSH concentration

	Trembling hands		Frequent palpitation		Sensitivity to heat		Fast thinking		Weight loss		Lethargy		Weak muscles		Poor memory	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
	Median n		Median n		Median n		Median n		Median n		Median n		Median n		Median n	
Excessive perspiration	1.82 2865	3.13 5	1.82 2857	1.79 12	1.82 2829	1.76 41	1.82 2844	1.85 24	1.82 2869	1.45 1	1.82 2843	1.72 26	1.82 2841	1.63 29	1.82 2846	1.85 24
Trembling hands			1.82 2855	1.58 15	1.82 2857	1.56 13	1.82 2856	1.97 14	1.82 2856	1.98 14	1.82 2822	2.03 48	1.82 2825	1.92 45	1.82 2856	1.97 14
Frequent palpitation					1.83 2844	1.38 26	1.82 2834	1.56 36	1.82 2856	1.37 14	1.82 2811	1.53 59	1.83 2820	1.45 50	1.82 2842	1.67 28
Sensitivity to heat							1.83 2793	1.63 77	1.82 2866	1.07 4	1.82 2810	1.76 60	1.82 2822	1.76 48	1.82 2845	1.67 25
Fast thinking									1.83 2819	1.66 54	1.82 2791	1.84 79	1.82 2802	2.00 68	1.82 2852	1.73 18
Weight lose											1.82 2831	1.42 39	1.82 2819	1.89 51	1.82 2846	1.85 24
Lethargy													1.82 2670	1.82 200	1.83 2769	1.61 101
Weak muscles															1.82 2779	1.72 91

Excessive perspiration with trembling hands Z*=-2.010, p 0.044, frequent palpitations with sensitivity to heat Z* =-2.370, p 0.018, frequent palpitations with weak muscles Z*=-2.067 p 0.039, lethargy with poor memory Z*=-2.262, p 0.024, * associated with the Mann Whitney U test

Table A8.9 Presence versus absence of pairs of hypothyroid symptoms; comparison of serum TSH concentration

	Hoarse voice Median (n)		Deep voice Median (n)		Dry skin Median (n)		Puffy eyes Median (n)	
	Absent	**Present**	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**
	Median n		**Median n**		**Median n**		**Median n**	
Lethargy	1.82 2815	1.85 55	1.82 2836	1.92 34	1.82 2667	1.78 203	1.82 2787	2.00 83
Weak muscles	1.84 2816	1.74 54	1.82 2840	1.96 30	1.81 2659	1.89 211	1.82 2785	1.94 85
Poor memory	1.82 2833	1.79 37	1.83 2846	1.32 24	1.83 2746	1.71 124	1.82 2802	1.85 68
Hoarse voice			1.82 2827	1.76 43	1.82 2790	1.78 80	1.82 2824	1.39 46
Deep voice					1.83 2804	1.93 66	1.82 2823	1.73 47
Dry skin							1.82 2705	1.95 165

Poor memory with deep voice Z*=-2.181, p<0.029, hoarse voice with puffy eyes Z*=-1.998, p 0.046, * assoacited with Mann Whitney U test

Table A8.9 Presence versus absence of pairs of hypothyroid symptoms; comparison of serum TSH concentration continued

	Muscle cramps Median (n)		Constipation Median (n)		Sensitivity to cold Median (n)		Slow thinking Median (n)		Weight gain Median (n)	
	Absent	**Present**	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**
	Median n		**Median n**		**Median n**		**Median n**		**Median n**	
Lethargy	1.84 2742	1.70 128	1.83 2765	1.55 105	1.82 2662	1.81 208	1.81 2781	1.77 89	1.82 2601	1.84 29
Weak muscle	1.83 2736	1.72 134	1.84 2763	1.60 107	1.82 2668	1.87 202	1.82 2783	1.88 87	1.82 2666	188 204
Poor memory	1.83 2810	1.68 60	1.82 2794	1.76 76	1.82 2735	1.81 135	1.83 2745	1.89 125	1.82 2744	1.78 126
Hoarse voice	1.83 2813	1.71 57	1.82 2830	2.32 40	1.83 2794	1.63 76	1.82 2834	1.88 36	1.82 2780	1.76 90
Deep voice	1.82 2831	1.57 39	1.82 2847	1.76 23	1.82 2802	1.73 68	1.84 2851	1.62 19	1.83 2756	1.79 114
Dry skin	1.83 2661	1.76 209	1.82 2703	1.94 167	1.82 2469	1.89 401	1.82 2759	1.89 111	1.81 2410	1.90 460
Puffy eyes	1.84 2774	1.74 96	1.82 2802	1.83 68	1.82 2707	1.75 163	1.82 2818	1.85 52	1.81 2662	2.00 208
Muscle cramps			1.84 2766	1.69 104	1.82 2660	1.90 204	1.82 2824	2.24 46	1.82 2636	1.83 234
Constipation					1.84 2692	1.77 178	1.82 2810	1.89 60	1.82 2692	1.85 178
Sensitivity to cold							1.82 2749	1.98 121	1.81 2441	1.91 429

Lethargy with constipation Z*=-2.513, p 0.012, p<0.029, puffy eyes with weight gain Z*=-2.070, p<0.038, sensitivity to cold with weight gain Z*=-2.322,p<0.020, * associated with Mann Whitney U test

Appendix 9 Results of univariate exploration of symptoms and serum FT4 concentration

FT4 in groups reporting presence of symptoms

The Mann Whitney U test was used to compare median serum FT4 concentration between groups reporting presence and absence of individual current and changed symptoms. In terms of current symptoms, a significantly greater median serum FT4 concentration was observed in the group reporting presence of weight loss compared with the group reporting absence of this symptom (15.30pmol/L versus 14.80pmol/L respectively, Z-3.778, $p<0.001$). Likewise, the group reporting presence of lethargy had a significantly greater median FT4 concentration compared with the group reporting absence of lethargy (15.30pmol/L versus 14.80pmol/L respectively, Z-3.905, $p<0.001$). To further corroborate this relationship between symptoms and serum thyroxine concentration, a significantly lower median FT4 concentration was observed in the group reporting presence of weight gain compared with the group reporting absence of this symptom suggestive of overt hypothyroidism (14.80pmol/L versus 15.00pmol/L respectively, $p<0.001$). Despite suggesting dissimilar relationships between symptoms and serum FT4 concentration these findings are consistent and in keeping with the symptom classification as suggestive of overt hyperthyroidism or hypothyroidism. An example of this is the association between weight loss, a symptom suggestive of overt hyperthyroidism and higher concentrations of FT4 and the association between weight

gain, a symptom suggestive of hypothyroidism and lower concentrations of FT4 concentration.

In terms of changed symptoms suggestive of overt hyperthyroidism and overt hypothyroidism, no significant differences in serum FT4 concentration were observed between groups (Table A9.1).

Table A9.1 Presence versus absence of individual sysmptoms; comparison of FT4 concentration

		Current symptom			Changed symptom		
	Symptom	Symptom absent Median, 95%CI (n)	Symptom present Median, 95%CI(n)	Z scores (p value)	Symptom absent Median, 95%CI (n)	Symptom present Median, 95%CI (n)	Mann Whitney test Z scores (p value)
Suggestive of hyperthyroidism	**Excessive perspiration**	14.9,14.8-15.0 (2778)	14.75,13.8-15.5 (90)	-0.46 (0.64)	14.9,14.8-15.0 (2802)	14.9,14.3-15.7 (60)	-0.22 (0.82)
	Trembling hands	14.9, 14.8-1.86 (2749)	15.1,14.6-15.6 (120)	-1.47 (0.14)	14.9,14.8-15.0 (2719)	14.8,14.5-15.1 (140)	-0.05 (0.96)
	Frequent palpitation	14.9,14.8-15.0 (2693)	15.2,14.3-15.2 (171)	-2.33 (0.02)	14.9,14.8-15.0 (2728)	15.2,14.5-15.7 (128)	-1.09 (0.28)
	Sensitivity to heat	14.9,14.8-15.0	14.7,14.3-15.0 (304)	-2.56 (0.01)	14.9,14.8-15.0 (2798)	14.8,14.1-14.7 (59)	-0.39 (0.70)
	Fast thinking	14.9,14.8-15.0 (2211)	15.0,14.8-15.2 (655)	-1.09 (0.28)	14.9,14.8-15.0 (2847)	13.9,13.7-15.5 (15)	-0.67 (0.50)
	Weight loss	14.8,14.7-14.9 (2660)	15.3,15.1-15.7 (206)	-3.78 (<0.001)	14.9,14.8-15.0 (2489)	15.0,13.6-15.5 (179)	-1.70 (0.09)
Either form of TD	**Lethargy**	14.8 14.7-14.9 (2408)	15.3,15.0-15.4 (460)	-3.91 (<0.001)	14.9,14.8-15.0 (2330)	15.0,14.7-15.1 (512)	-1.13 (0.26)
	Weak muscles	14.9,14.8-15.0 (2458)	14.9,14.7-15.2 (408)	-0.54 (0.59)	14.9,14.8-15.0 (2397)	14.9,14.8-15.4 (465)	-0.35 (0.73)
	Poor memory	14.9, 14.8-15.0 (2596)	15.0,14.8-15.2 (273)	-1.62 (0.11)	14.9,14.8-15.0 (2394)	14.9,14.7-15.1 (473)	-0.27 (0.79)
Suggestive of hypothyroidism	**Hoarse voice**	14.9,14.8-15.0 (2688)	14.7,14.2-15.1 (177)	-0.64 (0.64)	14.9,14.8-15.0 (2692)	14.5,14.1-14.8 (141)	-2.54 (0.01)
	Deep voice	14.9,14.8-15.0 (2674)	14.9,14.7-15.1 (188)	-0.85 (0.39)	14.9,14.8-15.0 (2789)	14.5,13.9-15.1 (57)	- 0.97 (0.33)
	Dry skin	14.9, 14.8-15.0 (1940)	14.8,14.7-15.0 (924)	-0.58 (0.56)	14.9,14.8-15.1 (2405)	14.9,14.6-16.9 (368)	-0.07 (0.95)
	Puffy eyes	14.9,14.8-15.0 (2475)	14.9,14.7-15.1 (390)	-0.94 (0.35)	14.9,14.8-15.0 (2685)	14.9,14.4-15.1 (173)	-1.50 (0.13)
	Muscle cramps	14.9,1.79-1.89 (2434)	14.7,14.6-15.0 (433)	-0.54 (0.59)	14.9,14.8-15.0 (2488)	14.8,14.6-15.1 (377)	-0.43 (0.67)
	Constipation	14.9,14.6-15.0 (2485)	14.7,14.5-14.9 (373)	-2.17 (0.03)	14.9,14.8-15.0 (2662)	15.0,11.6-14.6 (194)	-0.64 (0.52)
	Sensitivity to cold	14.8,1.76-1.88 (1837)	15.0,14.8-15.1 (985)	-1.09 (0.28)	14.9,14.8-15.0 (2492)	15.1,14.7-15.2 (365)	-1.15 (0.25)
	Slow thinking	14.9,14.0-15.0 (2638)	15.0,14.8-15.2 (228)	-0.91 (0.36)	14.9,14.8-15.0 (2525)	15.0,14.7-15.1 (337)	-0.10 (0.92)
	Weight gain	15.0,14.9-15.1 (1470)	14.8,14.6-14.9 (1396)	-3.49 (<0.001)	14.9, 14.8-15.0 (2405)	14.7,14.5-15.0 (463)	-2.11 (0.04)

The Kruskal Wallis test was use to examine the difference in median serum FT4 concentration between groups reporting absence of symptoms, presence of mild intensity symptoms and presence of severe intensity symptoms. At the Bonferroni adjusted alpha level ($p<0.003$) no significant differences were observed between these groups with respect to median serum FT4 concentration. (Table A9.2)

Table A9.2 Presence versus absence of current mild and severe intensity symptoms; comparison of serum FT4 concentration

		Median serum FT4 concentration			
	Symptom	Symptom absent %,95%CI (n)	Mild symptom present %,95%CI (n)	Severe intensity symptom %,95%CI (n)	p value
Suggestive of hyperthyroidism	**Excessive perspiration**	14.9,14.8-15.0 (2778)	14.7,13.7-15.5 (73)	15.1,14.0-17.4 (17)	0.873
	Trembling hands	14.9, 14.8-1.86 (2749)	15.1,14.4-15.6 (90)	15.2,13.7-16.3 (30)	0.578
	Frequent palpitations	14.9,14.8-15.0 (2693)	15.2, 14.8-15.6 (145)	15.1,1.5-16.5 (26)	0.102
	Sensitivity to heat	14.9,14.8-15.0	14.7, 14.3-15.0 (277)	14.4,13.8-15.8 (27)	0.111
	Fast thinking	14.9,14.8-15.0 (2211)	15.0,14.8-15.1 (595)	14.9,14.1-15.4 (60)	0.428
	Weight loss	14.8,14.7-14.9 (2660)	15.3, 15.1-15.7 (190)	15.6, 14.0-18.0 (16)	0.010
Either form of TD	**Lethargy**	14.8 14.7-14.9 (2408)	15.3, 15.0-15.5 (380)	15.3, 14.8-15.5 (80)	0.020
	Weak muscles	14.9,14.8-15.0 (2458)	14.9,14.6-15.1 (375)	15.3,14.5-16.0 (33)	0.938
	Poor memory	14.9, 14.8-15.0 (2596)	15.0,14.7-15.2 (253)	15.1,14.8-17.1 (20)	0.584
Suggestive of hypothyroidism	**Hoarse voice**	14.9,14.8-15.0 (2688)	14.7,14.3-15.2 (170)	13.6,11.7-25.0	0.284
	Deep voice	14.9,14.8-15.0 (2674)	14.9,14.7-15.4 (184)	13.9, 11.7-16.8 (4)	0.827
	Dry skin	14.9, 14.8-15.0 (1940)	14.8,14.6-15.0 (781)	15.2, 14.8-15.5 (143)	0.237
	Puffy eyes	14.9,14.8-15.0 (2475)	14.9,14.7-15.1 (373)	14.8,14.8-15.0 (2434)	0.841
	Muscle cramps	14.9,1.79-1.89 (2434)	14.71.69-1.90 (368)	14.8,1.50-2.04 (65)	0.544
	Constipation	14.9,14.6-15.0 (2485)	14.7, 14.2-14.9 (288)	18.0,14.6-15.4 (90)	0.203
	Sensitivity to cold	14.8,1.76-1.88 (1837)	15.0,1.77-1.94 (849)	14.8,1.77-2.17 (136)	0.104
	Slow thinking	14.9,14.0-15.0 (2638)	15.0,14.8-15.2 (215)	15.6,13.7-17.4 (13)	0.427
	Weight gain	15.0,14.9-15.1 (1470)	14.8,14.6-14.9 (1211)	14.7,14.3-15.0 (185)	0.080

Bonferroni adjusted alpha level,p<0.003 (0.05/18)

In terms of severity of changed symptoms no significant differences in serum FT4 concentration were observed between groups at the Bonferroni adjusted alpha value of p<0.003.

Table A9.3 Presence versus absence of mild and severe intensity changed symptoms; comparison of serum FT4 concentration

		Median serum FT4 concentration			
	Symptom	Symptom absent %,95%CI (n)	Mild symptom present %,95%CI (n)	Severe intensity symptom %,95%CI (n)	p value
Suggestive of hyperthyroidism	**Excessive perspiration**	14.9,14.8-15.0 (2802)	14.7,14.0-15.0 (2802)	15.1,14.4-18.4 (4)	0.50
	Trembling hands	14.9,14.8-15.0 (2719)	14.7,14.4-15.1 (129)	16.1,14.0-17.8 (11)	0.44
	Frequent palpitations	14.9,14.8-15.0 (2728)	15.2,14.6-15.8 (122)	14.5,9.1-17.9 (6)	0.48
	Sensitivity to heat	14.9,14.8-15.0 (2798)	15.1,14.1-15.7 (48)	14.4,11.2-16.4 (11)	0.77
	Fast thinking	14.9,14.8-15.0 (2847)	15.3,13.7-15.5 (12)	13.7,12.6-13.9 (3)	0.72
	Weight lose	14.9,14.8-15.0 (2489)	14.9,14.7-15.2 (362)	15.5, 13.3-17.8 (17)	0.66
Either form of TD	**Lethargy**	14.9,14.8-15.0 (2330)	14.9,14.7-15.0 (475)	15.5, 14.7-16.1 (57)	0.71
	Weak muscles	14.9,14.8-15.0 (2397)	14.9, 14.7-15.1 (443)	14.7,13.4-16.5 (22)	0.77
	Poor memory	14.9,14.8-15.0 (2394)	14.9,14.7-15.1 (457)	15.3,14.5-17.3 (16)	0.90
Suggestive of hypothyroidism	**Hoarse voice**	14.9,14.8-15.0 (2692)	14.4,13.5-14.8 (134)	15.5,13.9-20.4 (7)	0.01
	Deep voice	14.9,14.8-15.0 (2789)	14.4,14.0-15.1 (55)	12.5,11.7-13.2 (2)	0.23
	Dry skin	14.9,14.8-15.1 (2495)	14.8,14.0-14.7 (337)	15.2,14.6-16.1 (31)	0.97
	Puffy eyes	14.9,14.8-15.0 (2685)	14.9,14.4-15.1 (164)	14.0,13.2-16.1 (9)	0.84
	Muscle cramps	14.9,14.8-15.0 (2488)	14.814.8-15.0 (347)	15.3,14.2-16.0 (30)	0.38
	Constipation	14.9,14.8-15.0 (2662)	14.9,14.3-15.2 (168)	15.2,14.5-16.5 (26)	0.82
	Sensitivity to cold	14.9,14.8-15.0 (2492)	15.0,14.6-15.2 (339)	16.7, 4.8-17.4 (26)	0.28
	Slow thinking	14.9,14.8-15.0 (2525)	15.0,14.7-15.1 (327)	14.9,13.3-19.9 (10)	0.58
	Weight gain	14.9, 14.8-15.0 (2405)	14.7,14.5-15.0 (440)	14.8,13.1-15.7 (23)	0.23

Bonferroni adjusted alpha level, p<0.003 (0.05/18)

Serum FT4 and pairs of current hyperthyroid symptoms

At the Bonferroni adjusted alpha level of $p<0.0013$ no significant differences in median serum FT4 were observed between groups with respect to prevalence of the 36 possible pairs of symptoms suggestive of overt hyperthyroidism. At a level of 5% however a significant difference in median serum FT4 existed with respect to prevalence of six combinations of hyperthyroid symptoms; excessive perspiration with sensitivity to heat, frequent palpitation with poor memory, frequent palpitation with weight loss, fast thinking with weight loss, lethargy with weak muscles, lethargy with poor memory. (Table A9.4) Median FT4 was significantly higher in the group reporting presence of frequent palpitation with poor memory than in the group reporting absence of this symptom pair (16.60 mIU/L versus 14.90 mIU/L, Z-2.070, $p<0.0038$). Similarly, the presence of symptoms pairs; fast thinking with weight loss and frequent palpitation with weight loss was associated with significantly higher median FT4 concentrations compared with absence of these symptoms pairs (15.60 mIU/L versus 14.90 mIU/L, Z-2.357, p 0.018 and 16.75 m IU/L versus 14.90 mIU/L, 2.922, $p<0.003$ respectively). These results were consistent with the symptom classification (e.g hyperthyroid symptoms) and the biochemical profile of overt hyperthyroidism (e.g. elevated free FT4 concentrations). In contrast however the relationship between serum FT4 concentration and the symptom pair; excessive perspiration with sensitivity to heat was in conflict with both the symptom classification and the biochemical profile of overt hyperthyroidism (14.00 mIU/L versus 14.90 mIU/L, Z -2.245, $p<0.025$). Presence of lethargy with weak muscles (15.30 mIU/L versus 14.90 mIU/L, Z- 2.770, $p<0.006$) and lethargy with poor memory (15.30 mIU/L versus 14.90 mIU/L, Z- 2.222, $p<0.020$) was also associated with significantly higher

median serum concentration than absence of these symptom pairs. Since these symptoms manifest in both overt hyperthyroidism and overt hypothyroidism it is difficult to comment further upon this relationship.

FT4 and pairs of hypothyroid symptoms

With respect to combinations of symptoms suggestive of hypothyroidism at the Bonferroni adjusted alpha level of $p<0.0008$, no significant difference in median serum FT4 was observed with respect the possible 63 pairs of symptoms. At the 5% level however, a significant difference in serum FT4 was observed with respect to eight pairs of hypothyroid symptoms (Table A9.5) The relationship between serum FT4 concentration and the symptom pair; lethargy with muscle cramps, lethargy with dry skin, lethargy with sensitivity to cold and lethargy with slow thinking was discordant with the biochemical profile of overt hypothyroidism and the corresponding symptom classification. Presence of lethargy with muscle cramps was associated with a significantly greater serum FT4 concentration than absence of this symptoms pair (15.50 mIU/L versus 14.90 mIU/L, Z- 3.714, $p<0.001$). Similarly, presence of lethargy with dry skin (15.20 mIU/L versus 14.80 mIU/L, Z-2.398, $p<0.016$), lethargy with sensitivity to cold (15.30 mIU/L versus 14.90 mIU/L, Z-3.054, $p<0.020$) and lethargy with slow thinking (15.30 mIU/L versus 14.90 IU/L, Z-2.248, $p<0.025$) was associated with significantly greater serum FT4 concentrations than absence of these symptom pairs (ATable 9.5).

In contrast, the presence of dry skin with constipation (14.60 mIU/L versus 14.90 mIU/L, Z-3.037,$p<0.002$), dry skin with puffy eyes (14.50 mIU/L versus 14.90 mIU/L, Z-2.120,

p<0.034), constipation with weight gain (14.40 mIU/L versus 14.90 mIU/L, Z-3.307, p<0.001) and puffy eyes with weight gain (14.70 mIU/L versus 14.90 mIU/L, Z-2.025, p< 0.043) were associated with significantly lower concentrations of serum FT4 (Table A9.5).

Table A9.4 Presence versus absence of pairs of hyperthyroid symptoms; comparison of serum FT4 concentration

	Trembling hands		Frequent palpitation		Sensitivity to heat		Fast thinking		Weight loss		Lethargy		Weak muscles		Poor memory	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
	Median n		Median n		Median n		Median n		Median n		Median n		Median n		Median n	
Excessive perspiration	1.82 2865	3.13 5	1.82 2857	1.79 12	1.82 2829	1.76 41	1.82 2844	1.85 24	1.82 2869	1.45 1	1.82 2843	1.72 26	1.82 2841	1.63 29	1.82 2846	1.85 24
Trembling hands			1.82 2855	1.58 15	1.82 2857	1.56 13	1.82 2856	1.97 14	1.82 2856	1.98 14	1.82 2822	2.03 48	1.82 2825	1.92 45	1.82 2856	1.97 14
Frequent palpitations					1.83 2844	1.38 26	1.82 2834	1.56 36	1.82 2856	1.37 14	1.82 2811	1.53 59	1.83 2820	1.45 50	1.82 2842	1.67 28
Sensitivity to heat							1.83 2793	1.63 77	1.82 2866	1.07 4	1.82 2810	1.76 60	1.82 2822	1.76 48	1.82 2845	1.67 25
Fast thinking									1.83 2819	1.66 54	1.82 2791	1.84 79	1.82 2802	2.00 68	1.82 2852	1.73 18
Weight lose											1.82 2831	1.42 39	1.82 2819	1.89 51	1.82 2846	1.85 24
Lethargy													1.82 2670	1.82 200	1.83 2769	1.61 101
Weak muscles															1.82 2779	1.72 91

Excessive perspiration with sensitivity to heat Z=-2.245 p 0.025, frequent palpitation with weight loss Z=-2.922,p 0.003, frequent palpitation with Poor memory Z=-2.070, p 0.038, fast thinking with weight loss Z=-2.357,p 0.018, lethargy with poor memory Z= -2.222, p 0.020, lethargy with weak muscles Z=-2.770, p 0.006.

Table A9.5 Presence versus absence of pairs of hypothyroid symptoms; comparison of serum FT4 concentration

	Hoarse voice Median FT4 (n)		**Deep voice Median FT4 (n)**		**Dry skin Median FT4 (n)**		**Puffy eyes Median FT4 (n)**	
	Abs	Pres	Abs	Pres	Abs	Pres	Abs	Pres
Lethargy	14.90 2815	15.10 55	14.90 2836	15.45 34	14.80 2667	15.20 203	14.90 2787	15.30 83
Weak muscles	14.90 2816	14.45 54	14.90 2840	15.10 30	14.90 2659	14.80 211	14.90 2785	15.10 85
Poor memory	14.90 2833	15.10 37	14.90 2846	15.90 24	14.90 2746	14.90 124	14.90 2802	15.30 68
Hoarse voice			14.90 2827	15.60 43	14.90 2790	14.35 80	14.90 2824	14.80 44
Deep voice					14.90 2804	14.75 66	14.90 2823	15.10 47
Dry skin							14.90 2705	14.50 165
Puffy eyes								
Muscle cramps								
Constipation								
Sensitivity to cold								
Slow thinking								
Weight gain								

Lethargy with dry skin Z=-2.398, p 0.016, dry skin with puffy eyes Z=-2.120, p 0.034,

Table 9.5A Presence versus absence of pairs of hypothyroid symptoms; comparison of serum FT4 concentration continued

	Muscle cramps Median FT4 (n)		Constipation Median FT4 (n)		Sensitivity to cold Median FT4 (n)		Slow thinking Median TF4 (n)		Weight gain Median FT4 (n)	
	Abs	**Pres**	**Abs**	**Pres**	**Abs**	**Pres**	**Abs**	**Pres**	**Abs**	**Pres**
Lethargy	14.90 2742	15.50 128	14.90 2765	15.20 105	14.90 2662	15.30 2068	14.90 2781	15.30 89	14.90 2601	15.00 269
Weak muscles	14.90 2736	15.00 134	14.90 2763	14.70 107	14.90 2668	15.10 202	14.90 2783	15.10 87	14.90 2666	14.75 204
Poor memory	14.90 2810	15.25 60	14.90 2794	14.95 76	14.90 2735	15.10 135	14.90 2745	15.00 125	14.90 2744	15.05 126
Hoarse voice	14.90 2813	14.40 57	14.90 2830	14.30 40	14.90 2794	15.10 76	14.90 2834	15.20 36	14.90 2780	14.15 90
Deep voice	14.90 2831	14.40 39	14.90 2847	14.90 23	14.90 2802	15.35 68	14.90 2851	15.30 19	14.90 2756	14.90 114
Dry skin	14.90 2661	14.80 209	14.90 2703	14.60 167	14.90 2469	15.00 401	14.90 2759	15.00 111	14.90 2410	14.80 460
Puffy eyes	14.90 2774	14.75 96	14.90 2802	14.75 68	14.90 2707	15.00 163	14.90 2818	15.25 52	14.90 2662	14.70 208
Muscle cramps			14.90 2766	15.10 104	14.90 2666	14.70 204	14.90 2824	15.00 46	14.90 2636	14.60 234
Constipation					14.90 2692	14.85 178	14.90 2810	14.95 60	14.90 2692	14.40 178
Sensitivity to cold							14.80 2749	15.20 121	14.90 2441	14.90 429
Slow thinking									14.90 2762	15.00 108
Weight gain										

Lethargy with muscle cramps Z=- 3.714, p <0.001, dry skin with constipation Z=-3.037,p 0.002, Constipation with weight gain Z=- 3.307, p 0.001, puffy eyes with weight gain Z=-2.025, 0.043, lethargy with slow thinking Z=-2.248, p 0.025, Lethargy with sensitivity to cold Z= -3.054, p 0.020,

Symptom interactions and FT4

A logistic model was constructed to determine whether the relationship between serum thyroxine concentration and the symptom fast thinking was modified by the presence of lethargy demonstrated a significant interaction between the two symptoms.

Table A9.6 FT4 interaction model 1- Fast thinking and lethargy

Model	Co-efficient	Std. Error	t	p value
Constant	14.879	.048	311.423	.000
Fast thinking	.219	.098	2.244	.025
Lethargy	.525	.115	4.564	.000
Interaction term FTLA	-.657	.271	-2.426	.015

Table A9.7 FT4 interaction model 2 – Deep voice and muscle cramps

Model	Co-efficient	Std. Error	t	p value
Constant	14.980	.043	348.857	.000
Deep voice	.309	.174	1.774	.076
Muscle cramp	.011	.112	.097	.923
Interaction term DVMC	-.779	.386	-2.019	.044

Table A9.8 FT4 interaction model 3 – Dry skin and constipation

Model	Co-efficient	Std. Error	t	p value
Constant	15.005	.049	304.256	.000
Dry skin	.083	.089	.923	.356
Constipation	-.028	.149	-.190	.849
Interaction term DVC	-.548	.230	-2.381	.017

Table A9.9 FT4 interaction model 4 – Lethargy with muscle cramps

Model	Co-efficient	Std. Error	t	p value
Constant	14.966	.045	335.762	.000
Lethargy	.246	.121	2.039	.042
Muscle cramps	-.287	.125	-2.287	.022
Interaction term LAMC	.704	.247	2.853	.004

Table A9.10 FT4 interaction model 5–Lethargy with weight gain

Model	Co-efficient	Std. Error	t	p value
Constant	15.041	.057	264.103	.000
Lethargy	.689	.158	4.352	.000
Weight gain	-.232	.083	-2.787	.005
Interaction term LAWG	-.435	.210	-2.071	.038

Table A9.11 FT4 interaction model 6- Hoarse voice with constipation

Model	Co-efficient	Std. Error	t	p value
Constant	15.018	.042	354.876	.000
Hoarse voice	.203	.181	1.123	.261
Constipation	-.184	.119	-1.540	.124
Interaction term HVC	-.767	.387	-1.981	.048

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